9th World Congress of Biological Psychiatry

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ABSTRACTS

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Foreword

The Scientific Programme is considered the core of the 9th World Congress of Biological Psychiatry. Thus the International Scientific Programme Committee is proud to have compiled a well balanced blend of Plenary and Special Lectures, Symposia, Workshops, WFSBP Treatment Guidelines Sessions, Debates, Free Communications and Guided Poster Tours covering all aspects of psychiatric disorders from basic to clinical reasearch including the newest concepts for improving the patients' lives.

As with all congresses of the World Federation of Societies of Biological Psychiatry (WFSBP), the Scientific Programme greatly depends on the submitted proposals and abstracts. In this sense we first would like to thank all who actively gave an input for the programme and who accepted with enthusiasm to participate and to present high quality work. A WFSBP congress is not possible without the continuing support from its National Societies of Biological Psychiatry. We cordially thank the WFSBP National Societies for their engagement and for spreading the ideas that we are committed to.

In the last years there has been radical progress in neuroscience that is changing our concepts and attitudes on mental diseases. The advances in biology and molecular genetics, the availability of modern technologies such as brain imaging, the development of a new generation of treatments based upon neuroplasticity concepts are opening our field to new and exciting horizons.

The Scientific Programme reflects the recent developments, and state of the art in psychiatry and biological psychiatry by inviting leading international experts to present their latest findings and achievements and to give insights into the newest innovations in our field and their impact on diagnoses, treatment, and rehabilitation of patients with mental disorders. We will have the opportunity to discuss these themes as well as the integration between the rapid development of scientifc knowledge and the everyday clinical practice.

We believe that you will find interesting updates for a constantly improving treamtent of your patients and many inspirations for your research work in this Scientific Programme.

Yours sincerely

Prof. Siegfried Kasper

Congress President
President of World Federation
of Societies of Biological Psychiatry

Prof. Raquel Gur

Co-Chair of the WFSBP International
Scientific Programme Committee

Prof. Birte Glenthoj

Co-Chair of the WFSBP International
Scientific Programme Committee

Opening / Plenary Lectures

Opening Lecture

Opening
Is consciousness a relevant concept for psychiatry research?

Opening-001
Is consciousness a relevant concept for psychiatry research

Stanislas Dehaene
Unité INSERM-CEA, Neuroimagerie Cognitive, Saclay, France

Abstract: The cognitive neuropsychology approach to brain dysfunction was largely founded on a modular approach: individual patient's deficits were explained by a local impairment within a modular architecture of specialized subsystems. I will suggest, however, that in addition to specialized processors, which can operate without consciousness, the human brain also comprises a brain-scale communication infrastructure, the "global neuronal workspace", that breaks modularity by allowing conscious flexible recombination of new processing chains. Impairments at the level of workspace neurons, which are particularly dense in prefrontal and anterior cingulate cortices, might provide a new level of explanation for some of the cognitive deficits underlying psychiatric diseases such as schizophrenia. I will present converging behavioral and event-related potential data, collected in collaboration with Antoine Del Cul and Marion Leboyer, which indicate a dissociation between preserved subliminal processing and impaired conscious access in schizophrenia. Once top-down attention is controlled for, early visual processing appears to be largely preserved in schizophrenic patients, and only a late phase relating to conscious access is drastically affected.

Plenary Lectures

PL-01
From clinical studies to evidence-based treatment guidelines

T12 Other

PL-01-001
From clinical studies to evidence-based treatment guidelines

Hans-Jürgen Möller
Med. Universität München, Psychiatrie und Psychotherapie, Germany

Abstract: Psychopharmacotherapy and psychiatric treatment in general should now be regulated in the sense of evidence-based medicine, as is the case in other areas of therapeutic medicine. In general this is a meaningful development, which principally will have a positive impact on routine health care. But several related problems should not be ignored. So far, consensus was accepted that evidence graduation could not be reached on an international level, due to several difficulties related to this. For example, if placebo-controlled studies are prioritized in the evidence graduation, the evidence possibly deviates too far from the conditions of routine clinical care. However, the restriction to active comparative trials could lead to wrong conclusions about efficacy. And if the focus is placed on the results of meta-analyses instead of considering relevant single studies the result is a decision-making logic contrary to that of the licensing process. Due to inherent methodological problems of the meta-analytical approach, the narrative, systematic review should retain its traditional importance and be used to give a complementary view. Attempts to regulate psychopharmacotherapy in the sense of evidence-based medicine come closer to their limits the more complex the clinical situation and the respective decision-making logic are. Even in times of evidence-based medicine a large part of complex clinical decision-making in psychopharmacotherapy still relies more on clinical experience and a consensus about clinical experience and traditions than on results of sophisticated clinical studies.

The World Federation of Societies of Biological Psychiatry (WFSBP) has developed treatment guidelines for many psychiatric disorders, covering indications such as acute and long-term treatment of schizophrenia, acute and long-term treatment of unipolar and bipolar depression, acute and long-term treatment of anxiety disorders, treatment of personality disorders, etc. The specific aim of the work of the task forces was to include global knowledge and experience.

PL-02
Globalization, market and brain sciences

T8 Brain Function

PL-02-001
Globalization, markets and the brain sciences

Peter Whybrow
UCLA, Semel Institute, Los Angeles, USA

Objectives: It is the paradox of globalization and modernity that as choice and material prosperity increase health and personal satisfaction decline. In part, the roots of this conundrum are to be found in our evolutionary history. The human species, having evolved under conditions of danger and scarcity, is by instinct a reward-seeking animal that discounts the future in favor of the immediate present. In consequence material abundance can be dangerously addictive, as is evident in the USA the world's most affluent nation where epidemic rates of stress, anxiety, depression, obesity, and time urgency are now grudgingly accepted as part of everyday existence.
Methods: This lecture explores the neurobiology of market behavior offering a re-analysis of Adam Smith's original concept of a balanced market economy.
Results: Smith-the eighteenth century Scottish philosopher and capitalism's patron saint-was the first to argue the value of harnessing instinctual self-interest as the engine of economic growth. Smith understood the human propensity for greed but believed that in a free society it is constrained by the wish to be loved by others, (the drive for attachment) and by "social sentiment" (empathic and commonsense behavior).
Conclusions: But Smith lived before the invention of the mega-corporation, before instant communication, and before the double cheeseburger. While experience tells us that locally capitalized markets do sustain their own rational order based upon an interlocking system of self-interested exchange, today the tethers that once bound self-interest and which gave us Adam Smith's enduring metaphor of an "invisible hand" have been weakened by an intrusive global mercantilism that never sleeps.

PL-03
Addiction and the neurobiology of choice and self-control

T1 Addictive Disorders

PL-03-001
Addiction and the neurobiology of choice and self-control

Nora Volkow
National Inst. on Drug Abuse, Bethesda, USA

Abstract: At the essence of drug addiction is the inability of the drug abuser to inhibit the urge of drug taking and its consumption. This is believed to reflect both an enhanced incentive motivational value for the drug and associated cues (associated with neuroadaptations in circuits involved with reward/motivation, memory/conditioning/habits, stress reactivity and interoception) and the disruption of inhibitory control mechanisms (reflecting neuroadaptations in fronto-striatal circuits that include the inferior frontal cortex, anterior cingulate gyrus and lateral orbitofrontal cortex and both the ventral and dorsal striatum). However, despite the crucial role of loss of control in addiction, the extent to which an addicted individual can exert control over his/her responses to drug stimuli has not been adequately investigated. We will review prevailing contemporary models in the field and discuss the therapeutic implications of these findings.

PL-04
Emotion, decision making and psychopathology

T12 Other

PL-04-001
Emotion, decision making and psychopathology

Ray Dolan
Wellcome Trust Centre for, Neurology, London, United Kingdom

Abstract: RJ Dolan Director, Wellcome Trust Centre for Neuroimaging, UCL, London. Normative accounts of decision making invoke the idea that we choose in order to optimise the hedonic value, or utility, of the outcomes of our choices. Thus, a decision maker faced with a choice between a set of options should weigh the utility of each choice and choose an option that offers the maximal expected utility. However, there are many examples of deviation from rationality that appear in many instances to reflect the influence of emotion. The science of decision making is critical for psychiatry as it provides a theoretical underpinning for understanding core processes including reward and risk representation, loss aversion and how we discount the value of future options. In this talk I will illustrate key themes in decision science by showing how the human brain encodes reward value, under a range of contexts. I will suggest that a corruption of this encoding can explain core deficits in psychiatric disorders such as anhedonia, amotivation and impulsivity. I will conclude with a plea for a psychopathology that is firmly grounded in knowledge emerging from a systems neuroscience understanding of the human mind.

PL-05
Advancements in molecular (PET) imaging provide a cornerstone in future psychiatry research

T10 Neuroimaging

PL-05-001
Advancements in molecular (PET) imaging provide a cornerstone in future psychiatry research

Lars Farde
Karolinska University Hospital, Dept of Clinical Neuroscience, Stockholm, Sweden

Abstract: The imaging technology Positron Emission Tomography (PET) is used to trace radiolabeled molecules in the human brain. The concept 'molecular imaging' refers to the study of radioligand binding to neuroreceptors, enzymes or transport proteins. Molecular imaging is currently widely applied to research on normal brain functioning, the pathophysiology of brain disorders, and in clinical psychopharmacology. Work on recently identified proteins is a particular challenge in neuroscience because approximately half of the human genes are expressed in brain. This availability of numerous new proteins provides vast opportunities for new drug treatments. However, using the suitable radioligands so far developed, only about 25 CNS-proteins can be examined by PET. The field benefits from the present industrial investments in PET imaging and access to chemistry resources, which facilitates more effective developments of new radioligands. Interestingly, these efforts may in addition provide academia with new tools to reveal the functional role of recently discovered proteins in the human brain. Such research takes advantage of recent advancements of the PET technology. The High Resolution Research Tomograph (HRRT) and recent implementation of improved image reconstruction software provides brain imaging at a resolution of about 1.6 mm. This high resolution allows for detailed mapping of proteins and disease biomarkers in the human brain. Moreover, advanced image analysis including statistical methods for recognition of patterns of protein distribution in brain are now developed to take benefit of the vast amount of information generated by a single PET measurement. Taken together, these methodological advancements paves the way for a new era of PET imaging in psychiatry research. One such area is the dynamic interplay between brain biochemistry and environment, including therapeutic interventions.

Special Lectures

SL-01
Financial and non-financial conflicts of interest in psychiatry

T12 Other

SL-01-001
Financial and non-financial conflicts of interests in psychiatry

Mario Maj
University of Naples, Department of Psychiatry, Italy

Abstract: A conflict of interests occurs when a physician is unduly influenced by a secondary interest (i.e., a personal incentive) in his acts concerning one of the primary interests to which he is professionally committed (the welfare of patients, the progress of science, or the education of students or residents). Conflicts of interests may be potential or actual, and harmful or non-significant. They may or not be perceived as such by the involved person. One specific variety of conflicts of interests has almost completely monopolized the attention of scientific and lay press: the financial conflicts of interests arising from the relationships between physicians and drug companies. A large literature has described the many, sometimes subtle, ways by which a psychiatrist can be influenced in his prescribing habits, or in his research activities, by his relationships with the industry. Some empirical evidence is now available in this area. On the other hand, it has been pointed out that the current debate on this issue is sometimes "affectively charged", or fails to take into account that the interests of patients, families and mental health professionals and those of the industry may be often regarded as convergent. Other types of conflicts of interests are beginning now to be discussed (1). There is an emerging evidence about how the allegiance of a researcher to a given school of thought may influence the results of studies comparing different psychotherapeutic techniques, thus colliding with the primary interest represented by the progress of science. There is also a small body of literature concerning political commitment as a source of conflict of interests. Financial and non-financial conflicts of interests are widespread in psychiatric practice and research. They cannot be eradicated, but must be managed more effectively than is currently the case.

SL-02
From tragedy to tears: A neurobiological perpective

T8 Brain Function

SL-02-001
From tragedy to tears: A neurobiological perpective

Michael Trimble
Institute of Neurology, London, United Kingdom

Abstract: The presentation will begin by adopting an evolutionary perspective to the development of the human brain and the relationship of that to the development of artistic creativity. The presentation will begin by considering the importance of music to human culture and the links between music, poetry and religion. The neurological circuitry that relates to language in the brain will be presented, in particular the association in the human brain between the right hemisphere and aprosody. This will lead on to a discussion of the links between music and poetry, as forms of language which are related but differ from propositional speech in form and content and cerebral representation. Data from patients with neurological disorders, particularly epilepsy, who have experienced religious conversions or ecstasies will be presented showing a relationship with right sided temporal lobe epilepsy. The role of the right hemisphere will then be discussed as the progenitor of the highest cultural achievements of Homo sapiens namely religious and artistic values. Finally there will be a discussion of crying from an evolutionary and biological perspective and the significance of tragedy as the cynosure of high and low art, from opera to Hollywood kitsch.

SL-03
Brain, mind, society: The threefold cord

T8 Brain Function

SL-03-001
Brain, mind, society: the threefold cord

Alain Ehrenberg
INSERM, Ctr de Recherche Psychotropes, Paris, France

SL-04
Depression and Mens Health – what s new?

under the auspices of WFSBP and ISMH

T3 Affective Disorders (Unipolar)

SL-04-001
Depression and Mens Health – what s new?

Siegfried Meryn
President ISMH, Vienna, Austria

Symposia

S-23
Are first experiences with alcohol predicting later risk of alcohol-dependence? Clinical and biological approaches

S-23-001
Alcohol consumption and dependence: A study of medical students

Sami Richa
Psychiatric Hospital of Cross, Beirut, Bsalim, Lebanon

Objectives: To evaluate alcohol dependence of medical students, and to compare it to the one in another population (students in different faculties), in order to bring out the harmful effect of university on medical student's dependence.
Methods: Three parts questionnaire has been distributed to a sample of medical students at the St Joseph University (USJ), and to 140 students in many other USJ's Faculties, either at the beginning or at the end of courses, and filled in anonymously. The first part is about demographic criterions and the second and third parts are respectively, alcohol and drug dependence, and behavioral dependence.
Results: There is no statistically significant difference between the two studied populations concerning the dependence on alcohol. However the prevalence of addiction on caffeine, cocaine, nicotine; sexual addiction, and compulsive buying is significantly lower in medical students when comparing them to the other population. There is no variation in dependence through the years of medical studies.
Conclusions: The prevalence of alcohol dependence of medical students is not higher than the other population.

S-23-002
Early alcohol experiences and adolescent mental health: A population-based study in Taiwan

Wei J. Chenb
Institute of Epidemiology, Psychiatry, Taipei, Taiwan

S-23-003
Alcohol initiation experiences and family history of alcoholism as predictors of problem-drinking trajectories

Warner La
Psychiatric Hospital, Psychiatry, New York, USA

S-35
Behavioral addictions: Neurobiology and treatment

S-35-001
The neuropsychopharmacology of pathological gambling

Marc Potenza
Yale School of Medicine, Dept. of Psychiatry, New Haven, CT, USA

Objectives: Pathological gambling has been conceptualized as an impulse-compulsive-spectrum disorder and as a "behavioral" addiction. Its classification has important clinical implications, and investigations into biological underpinnings of the disorder should provide empirical data to assist in its categorization.
Methods: Brain imaging, genetic and pharmacological approaches have been used to investigate individuals with pathological gambling, substance addictions, other psychiatric disorders, or no mental health conditions.
Results: Like individuals with substance addictions, those with pathological gambling (as compared with control subjects) show relatively diminished activation of the ventromedial prefrontal cortex and ventral striatum across fMRI paradigms. Like with alcohol dependence, opioid antagonists appear efficacious in the treatment of pathological gambling and factors associated with positive treatment outcome include strong gambling urges at treatment onset and a family history of alcoholism.
Conclusions: In addition to phenomenological commonalities, pathological gambling and substance addictions share neuropsychopharmacological features that have theoretical and direct clinical implications.

S-35-002
Compulsive buying

Michel Lejoyeux
Bichat-Claude Bernard Hospital, Dept. of Psychiatry, Paris, France

Abstract: Compulsive buying corresponds to repetitive, uncontrolled urges to buy items which are not needed. Buying sprees induce financial difficulties, reproaches and conflicts with their families. Mc Elroy et al. proposed diagnostic criteria for compulsive buying and excluded buying sprees by manic patients. Compulsive buyers experience irresistible and overpowering impulses leading them to buy items they do not need. They feel mounting tension which may only be relieved by buying. We assessed the prevalence of compulsive buying among "normal consumers" and to describe the specificities in the buying style of compulsive buyers. Prevalence of compulsive buying was 32.5%. The proportion of married women was lower among compulsive buyers (66%) than in controls (85%). Compulsive buyers do not seek sales more than controls. Their decision to buy is more often made during their stay in the shop (48% versus 24%, $\chi 2$ =117, $p<0.001$). Women buying compulsively consider more often their purchases as opportunities not to be passed by (33.7 versus 23.1%, $p=0.006$). They have a higher tendency to use items less than expected (23.4% versus 14.4% in the control group $p<0.001$). They more often make purchases to impress others (6.5% versus 2.5%, $p=0.04$) and consider more often their purchases as personnaly gratifying (44 % versus 23 %, $p<0.001$). Their connections to on-line shopping sites are longer and more frequent They spend significantly more time than controls speaking on their cellular phones.

S-35-003
Sexual addiction and paraphilias

Florence Thibaut
CHU Ch Nicolle, Psychiatry, Rouen, France

Objectives: The term sexual addiction appeared in the literature in the nineties. It is characterized by persistent and escalating patterns of sexual behavior acted out despite increasingly negative consequences to self and to others. In the great majority of cases, the definition of sexual addiction relies on non deviant sexual behavior. On the other hand, in most cases, paraphilic, or deviant sexual behavior, is associated with hypersexuality. The term paraphilia involves the fixation of an unusal object (e. g. animals, underwears…), a child or another non consenting person, or an act that leads to the suffering or humiliation of oneself or one 's partner. The relationships between sexual addiction and deviant sexual behavior (e.g. rape, pedophilia or exhibitionism) remains unclear and will be discussed. In both syndromes, patients report histories of childhood sexual abuse. Cognitive behavioral therapies and serotonin reuptake inhibitors (SSRIS) are also widely used in both syndromes.

S-35-004
Dopamine release during computer game playing

Aviv Weinstein
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Hedva Lerman, Isachar Herman, Shaul Schreiber, Omri Frish, Rachel Bar-Hamburger, Roland Chisin, Einat Even-Sapir, Yodphat Krausz

Objectives: There is increasing evidence that behavioral addictions like compulsive gambling, overeating, sex and shopping lead to long term changes in the reward circuitry that resemble the effects of substance dependence. Notably, behavioral paradigms such as playing a video game, monetary reward tasks and non-hedonic food motivation also release DA in brain meso-limbic reward centers. Using the dopamine competition paradigm we have investigated dopamine release as result of natural reward- the performance on a computer game in ex-recreational users of "ecstasy" and healthy control subjects.

Methods: We have scanned 10 ex- "ecstasy" users up to a year and a half after recovery and 8 control subjects at baseline and after performing on a motorbike riding computer game while imaging dopamine in vivo with [123I] IBZM (a D2 receptor antagonist radiotracer) in Single Photon Computerized Tomography (SPECT). Imaging procedure included bolus injection and continuous infusion (total 10 mCi [123I] IBZM, baseline scan (3 hours later), motorbike game (45 min.), scan (30 min. later), follow-up scan (1 hour later). Region of Interest analysis summed slices with the highest striatal uptake and Chang attenuation corrected VOI of striatum (rich with D2) and occipital control regions were calculated to measure specific vs. non-specific partition coefficients (V3").
Results: 1) similar measures of D2 receptor occupancy at baseline in ex-"ecstasy" users compared with control subjects 2) Partition coefficient (V3") after challenge was lower in control subjects compared with ex-"ecstasy" users indicating greater dopamine release after challenge.
Conclusions: This is preliminary evidence that ex-"ecstasy" users release less dopamine during a naturally rewarding game. This evidence supports the notion that psycho-stimulant users use drugs in order to feel their euphoric and pleasurable effects and they have decreased sensitivity to natural reward. This may constitute a vulnerability factor for the development and maintenance of drug abuse.

S-46
Dysregulation of neurogenesis in the brain action: The common mechanism of alcoholism and depression

S-46-001
Stem cells and alcohol dependence: Suppressed neurogenesis after long periods of abstinence

Anita C. Hansson
Central Inst. of Mental Health, Dept. of Molecular Biology, Mannheim, Germany
Kimberly Nixon, Roberto Rimondini, Wolfgang H. Sommer, Fulton T. Crews, Markus Heilig

Objectives: Exposure to repeated cycles of ethanol intoxication and withdrawal results in a well characterized persistent post-dependent increase in excessive voluntary ethanol consumption and behavioral sensitivity to stress. We have previously described some molecular neuroadaptations that contribute to these behaviors. Formation of new neurons in the adult brain, or adult neurogenesis, is related to stress responsiveness, and previous work has established that it is modulated by ethanol intoxication and withdrawal. Here, we asked whether adult neurogenesis is altered in the post-dependent state, in a manner that could contribute to the functional phenotype observed in this condition.
Methods: We studied cell proliferation and neurogenesis in the subgranular zone of the dentate gyrus (SGZ) and in the subventricular zone (SVZ) in rats over a period of 3 weeks following induction of dependence by intermittent ethanol vapor exposure and compared to controls without a history of ethanol exposure. A single dose of 5-bromo-2-deoxyuridine (BrdU, 200 mg/kg, i.p.) was administered 5 h prior to euthanasia on day 0, 3, 7 and 21 of abstinence. Changes on cell proliferation/neurogenesis were identified using immunohistochemistry for BrdU and doublecortin.
Results: A history of dependence modulates rates of neurogenesis in the SVZ. The initial pattern is similar to what others have previously described for the dentate gyrus, i.e. suppression during intoxication, and a rebound increase in early abstinence. However, within the SVZ, neurogenesis rates then return to subnormal levels, and remain subnormal for a long time.
Conclusions: Our data indicate a long-lasting suppression of neurogenesis in the SVZ of post-dependent rats, potentially leading to reduced neuronal turnover in the olfactory bulb and possibly also in prefrontal cortex circuitry. Although, the functional correlates of SVZ suppression are unknown, loss of olfactory discrimination is common in alcoholics and correlates with loss of executive functions.

S-46-002
Depending on dose and context, alcohol consumption can both increase and decrease hippocampal neurogenesis in rodents

Stefan Brene
Karolinska Institutet, Neuroscience, Stockholm, Sweden
Elin Aberg

Objectives: Alcohol can affect parts of the adult brain in different ways depending on dose, genetics, gender and other external circumstances. The present work contributes to the understanding of the putative role hippocampal neurogenesis and plasticity in alcoholism. We have analyzed the effect of voluntary ethanol consumption and withdrawal episodes on hippocampal cell proliferation/neurogenesis in female C57BL/6 mice and Wistar rats.
Methods: Female Wistar rats or C57BL/6 mice were exposed to ethanol via the two-bottle free-choice model. Rats and mice had unlimited and continuous access to a 5 and 10% v/v ethanol bottle respectively and a tap water bottle during two weeks or two months. Control animals had two bottles of tap water in their cages during the same time periods. Additional animals were similarly exposed to ethanol using the two-bottle free-choice model for two months, but with four inserted irregular episodes of ethanol withdrawal.
Results: Voluntary low ethanol consumption during short or longer periods can affect hippocampal neurogenesis and key plasticity genes. However, in our models with high and low ethanol consumption as well as regular and irregular access to ethanol we can in the various models detect no effect of treatment alternatively increased or decreased hippocampal neurogenesis.
Conclusions: Both the context around the ethanol intake and dose of ethanol consumed can be important for regulating hippocampal neurogenesis and plasticity genes in hippocampus. Hypothetically, new neurons detected after ethanol intake and regulation of hippocampal plasticity genes could be involved in the development and maintenance of addictive behavior.

S-46-003
Effects of chronic ethanol exposure on long-term differentiation of SH-SY5Y human neuroblastoma cells

Julian D. Hellmann
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Objectives: Chronic ethanol exposure exerts profound effects on the development of neuronal cells. Various cell signaling pathways have been shown to be affected by ethanol exposure, including protein kinase C (PKC) and MAP kinase signaling. We previously described a possible role for the signaling modulator Raf kinase inhibitor protein (RKIP) in ethanol-impaired neuronal differentiation (ND). RKIP, which mediates the differentiation-associated crosstalk between PKC and MAP kinases, was found to be continuously and significantly reduced in long-term ethanol treatment and thus hypothesized to mediate the effects of ethanol on ND (Hellmann et al., ACER 33:1-13 (2009). In this study, we elucidate a direct role for RKIP in regulating ND, mimicking the effects of previously observed ethanol-impaired ND.
Methods: Yielding a well established model for studying ND, human SH-SY5Y neuroblastoma cells were differentiated in the presence of retinoic acid and exposed to ethanol at various concentrations. RKIP overexpression, shRNA-guided downregulation, quantitative RT-PCR and Western analysis were carried out by common procedures.
Results: While long-term differentiation with RA led to the development of a highly organized neuronal network, ethanol treatment inhibited morphological characteristics such as cluster formation, extension of long, parallel neurites and significantly reduced neuronal marker expression. Both RKIP and PKC expression were found to be significantly downregulated in ethanol treated cells. At the functional level, BDNF- and PKC-mediated ERK transactivation were significantly impaired. While RKIP overexpression led to rapidly enhanced ND and enhanced signaling, RKIP downregulation was able to mimic the effects on morphology and cell signaling observed in chronic ethanol exposure.
Conclusions: Overexpression and downregulation of RKIP revealed a positive correlation between RKIP levels and the development of the neuronal phenotype. The observed effects of ethanol on both RKIP and PKC expression are thus suggested as a molecular correlate for ethanol-inhibited cell signaling, finally resulting in impaired ND.

S-46-004
Potential regulation of neurogenesis by psychotropics in the damaged brain by ethanol

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Toshihiro Yoshinaga, Takao Ishii, Wataru Ukai, Masaru Tateno, Takafumi Ono, Kimihiko Watanabe, Ippei Watanabe, Tomohiro Shirasaka

Objectives: Recent clinical neuroimaging studies have revealed the possible relation between morphological brain changes and cognitive impairments in the course of alcoholism and depression. Although its biological mechanism is still unclear, the emerging evidences suggest that the alteration of neurogenesis is the key factor for the pathophysiology of alcohol-induced brain dysfunction and depression.
Methods: In the previous work, we have been analyzed the mechanism of neural network disruption by ethanol using cultured cells and postmortem human brain, and found the suppressive effect of ethanol on the neural stem cell (NSC) differentiation to neurons.
Results: Antidepressants and mood-stabilizing drugs, which have neurotrophic action, reduced the suppression by ethanol of neuronal differentiation. We also observed the alterations of the NRSF/REST binding activity which regulate the neuronal gene expression, and revealed that ethanol potentiate the activity in a concentration–dependent manner. On the other hand, the CREB activity was reduced by ethanol. Antidepressants and mood-stabilizing drugs changed both CREB and NRSF/REST activities in a different proportion. In addition, we demonstrated the effectiveness of intravenous transplantation of NSCs to the fetal alcohol spectrum disorders (FASD) model for the purpose of reconstituting the impaired neural network and investigating the possibility of regenerative therapy for children with alcohol-induced neurobehavioral deficits. We have shown the potential migration of transplanted NSCs into the brain by visualizing fluorescent cell marker and RI, and the possible recovery of behavioral abnormality of FASD model rat in the evaluation of anxiety-like behavior, cognitive function, and social interaction.
Conclusions: Theses results suggest that the combined therapy of transcriptional regulation by psychotropics and NSC transplantation those have neuroprotective/neurogenetic potential may be an advanced approach to recover the alcohol-induced damage of neuronal network and CNS dysfunction in FASD.

S-51
Cannabis: What's happening?

S-51-001
Pharmacological treatment of cannabis dependence

Margaret Haney
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Objectives: Cannabis is the most frequently used illicit drug worldwide, and a subset of individuals develop dependence characterized by high rates of relapse. Abstinence from daily cannabis smoking can produce irritability, anxiety, anorexia, and disrupted sleep, while the resumption of cannabis smoking alleviates these symptoms. Thus, one factor that may contribute to cannabis relapse is the onset of withdrawal symptoms. The objective of this presentation is to review the effects of a range of medications on cannabis withdrawal and relapse.
Methods: Daily cannabis smokers, not seeking treatment for their cannabis use, were enrolled in double-blind, placebo-controlled inpatient studies. Each individual was maintained on placebo and active doses of medication, and the direct effects of active and placebo marijuana administration were assessed.
Results: Both the antidepressant, bupropion, and the mood stabilizer, divalproex, significantly worsened mood during cannabis abstinence. The antidepressant, nefazodone, alleviated a subset of withdrawal symptoms, but the most effective medication to date was the cannabinoid agonist, dronabinol, given frequently at low doses (10 mg, 5 times/day p.o.); this dose regimen also produced no intoxication. Follow up studies investigated whether medications that decrease withdrawal decrease the likelihood that abstinent cannabis users will return to cannabis use. We found that the anti-hypertensive, lofexidine administered in combination with dronabinol significantly decreased both cannabis withdrawal and relapse. The effects of: the muscle relaxant, baclofen, the antidepressant, mirtazapine, and the mood stabilizer, quetiapine, on cannabis withdrawal and relapse will also be discussed.
Conclusions: More treatment options for cannabis dependence are needed. Although cannabis has lower abuse liability than most other abused drugs, its ubiquitous use results in a subset of individuals who want to stop smoking but who are unable to achieve abstinence. These laboratory studies provide data on the interaction between cannabis and a range of medications, and can be used to inform controlled clinical trials in individuals seeking treatment for their marijuana use.

S-51-002
Cannabis and psychiatric co-morbidity

Stanley Zammit
Cardiff University, Psychological Medicine, United Kingdom

Objectives: It remains unclear whether use of cannabis leads to an increased risk of developing psychotic or affective disorders. I will briefly summarise the empirical evidence from epidemiological studies that have examined whether use of cannabis is associated with subsequent risk of psychotic or affective mental health outcomes, and will discuss the difficulties that exist in determining whether any such associations are causal or not.

S-51-003
Cannabis: Legal aspects and decriminalisation

Wim van den Brink
University of Amsterdam, Dept. of Psychiatry, Netherlands

Objectives: This presentation reviews the case for decriminalization of cannabis use based on a careful weighting of the currently available evidence regarding advantages and risks of such a policy change.
Methods: Review of the available literature. The following issues will be reviewed: addictive potential of cannabis; role of cannabis as a gateway drug; mental and physical risks of cannabis use; effect of prohibition and decriminalization on cannabis consumption rates; and side effects of prohibition and criminalization.
Results: This review shows that cannabis use is not without risks, that criminalization is an expensive strategy involving considerable policing, prosecution and a fair amount of incarceration, that decriminalization does not result in lower prices and higher consumption rates, nor in more severe patterns of cannabis use, that prohibition and criminalization are associated with social harms to the cannabis user, that decriminalization may reduce the association between cannabis use and schizophrenia and between cannabis use and the use of other illicit drugs, and that criminalization may reduce the legitimacy of the judicial system.
Conclusions: Given the available scientific data, existing repressive, expensive and unsuccessful criminal justice policies should be replaced by humane, effective and more efficient health policies such as those currently implemented in many of the European countries, including the Netherlands, Switzerland, Spain and many others.

S-51-004
Pharmacogenetic vulnerability

Amine Benyamina
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Objectives: Prolonged cannabis use has a significant impact on health and well-being. Genetic factors are known to influence cannabis dependence, but few specific genetic markers have been identified. Genetic vulnerabilities exist at several levels, notably neurobiological, enzymatic and pharmacokinetic. One interesting hypothesis in cannabis dependence lies in individual variance in delta-9 THC pharmacokinetics. A protein which has long been known for modifying substance kinetics is ABCB1 (P-glycoprotein, MDR1). Certain ABCB1 polymorphisms have been associated with altered kinetics and may be implicated in cannabis addiogenesis.

Other proteins such as FAAH, an enzyme which breaks down anandamide in the organism, and its polymorphisms have been associated with increased vulnerability to cannabis withdrawal symptoms. The results from our studies as well as others pave the way to a new pharmacogenetic hypothesis in cannabis dependence. This in turn may lead to new pathways to diagnosing cannabis dependent patients and to new methods of treatment.

S-64
Brain imaging in addiction

S-64-001
Role of dopamine in human drug self-administration

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Objectives: An extensive animal literature suggests that mesocorticolimbic dopamine (DA) transmission influences behavioral responses to natural rewards, addictive drugs, and associated cues. In humans, though, the evidence is less clear. Only a few substances have been tested for their ability to increase extracellular DA levels, and DA antagonists do not consistently decrease the drug's subjective effects.
Methods: Given the above discrepancies, we recently initiated studies using two approaches. First, we have been measuring the ability of abused substances, across pharmacological classes, to increase extracellular DA levels in human striatum. Second, we are assessing whether diminishing the ability of drugs to increase DA transmission alters drug craving, drug "high", or drug self-administration. The former studies use a positron emission tomography (PET) [11C]raclopride method, the latter use acute phenylalanine/tyrosine depletion (APTD).
Results: The studies suggest that, across pharmacological classes, drugs of abuse increase extracellular DA levels with preferential effects in the ventral limbic sub-region. Repeated stimulant drug administration can lead to progressive increases in this DA response, providing the first direct evidence of DA sensitization in humans. Moreover, very recent work suggests that, in stimulant drug abusers, these drug effects can become potently modulated by the environmental context, such that DA system reactivity is augmented or inhibited in the presence vs. absence of drug cues. Finally, diminishing DA transmission decreases the salience of reward-paired stimuli, the ability of drugs and drug-related cues to sustain interest, and self-administration behavior, at least under some conditions; drug-induced euphoria, in comparison, remains unaffected.
Conclusions: Together, the results suggest that context-dependent modulations of the DA system may lead to both increases and decreases in limbic system functioning, accounting in large part for the progressive narrowing of interests seen in addiction. Euphorigenic effects of abused drugs, in comparison, are likely more closely related to non-DA systems.

S-64-002
Role of brain mu-opioid receptors in cocaine addiction

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Objectives: Animal studies show that cocaine exposure elevates regional brain mu-opioid receptor (mOR) binding. Our previous human positron emission tomography (PET) studies using [11C]-carfentanil, a selective mOR agonist, in non-treatment-seeking chronic cocaine users found that elevated mOR binding in frontal and temporal cortices was associated with increased cocaine craving and shorter time to relapse after discharge from monitored abstinence. This study evaluated the association between brain mOR binding and cocaine use during outpatient treatment.
Methods: Twenty-five medically screened adults seeking outpatient treatment for cocaine abuse or dependence (DSM-IV criteria), and with no other current substance dependence (except tobacco) or major psychiatric disorder, received up to 12 weeks of cognitive-behavioral therapy and cocaine-abstinence reinforcement during which each cocaine-free urine sample was reinforced with vouchers redeemable for goods. Regional brain mOR binding was measured before treatment using PET with [11C] carfentanil. Observed urine specimens were collected thrice weekly during treatment and assayed for drugs.
Results: Elevated mOR binding in the medial prefrontal and lateral temporal cortices prior to treatment was associated with greater cocaine use (higher proportion of cocaine-positive urine specimens) during treatment. Elevated mOR binding in the inferior parietal cortex was associated with shorter duration of continuous cocaine abstinence. These associations remained significant after statistically accounting for standard clinical variables such as patients' pretreatment drug and alcohol use.
Conclusions: These findings extend our previous findings in non-treatment-seeking cocaine users and suggest a key role for the brain endogenous opioid system in cocaine addiction, with implications for treatment.

S-64-003
Brain serotonin function in MDMA (ecstasy) users

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Objectives: Chronic administration of the MDMA ("Ecstasy") is associated with long-term depletion of serotonin and loss of serotonin axons in the brains of rodents and non-human primates. Moreover, it has been consistently shown that MDMA users display dose-related neurocognitive deficits suggesting that MDMA also affect the human serotonin system. However, because of a multitude of methodological problems and a limited number of studies, no firm conclusions can be established whether chronic MDMA exposure in fact produces a long lasting serotonin deficiency in humans. Therefore, we developed a novel method to assess serotonin release capacity in the human brain employing [18F]altanserin positron emission tomography (PET) after dexfenfluramine and placebo challenge. This approach enables measuring altered serotonin-2A receptor occupation after forced serotonin release.
Methods: We investigated serotonin release capacity in 15 current and 12 former male MDMA users, as well as in 15 matched male drug-naïve controls. Subjects received placebo or oral doses of 60 mg of the potent serotonin releaser dexfenfluramine on two days separated by an interval of 14 days. Two hours after dexfenfluramine intake, 250 MBq of the serotonin-2A receptor selective PET-radiotracer [18F]altanserin were administered intravenously as a 30 sec bolus. Dynamic PET data were subsequently acquired over 90 min. Moreover, in arterial blood samples drawn for measurement of total activity, dexfenfluramine levels as well as prolactin plasma concentration-time profiles were quantitatively determined.
Results: Current MDMA users a displayed blunted prolactin response, and decreased serotonin-2A receptor densities and diminished serotonin release capacity overall investigated brain regions when compared to drug-naïve controls. Former MDMA users still showed a blunted prolactin response and decreased serotonin-2A receptor densities, but they did not significantly differ in their serotonin release capacity from controls.
Conclusions: These first functional data suggest that MDMA use leads to long-lasting alterations in the serotonin system that might be reversible only in part.

S-64-004
Brain imaging studies of cognitive effects of recreational drugs

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Objectives: Regular of recreational drugs such as marijuana and "ecstasy" has been associated with deficits of learning, memory and attention in cognitive and brain imaging studies. Recreational use of "ecstasy" is associated with long-lasting effects on metabolism in the human brain. In particular, there is evidence of long-term damage to the brain's neurotransmitter serotonin (5-HT). Although there is some evidence for impairment of working and associative memory in regular "ecstasy" users, the association has been confounded by the concurrent use of other drugs. Heavy use of marijuana is claimed to damage critical skills related to short-term memory, visual scanning and attention. Acute use of marijuana is linked to impairment of motor skills and may affect driving safety. We report a study investigating the acute effects of Δ9 THC on cognitive-motor tasks and associated brain metabolism in regular users of marijuana.
Methods: Twelve regular users of marijuana underwent 2 Positron Emission Tomography (PET) scans using [18F] Fluorodeoxyglucose (FDG), one while subject to the effects of 17 mg THC, the other without THC. In both scanning sessions, a virtual reality maze task requiring attention and motor coordination was performed during the FDG uptake period.
Results: When subject to the effects of 17 mg THC, regular marijuana smokers hit the walls more often on the virtual maze task than without THC. Compared to results without THC, 17mg THC increased brain metabolism during task performance in areas that mediate motor coordination and attention in the middle and medial frontal cortices and anterior cingulate, and reduced metabolism in areas that mediate visual integration of motion in the occipital and parietal lobes.
Conclusions: These findings suggest that in regular marijuana users, the immediate effects of marijuana may impact on cognitive-motor skills and brain mechanisms that modulate coordinated movement and may affect driving safety.

S-02
Comparative neuropathology of schizophrenia and bipolar disorder

S-02-001
Peripheral biomarkers as indicators of brain pathology in schizophrenia and affective disorder

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Objectives: At present, little is known about the basic mechanisms that underlie the schizophrenia disease process. This lack of knowledge is most likely due to the fact that until recently large-scale expression profiling studies were technologically impossible. Thus, most researchers employed a "candidate gene/protein" approach. With recent technological advances in genomics, proteomics and metabolomics techniques, it is now possible to globally investigate the molecular underpinnings of psychiatric conditions which should result in improved knowledge and hopefully new (pre-symptomatic) diagnostic, therapeutic and preventative regimes.
Methods: Our laboratory combines advanced computing and bioscience technologies with multi-omics studies. Using this powerful approach we explore the molecular "fingerprints" of psychotic disorders from early onset through their progressive stages, exploring alterations at the gene, protein, lipid and metabolite level.
Results: I will present results from our biomarker discovery studies. To date we have identified a number of highly significant peptides and metabolites that distinguish first-onset paranoid schizophrenia patients from healthy controls. Our findings suggest brain-specific alterations in glucoregulatory processes in CSF of drug-naïve patients with first-onset schizophrenia, implying that these abnormalities are intrinsic to the disease, rather than a side effect of antipsychotic medication. Short-term treatment with atypical antipsychotic medication resulted in a normalization of the CSF disease signature in half the patients well before a clinical improvement would be expected. Furthermore, our results suggest that the initiation of antipsychotic treatment during a first psychotic episode may influence treatment response and/or outcome.
Conclusions: We have also identified ~30 candidate biomarkers in patient serum, specifically up-or down-regulated in drug naive, first onset schizophrenia patients compared to healthy controls using high throughput proteomic profiling methods. Currently we develop high throughput, sandwich immunoassays to allow the validation of these candidate biomarkers in a large cohort of patients and controls. I hope to be able to present some of these results.

S-02-002
White matter abnormalities in schizophrenia and bipolar disorder

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Objectives: Myriad studies demonstrate abnormalities of water diffusion in cerebral white matter in schizophrenia and bipolar disorder (BPD). Disordered myelination is a mechanistically attractive explanation, since demyelination or dysmyelination would retard axonal conduction, diminishing cognitive processing speed and potentially explaining some of the cognitive deficits in schizophrenia, even those present premorbidly. However, similar abnormalities of diffusion imaging are observed in bipolar disorder, where cognitive deficits are less prominent and premorbid cognitive status may on average be even above normal (Koenen et al. Am J Psychiat 2009;166:50). We sought to explore the structure of myelin and its relationship to cognitive status in these conditions.
Methods: We performed systematic semiquantitative evaluations of myelin histology throughout the dorsal prefrontal white matter from 81 schizophrenia and 9 BPD subjects who died in state hospitals, and 28 nonpsychiatric, cognitively intact patients who died in a university hospital (overall age 75±14). Cognitive function throughout the psychiatric illnesses was evaluated from medical records (Ortakov et al., Schiz Res1999;35:131).
Results: Adjusting for age, there was no difference in myelin ratings among the 3 diagnostic groups. In the schizophrenia subjects, lower myelin ratings were associated with significantly lower cognitive function at both the onset of illness and the end of life, with no effect on the change over the course of illness. Among the bipolar subjects, lower myelin ratings were associated with significantly lower cognitive function at the end of life but not at the onset of illness, and with greater change over the course of illness; significance of the bipolar findings was ~0.1 after covarying for age.
Conclusions: Myelination of dosal prefrontal white matter is not visibly impaired in elderly subjects with schizophrenia or bipolar disorder. Premorbid quality of myelin may affect cognitive function in schizophrenia. The association with cognitive function in bipolar disorder is probably related to processes of aging.

S-02-003
Immunohistochemical studies in schizophrenia and bipolar disorder

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Objectives: Neuropathological studies in schizophrenia suggest that in contrast to well known degenerative brain diseases the focus of pathology is not situated in typical pyramidal neurons but rather in connecting elements between nerve cell bodies, as well as in glial cells and inhibitory interneurons. Immunohistochemistry is an ideal method to study various peptides characteristic for special subcomponents of neuronal and glial cells. Here we present the analysis of two cell types that play a major role in the in current theories of schizophrenia; these are GABAergic interneurons and neuregulin expressing cells and compared the results of schizophrenics with those of normal controls and patients with mood disorder.
Methods: Whole brain serial sections (20 microns, paraffin embedded) of 20 schizophrenics, 20 mood disorder patients (11 bipolar, 9 unipolar depressed) and 20 well matched controls from the Magdeburg brain bank were stained immunohistochemically for the GABA synthesizing enzyme GAD65/67 as well as for neuregulin-1-alpha. Cell densities in various cortical regions were determined by light microscopy.
Results: With the exception of the thalamus, schizophrenics and unipolar depressed patients and had in all analysed cortical regions (DLPFC, cingulate gyrus, STG) and limbic structures (hippocampus, parahippocampal gyrus) a significant increase in GAD positive neurons by about 50%, as compared to normal controls and bipolar patients. Neuregulin-1-alpha expressing cells were highly significantly reduced in the frontal cortex of schizophrenics and unipolar depressed patients, while in frontal white matter neuregulin was diminished only in schizophrenics.
Conclusions: Comparison of the two peptides crucial in the pathophysiology of psychosis and mood disorder show widely overlapping histopathology, while differences seem to exist between unipolar depressed and bipolar patients. Increased numbers of GAD67/65 immunoreactive cells may reflect an accumulation of this peptide in interneurons due to degeneration peripheral inhibitory GABA synapses in depression and schizophrenia. Abnormal expression of neuregulin-1 also seems to play a role in both groups of diseases.

S-02-004
Ultrastructural studies in schizophrenia and bipolar disorder

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Objectives: In vivo studies provide evidence for white matter abnormalities in schizophrenia (SZ) and bipolar disorder (BPD). Previously we found deficit of oligodendrocytes in the prefrontal cortex (PFC) in SZ, BPD and major depression. The aim of the study was to detect ultrastructural changes of oligodendrocytes in SZ and BPD and myelinated fibers and synapses in SZ as compared to controls.
Methods: We studied postmortem PFC, BA10, adjacent white matter, visual cortex, (VC), BA17, caudate nucleus and CA3 hippocampus from 30 SZ subjects and 26 normal controls. Electron microscopy was applied to detect qualitative changes of oligodendrocytes in PFC in 5 cases of BPD and 5 controls. Morphometric study was performed to estimate ultrastructural parameters of oligodendrocytes, myelinated fibers and synapses in SZ and control brains.
Results: Both dystrophic and degenerative changes of oligodendrocytes were found in PFC in SZ and BPD, in caudate nucleus and hippocampus in SZ compared to controls. The percentage of myelinated fibers with atrophy of axon increased in gray matter in all brain structures studied and in white matter adjacent to PFC in SZ vs. controls ($p<0.01$). A significant reduction of the number of mitochondria in oligodendrocytes, myelinated fibers and presynaptic axon terminals was found in PFC in SZ. The number weighted volume (Vn) of presynaptic axon terminals, postsynaptic spines and length density of postsynaptic membranes in axospinous synapses decreased significantly in PFC but not in VC in SZ. Vn of presynaptic axon terminals tended to correlate with duration of SZ ($p=0.06$).
Conclusions: Ultrastructural damage and previously found deficit of oligodendrocytes in PFC overlap in SZ and BPD. Alterations of oligodendrocytes and myelinated fibers in SZ are associated with atrophy of axons and might contribute to atrophy of neurons and altered neuronal connectivity in SZ. Supported by Stanley Medical Research Institute and by McDonnell Foundation.

S-11
Vigilance regulation in affective disorders

S-11-001
Is mania an autoregulatory attempt to stabilize vigilance and are psychostimulants a treatment option?

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Objectives: Disturbances of vigilance regulation are discussed as pathophysiological aspect of psychiatric disorders such as mania or depression. It is proposed that the behavioural syndromes typical for these disorders reflect an attempt to stabilize vigilance regulation.
Methods: EEG-based measurement of vigilance regulation referes to the assumption of different functional cerebral states parallel to the transition from active wakefulness to deep sleep. These functional states which are reflected in the spectral composition and topography of the EEG are termed vigilance stages.
Results: In this context, manic behaviour can be in part explained as expression of an autoregulatory mechanism to stabilize vigilance. A similar autoregulatory mechanism is presumed to obtain in Attention Deficit/ Hyperactivity Disorder (ADHD). The therapeutic effect of psychostimulants, which is well proven for ADHD, has repeatedly been observed as a paradoxical effect in manic patients. This effect is can be explained by the present proposed model by the vigilance stabilizing properties of psychostimulants.
Conclusions: The proposed model provides not only an explanation for those manic symptoms which serve the stabilization of vigilance but also for other neuropsychological findings in manic patients. Such deficits are also observed in BD patients during euthymic states and have been considered as a state-modulated trait-marker for bipolar disorder.

S-11-002
Excessive daytime sleepiness: The role of anxiety, insomnia and depression

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Objectives: Excessive daytime sleepiness (EDS) is a symptom with high clinical and public health importance because its association with increased risk for accidents, decreased productivity, and impaired quality of life. Little information is available regarding the longitudinal course, clinical correlates and underlying neurobiology of EDS. In "study 1" we explored associations between EDS, sleep disorder symptoms, major depression and anxiety in a longitudinal community study of young adults. In "study 2", we used catecholamine depletion induced by oral administration of alpha-methyl-para-tyrosine (AMPT) to examine the roles played by dopamine and norepinephrine in daytime sleepiness.
Methods: Study 1: prospective single age community study of young adults (Zurich Cohort Study). Information was derived from four interviews when participants (N=591) were ages 20, 22, 27, 29, 34, and 40. Trained health professionals administered a semi-structured interview for health habits, psychiatric and medical conditions. Study 2: Fifteen unmedicated subjects with major depression in full remission and 13 healthy controls were included in a randomized, double blind, placebo-controlled crossover trial (catecholamine depletion induced by AMPT versus placebo). Quantitative positron emission tomography of regional cerebral glucose utilization was used to study the neural correlates of AMPT-induced sleepiness.
Results: EDS was a relatively stable symptom with increasing prevalence with age. Cross-sectionally, EDS was associated with insomnia and nocturnal hypersomnia, anxiety, somatization, and reduced quality of life. Longitudinally, EDS was consistently associated with anxiety. Catecholamine depletion consistently induced clinically relevant daytime sleepiness in subjects with a history of major depression and in healthy controls. The strongest correlations between AMPT-induced sleepiness and brain metabolism were found in the bilateral superior temporal gyrus, the bilateral ventrolateral prefrontal cortex and the mid-cingulate gyrus.
Conclusions: Insomnia, anxiety and hypofunction of central catecholamine systems were identified as important risk factors of EDS.

S-11-003
Vigilance and cognition in bipolar affective disorders

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Objectives: There is increasing interest for studying cognitive functioning in bipolar disease, cognitive abnormalities appearing as intermediate features between the symptoms and the neurobiological mechanisms underlying the disorder. Of all the neurocognitive deficits examined in bipolar patients, impaired vigilance (or sustained attention) is one of the most robust findings. Our objective was to better elucidate the physiological mechanisms implied in vigilance abnormalities.
Methods: Vigilance can be quantified using a variety of tasks that require an adequate level of arousal associated with the ascending neurotransmitter projections from subcortical structures to the cortex. Emotional-laden material in neuropsychological testing is useful to measure the influence of emotional processing on cognitive functioning.
Results: Decrements in vigilance have been well documented during affective episodes. However, the demonstration of persistent deficits between acute phases independently of residual symptoms strongly suggests that impaired vigilance is a trait-related factor, that could emerge early in the course of bipolar disorder. Futhermore, recent data obtained in unaffected relatives of bipolar patients indicate that vigilance deficits may represent an endophenotype in bipolar disorder. The findings of impaired attentional performances when treating emotional cues illustrate the impact of emotional information on cognitive processes. This suggests that vigilance abnormalities may result from a disruption of attentional brain regions by the activation of emotional, anterior limbic networks, which is consistent with findings from neuroimaging studies.
Conclusions: Characterizing vigilance deficits at a neuropsychological and a neurochemical level may help to define future psychotherapeutic and pharmacological targets for treating bipolar disorder.

S-11-004
Sleep disturbances in patients with affective disorders

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Objectives: The clinical finding that depression and related symptoms such as sleep-wake disorders, loss of appetite and diurnal changes of mood are associated with altered circadian biological rhythms has encouraged the idea that resetting normal circadian rhythms may have antidepressant potential. In particular, insomnia and daytime fatigue show up in about 80% of patients during the course of their disaese and represent the most prominent symptoms of disturbed circadian functions.
Results: Treatments based on the principles of circadian rhythm organization and sleep physiology – have been introduced as an adjuvant to current pharmacological treatments of affective disorders. These non-pharmaceutical and biologically-based clinical interventions include sleep deprivation, shifting of sleep time (sleep phase advance), light and dark therapy as well as other circadian entrainment strategies (e.g. social rhythm sleep deprivation, shifting of sleep time (sleep phase advance), light and dark therapy as well as other circadian entrainment strategies (e.g. social rhythm therapy), and the development of new pharmaceutical agents. All treatment approaches target to reset and stabilise the circadian rhythm regulated by central and peripheral clocks, which have to be entrained by environmental and social cues. This demands appropriate entrainment to the light-dark and sleep-wake cycle as well as sufficient social zeitgebers, including regular interpersonal contact, timed activities and meals.
Conclusions: The resynchronisation, normalisation and stabilising of circadian rhythms represent promising new pathways to treat depression and related sleep-wake problems.

S-22
Suicide prevention: Focusing on modifiable risk factors

S-22-001
Prophylaxis of bipolar disorder

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Objectives: There are three phases of drug treatment of mood disorders: control of acute symptoms, continuation treatment to keep control of the treated acute episode, and ultimately long-term stabilization in order to prevent further recurrences and not simply to control the acute episode. A mood stabilizer should show efficacy in the acute treatment of either mania or depression and in the prevention of both, without worsening either. Lithium is the standard agent for all illness phases but its use has been eroded mainly by competitive marketing. Lithium prevents both manic and depressive episodes, seems to be more effective for the hypomanic recurrences, and it may also be effective in the prevention of unipolar disorder. Among anticonvulsants, carbamazepine is less effective than lithium, valproate is not approved as a mood stabilizer but widely used as such; lamotrigine is especially effective in depressed phase. No efficacy is proved for other anticonvulsants. Antipsychotics are all antimanic agents and may be effective in long-term treatments. Antidepressants are certainly overused also in bipolar depression even if there is no consistent evidence of their effectiveness. When used in bipolar depression, SRIs are usually preferred for less chance of association with manic episodes compared to tricyclics. Despite all these possible treatments in BPDs, still most patients remain ill 30–40% of the time, mainly in depression. Since, virtually all suicides occur during a depressive-mixed episode, the major challenge in long term management of BP and the prevention of suicide is the treatment and prevention of depression. For recording long-term treatment of the disorder it is recommended the use of life charts that help count episodes and time ill in different polarities. The best possible treatment of a BPD also includes: management of side-effects; treatment of substance abuse; assessment of suicidal risk; psychotherapy, especially focusing on psychoeducation; and treatment adherence.

S-22-002
Treatment of depression

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Objectives: In spite of the fact that around two-thirds of suicide victims have current major depressive episode, and up-to half of them contact different levels of health-care services during the last 4 weeks of their life, over 80% of depressed suicides are untreated or inadequately treated. However, several large-scale, naturalistic, observational follow-up studies show that successful acute and long-term treatment of major depression (with antidepressants) and bipolar disorders (with mood stabilizers, antidepressants and/or antipsychotics) markedly reduces the risk of further suicide attempts and committed suicide. Suicidal behaviour in unipolar depressives taking antidepressants is relatively most frequent among nonresponders and in the first 10-14 days of the treatment, several days before the start of the drug action. Register based cohort studies also found that continuous treatment with antidepressants or mood stabilizers substantially reduced the risk of subsequent suicidal behaviour in unipolar or bipolar patients compared to those who were not pharmacologically treated. The marked decline of national suicide rates in countries where antidepressant utilization increased by three-to-eightfold recently also supports the antisuicidal effect of antidepressants, even on the level of general population. On the other hand, however, the meta-analysis of Phase II/III randomized controlled clinical trials on antidepressant monotherapy in unipolar major depression (from which studies the most severe and acutely suicidal patients are excluded, but subthreshold bipolar depressives are included) show a nonsignificant increase of suicidal behaviour in patients taking antidepressants compared to those who are taking placebo. Recent findings show that this relatively small increase in suicidality relates to depression-worsening potential of antidepressant monotherapy (unprotected by mood stabilizers or atypical antipsychotics) in subthreshold bipolar depressives (in clinical trials on unipolar depression) and in unrecognized threshold and subthreshold bipolar depressives (in real life situation). The main component of the acute and long-term treatment of bipolar disorders should be the mood stabilizer pharmacotherapy.

S-22-003
Are sudden dips in mood the final common pathway of suicide?

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Objectives: Of the modifiable risk factors in suicide, affective disorders represent a prevalent substrate. It is therefore important to understand what aspects of these disorders are proximal to the suicidal act. The NIMH Collaborative Depression study of nearly 1000 affectively ill probands in a prospective design of 14 years has shown that 36 patients committed suicide and 120 made near-lethal suicide attempts. In comparison with 373 mood disorder patients with no recorded suicidal acts, clinical and temperament measures obtained years before the index suicidal act revealed that the most important long-term predictors of suicidality were previous attempts, impulsivity, lack of assertiveness, substance and/or alcohol abuse, psychic turmoil in the setting of a cycling, mixed bipolar state. International research more recently has upheld the relevance of mixed states as being central to suicide, whether one studies "unipolar", bipolar I or bipolar II patients. Bipolar II, in particular, appears to have the highest lethality in terms of low ratio of attempts to completed suicides. These data suggest the hypothesis that rapid mood shifts with sudden dips might be the final common pathway of suicidal acts in most patients with affective disorders, as well as those with epilepsy, physically disabled elderly, or those recovering from depression, and possibly those rare individuals without mental illness -- especially if they are knowledgeable of or have access to lethal means. I further submit that strong family, social and spiritual bonds are protective in part because they buffer against taking action when sudden dips in mood supervene. These data and considerations must be taken into consideration in interventions for suicide prevention.

S-22-004
Are any of the biological substrates of suicidality modifiable?

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Objectives: A number of neurotransmitter system abnormalities have been identified that predict both the risk of future suicidal behavior and the lethality of that future suicidal behavior. The implications of such observations is that modifying this biology in the direction of "normality" may reduce the risk of a suicide attempt, or in the event a suicide attempt takes place it will be of lower lethality.
Methods: For example low serotonergic function as measured by CSF 5-HIAA, the prolactin response to fenfluramine or Positron Emission Tomography all generate findings consistent with serotonin hypofunction predicting suicide or higher lethality suicide attempts. The implication is that raising serotonin input to key brain regions such as the ventromedial prefrontal cortex, the anterior cingulate cortex or the lateral prefrontal cortex may reduce the risk of suicide or highly medically damaging suicide attempts.
Results: Hypofunction of the noradrenergic system also appears to predict both the probability of a suicide attempt as well as the degree of medical lethality or medical damage resulting form a suicide attempt. Again the implication is that enhancing noradrenergic function will reduce risk of a suicide attempt or if one occurs it will less medically threatening. Polyunsaturated fatty acids affect both brain function and the risk of suicide attempts and raise the question of the possible benefit of omega-3 fatty acid dietary supplements. Finally abnormal or excessive stress responses in the hypothalamic pituitary adrenal axis predict the risk for suicide.
Conclusions: New treatments such as CRHR1 antagonists are being tried in major depression and their effect on suicide risk is an important area for research. The advances in identifying the biological correlates of suicidal behavior have offered many new therapeutic targets that warrant evaluation as new suicide prevention approaches.

S-39
Genetic and environmental risk factors in early onset bipolar affective disorder

S-39-001
Whole genome association studies in bipolar I affective disorder

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Objectives: Bipolar disorder is a chronic and generally life-long psychiatric condition with recurring episodes of mania and depression. Formal genetic studies strongly suggest that bipolar disorder is a complex disorder with genetic and environmental factors contributing to disease development. There is growing evidence that genome-wide association studies (GWAS) are a powerful tool to identify the genetic factors underlying complex disorders.
Methods: We have performed a GWAS in a sample of 700 DSMIV-diagnosed patients with bipolar I disorder, all of German descent, and 1,300 ethnically matched population-based controls, using Illumina's HumanHap550 genotyping platform. Promising hits were followed-up in a sample of approximately 2,000 independent bipolar I patients and 2,000 controls using Sequenom's iPLEX assays.
Results: 120 SNPs produced nominal p-values <10E-04, with top hits (p=6x10E-07 – p=1x10E-06) located in the genes NCAN (chr. 19), MAD1L1 (chr. 7), and GNG4 (chr. 1). These 120 SNPs were subjected to a replication study, and we found independent support for association with 11 SNPs. The strongest support was again obtained for the genes NCAN and MAD1L1.
Conclusions: Our study, in total involving more than 2,400 patients and 3,600 controls, provides strong evidence for the involvement of NCAN and MAD1L1 in the development of bipolar I disorder.

S-39-002
Candidate gene analyses in early onset bipolar affective disorder

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Objectives: Twin, family and adoption studies have suggested that genetic factors are involved in bipolar disorders, but no causal mutation has yet been identified. Early onset bipolar disorder has been shown to be the most severe and familial form. We recently carried out a whole-genome linkage analysis on sib-pairs affected by early-onset bipolar disorder and showed suggestive linkage in the 20p12 region. The synaptosomal-associated protein SNAP25 is located in this chromosomal region; it is a presynaptic plasma membrane protein essential for the triggering of vesicular fusion and neurotransmitter release. Previous studies have reported abnormal protein levels in post-mortem studies of bipolar patients. We hypothesised that variations in the gene encoding SNAP25, located on chromosome 20p12, might influence the susceptibility to early-onset bipolar disorder.
Methods: The SNAP25 gene was screened for mutation and we used identified SNPs for a case–control association study using 197 patients with early-onset bipolar disorder, 202 patients with late-onset bipolar disorder and 136 unaffected subjects. We have also studied the influence of the associated SNPs on the expression level of the two SNAP25 isoforms in 60 brains (bipolar patients and healthy controls).
Results: One SNP, located in the promoter region, was associated with early-onset bipolar disorder but not with the late-onset subgroup. Individuals that were homozygous for this variant showed a significant higher SNAP25b expression level in prefrontal cortex.
Conclusions: Variations in SNAP25, associated with an increased gene expression level in prefrontal cortex, might predispose to early-onset bipolar disorder. This results also suggest that this gene might be shared between early onset bipolar disorder and Attention Deficit with Hyperactivity Disorder and thus explain the high rate of comorbidity between the two disorders.

S-39-003
Whole genome association analyses in early onset bipolar disorder

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Objectives: Many genome-wide association studies (GWAS) have been recently performed on bipolar disorder, leading to discrepant results and difficulties in replication between independent samples. One possible explanation could come from a lack of common genetic variation influencing the vulnerability to bipolar disorder in general, but different susceptibility genes might influence clinical subsets of the disease. Thus, we focused our study on potentially more homogenous and more familial sub-forms of bipolar disorder in order to unravel heterogeneity of the classical categorical entity bipolar disorder and to identify genetic susceptibility genes.
Methods: We carried out a genome-wide association study using 313,952 single nucleotide polymophisms (SNPs) on 468 patients with early age at onset or familial history of bipolar disorder and 2832 controls.
Results: The strongest association was observed on chromosome 15 (P=4.4 x 10 7) for the whole sample. An additional analysis, including only patients with an early age at onset (N=318), identified several regions for which the association was stronger despite a smaller sample size. Among them, two SNPs located on chromosomes 12p12 and 5p13 (P=2.7 x 10 7 and P=3.6 x 10 6, respectively) are located in genes encoding proteins playing a role in phosphoinositide signalling pathway, which is consistent with the hypothesis that several genes in one pathway may be involved in the pathophysiolgy of bipolar disorder.
Conclusions: Our results suggest, at least for bipolar disorder, that the phenotype issue remains an important challenge to identify susceptibility genes.

S-39-004
Gene-environment interactions in early onset bipolar disorder

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Objectives: Bipolar affective disorder is known to be a multifactorial heterogeneous disorder. The implication of genetic, environmental and developmental risk factors has been demonstrated. Childhood traumatic events are probably the most promising environmental risk factor. Trauma during childhood may also modulate the clinical expression of the disorder, being associated with several characteristics of the disease such as an earlier onset of the disease (Garno et al., 2005) and suicidal behavior (Leverich and Post, 2006, Brown et al., 2005, Garno et al., 2005).
Methods: We recently performed a genome-wide association study (GWAS) on early-onset bipolar disorder using 287,288 single nucleotide polymorphisms (SNPs) and were able to identify candidate SNPs associated with suicidal behavior in bipolar disorder.
Results: On a sub-sample of 124 patients, who were both assessed for lifetime history of suicidal behavior and childhood trauma, we tested the interaction between history of childhood trauma and candidate SNPs for the vulnerability to suicidal behavior.

S-44
60 years of lithium in neuropsychiatry – recent discoveries in basic and clinical research

S-44-001
Response to long-term lithium treatment and its use as an endophenotype for bipolar disorder

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Objectives: Lithium is a well established treatment for bipolar disorder (BD), effective in preventing recurrences of mania and depression as well as reducing overall and suicide-specific mortality. However, data from controlled trials and from naturalistic studies show that only a proportion of patients benefit from lithium. The search for variables associated with the treatment response has pointed to genetic factors as particularly relevant.
Methods: In a series of studies we investigated the clinical and neurobiological characteristics of patients responsive to lithium. We explored differences among responders and non-responders and healthy subjects, and examined the familiality of lithium-response-specific traits.
Results: Responders to lithium appear to meet the Robins and Guze (1970) criteria for a diagnostic subtype. They have a distinct clinical presentation with low rates of comorbidity and episodic clinical course. These features make them different from responders to other mood stabilizers. Importantly, the response to lithium is longitudinally stable (Berghofer et al. 2008). Family studies show higher prevalence of BD in relatives who themselves are almost 4 times more likely to respond to lithium than subjects with BD in general. In a cohort of lithium responsive patients and their families we performed linkage and association studies, in which we obtained findings distinct from other groups of BD.
Conclusions: Response to lithium in BD meets the criteria for an endophenotype and defines a homogeneous diagnostic subgroup of BD. In light of our findings, comparison of responders and non-responders is a promising way to identify genetic variants associated with the treatment outcome. Success of such studies will depend on availability of patient cohorts prospectively followed and assessed for their illness outcome.

S-44-002
Neuroprotective properties of lithium

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Objectives: Lithium inhibits inositol monophosphatase activity as well as inositol transporter function. To determine if one or more of these mechanisms might underly lithium's behavioral effects, we studied inositol monophosphatase-1 gene knockout and inositol transporter (SMIT) knockout mice.
Methods: PCR for confirmation of genotypes, behavioral phenotyping, gas chromatography for brain inositol, enzyme activity measurement for inositol monophosphatase.
Results: In brains of adult IMPA1-/- mice, IMPase activity levels were found to be reduced; however, inositol levels were not found to be altered. Behavioral analysis indicated an increased motor activity in both the open-field test and the forced-swim test as well as a strongly increased sensitivity to pilocarpine-induced seizures, the latter supporting the idea that IMPA1 represents a physiologically relevant target for lithium. In SMIT-/- knockout mice, free inositol levels were reduced in the frontal cortex and hippocampus. They behave like lithium treated animals in the model of pilocarpine seizures and in the Porsolt forced swimming test model of depression. In contrast to O'Brien et al (2004), we couldn't confirm that GSK-3beta-/+ knockout mice exhibit reduced immobility in the Porsolt forced swim or reduced amphetamine-induced hyperactivity in a manner mimicking lithium's behavioral effects.
Conclusions: These data support the role of inositol related processes rather than GSK-3beta in the mechanism of therapeutic action of lithium. Bersudsky Y, Shaldubina A, Kozlovsky N, Shoham S, Woodgett JR, Agam G, Belmaker RH. Glycogen Synthase Kinase-3beta Heterozygote Knockout Mice: Negative Results. Behavioral Pharmacology 10:217-24, 2008 Bersudsky Y, Shaldubina A, Agam G, Berry G, Belmaker RH. Homozygote inositol transporter knockout mice show a lithium-like phenotype. Bipolar Disorders 10:453-459, 2008. Cryns K, Shamir A, Levi I, Daneels G, Goris I, Delille P, Bouwknecht A, Kass S, Agam G, Belmaker RH, et al. IMPA1 is essential for embryonic development and lithium-like pilocarpine sensitivity. Neuropsychophopharm 33:674-84, 2008.

S-44-003
Genome-wide findings from the Consortium on Lithium Genetics (ConLiGen)

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Objectives: Besides its use as a first-line mood stabilizer in bipolar disorder (BD), lithium has antimanic and antisuicidal effects. There is little knowledge of the genetic basis of lithium response. Large-scale pharmacogenetic studies are urgently needed.
Methods: We formed the Consortium on Lithium Genetics (ConLiGen), currently including researchers from Canada, Germany, Italy, Japan, Poland, and the USA. The combined sample includes more than 1000 patients with BD, phenotyped for lithium response using a well established rating scale (Grof et al. 2002). This sample will be used for both candidate-gene and genome-wide association studies (GWAS). In a first step, we performed a GWAS on 1000 patients under the auspices of GAIN for whom we had data on duration of current lithium treatment and the Global Assessment Scale (GAS). The 85 patients who reported using lithium over the past 2 or more years and a current GAS score of >70 were tentatively classified as "lithium responsive." Genotyping was performed, using the Affymetrix 6.0 SNP array. After several steps of quality control, 727, 214 SNPs were tested.
Results: 88 SNPs in 15 genes showed significant association (min p=0.00007) with the phenotype studied. Several genes belong to the inositol-trisphosphate pathway, a key element in lithium action. Other implicated pathways include cell-adhesion and neuronal transport.
Conclusions: This GWAS of this potential proxy phenotype for lithium response does not only highlight genes involved in lithium-relevant pathways but novel leads. ConLiGen, the largest consortium to study lithium response genetics, invites other researchers to join its efforts.

S-44-004
Lithium at work: The neurobiologist's perspective – from animal models to the development of novel therapeutics

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S-63
How far are we from reducing suicide in bipolar disorder?

S-63-001
Suicidal risk in BP patients and bipolar risk in suicidal patients?

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Sébastien Guillaume

Objectives: Identification of patients with a bipolar disorder (BPD), among those presenting a major depressive episode is often difficult, resulting in common misdiagnosis and mistreatment. Our aim was to identify clinical variables unrelated to current depressive episode and relevant to suicidal behavior that may help to improve the detection of BPD in suicide attempters presenting with recurrent major depressive disorder.
Methods: 135 inpatients suffering from recurrent major depressive disorder and 76 suffering from BPD, hospitalized after a recent suicide attempt (SA), were interviewed about DSM-IV axis I disorders, history of suicidal behavior, suicidal intent and seriousness of the most severe SA. Moreover a wide range of personality traits relevant to suicidal vulnerability was assessed.
Results: BPD patients made more serious SA, were more likely to have a family history of completed suicide and had more comorbid substance use disorders. Novelty seeking and affect intensity were higher in BPD samples. Multivariate analysis showed that serious SA and family history of suicide are closely associated with a diagnosis of BPD [respectively OR=2.28 p= 0.0195; OR=2.98 p=0.0081]. Conversely, when looking for the features associated with a serious SA, BPD was the only associated diagnosis [OR=2.03, p=0.0408].
Conclusions: Suicide attempt, particularly serious or violent in its nature, in patients with major depression seems to be a clinical marker of bipolarity. Facing suicide attempters with recurrent depression, clinician should be awareness to these characteristics to detect BPD.

S-63-002
Gene-environment interaction and the risk of suicidal behavior in bipolar patients

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Objectives: Genetic and environmental factors has been involved in the determinism of suicidal behaviours in bipolar disorder. These factors might interact to influence some psychopathological dimensions (impulsivity, affect intensity, affective lability) that in turn will increase the risk of suicidal attempts.
Methods: First, we have studied correlations between childhood trauma (in particular emotional abuse and sexual abuse) and several dimensions among euthymic bipolar patients (trait impulsivity, affective lability, affect intensity measures). Second, we have studied the interaction between the long/short variant of the serotonin transporter gene and childhood trauma onto these psychopathological dimensions.
Results: Childhood trauma, in particular emotional abuse, correlated with several psychopathological traits such as impulsivity, or affective abnormal regulation. The long/short variant of the serotonin transporter gene might moderate the influence of childhood trauma onto these dimensional clinical expression of bipolar disorder, being associated with more suicidal behaviours.
Conclusions: Suicidal behaviours in bipolar disorder might result of complex interactions between environmental and genetic susceptibility factors. Such interactions might influence the dimensional expression of the disease, leading to an increased prevalence of suicidal behaviours.

S-63-003
Psychosocial interventions in bipolar disorder: Impact on morbidity and mortality

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Conclusions: Patients with bipolar disorder are known to suffer a considerable number of associated psychiatric pathologies. In addition to the psychiatric comorbidities an increasing body of evidence suggests that in comparison to the normal population patients with bipolar disorder have a worse physical health and a far shorter life expectancy in developed countries. For example, migraine, headaches, cardiovascular, cerebrovascular, pulmonary and infectious diseases are frequently cited as comorbid conditions. Bipolar disorder, in particular, is highly correlated with overweight and obesity which are established risk factors for morbidity and mortality, as well as having negative psychological consequences. Furthermore, medical comorbidities and obesity have been associated with a worse disease course.
Also, an estimated 25% to 50% of all individuals with bipolar disorder will make a suicide attempt, with a completed annual suicide average rate approximately of 1%. Group psychoeducation, family-focused psychoeducation and cognitive behavioral therapy seem to be the most efficacious interventions in the reduction and prophylaxis from recurrences in medicated bipolar patients and therefore reduce mortality or morbidity. The interventions help also patients and family members to identify triggering factors and early warnings of evolving episodes. Moreover, psychosocial interventions on problem-solving skills and improved tolerability of distress should help to prevent suicide or suicide attempts. In the same line, prevention of weight gain and metabolic disturbances or early intervention in improving patients' health behaviours may have a positive impact on overall health and quality of life of our patients. Preliminary research indicates that educational interventions may help patients minimize or loose antipsychotic-related weight.

S-63-004
Suicide prevention in bipolar patients

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S-86
Clinical and biological correlates of outcome prediction in major psychoses

S-86-001
Bipolar disorder

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Objectives: To discuss biological correlates of outcome and the concept of staging in bipolar disorder
Methods: We will review the data from studies that were conducted in Vancouver that assessed biological corrleates such as cytokines and oxidative stress markers in bipolar disorder at various stages.
Results: Both early and late stage bipoalr patients have increase in inflammatory cytokines but only early stage patients have elevations in anti-inflammatory cytokines. Furthermore, Brain derived neurotropic factor levels were within normal limits in early stage patients but were significantly decreased in late stage patients. Similarly, some markers of oxidative stress such as glutathione reductase and glutathione s-transferase were only increased in late stage bipolar patients.
Conclusions: These data suggest that there is an increase in anti-inflammatory response in early but not in late stage disease. Further, there is a compensatory increase in anti-oxidant defense system in late stage disease to combat an increase in oxidative stress. These are the first data to provide support from a biological perspective for staging the bipolar disorder.

S-86-002
Neuromorphology and outcome prediction

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S-86-003
Psychoimmunology and drug response

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Objectives: Recent research points out that not one single pathogen but the immune response of the mother is related to the increased risk for schizophrenia. Several reports described increased serum IL-6 levels in schizophrenia. Moreover, several other signs of activation of the type-2 immune response are described in schizophrenia, while the type-1 immune response is decreased in the majority of schizophrenic patients.
Methods: The contribution gives an overview on the relationship between drug response and the immune system.
Results: Data underline that an inflammatory process might play a role in the pathophysiology of psychiatric disorders. Pro-inflammatory cytokines, such as IL-6, IL-1 and TNF-α appear to be elevated at least in the peripheral blood of depressed patients and typically induce 'sickness behaviour', a state similar to depression in an animal model. This fits with a report on the correlation of increased in vitro IL-6 production with decreased tryptophan levels in depressed patients emphasizing the influence of IL-6 on the serotonin metabolism.
Conclusions: Since antidepressants and antipsychotics influence the immune response, cytokines and other molecules of the immune system are discussed to be markers for the therapeutic response of these drugs, data on IL-6, TNF-α, and B-cells are demonstrated. On the other hand, anti-inflammatory drugs such as the COX-2 inhibitor celecoxib shows therapeutic effects in psychiatric disorders, TNF-receptors and markers of the kynurenine metabolism showing possible impact on the therapy response are demonstrated. COX-2 inhibition reduces proinflammatory cytokines. COX-2 inhibition has an impact to the glutamatergic neurotransmission and influences the tryptophan/kynurenine metabolism: all three components seem to be involved in the pathophysiology of psychiatric disorders, particularly in schizophrenia and major depression.

S-86-004
Duration of untreated psychosis: is it a criterion for outcome prediction?

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Objectives: The Duration of Untreated Psychosis (DUP), defined as the gap in time between the onset of psychotic symptoms and the administration of antipsychotic treatment, has been increasingly investigated as a potential predictor of course and outcome in Schizophrenia (Altamura et al., 2007). It has been hypothesized that a neurodegenerative process present during the psychotic phase of the illness produces a damage to neural function. Early intervention could stop or slow the progression of these brain abnormalities.
Methods: A review of the relevant literature about DUP and its relationship with outcome was conducted.
Results: In some recent studies, conducted on first-episode schizophrenic patients, a longer DUP was associated with more severe negative symptoms at first therapeutic contact, with higher rates of suicide and with a greater risk of recurrence. Concerning treatment response longer DUP was associated with poorer response to antipsychotic treatment in terms of global psychopathology, positive and negative symptoms and social functioning. Most data about the relationship between DUP and outcome stem from short-term studies and on the other hand, the influence of DUP on outcome in the medium to long-term remains still unclear. In a prospective, naturalistic study that included patients with first psychotic episode followed up to 8 years after the treatment initiation, a DUP longer than 12 months was associated with significantly poorer outcome. Similar conclusions were obtained from another long-term study in which patients have been assessed 15 years after the first psychiatric admission.
Conclusions: The current interest in DUP comes primarily from the postulate that it is an independent prognostic factor that could be modified with early detection strategies and specific early intervention programs resulting in better outcome. The AA. will discuss these points and their implications for the overall management of course of the disorder. - Altamura AC, Bobo WV, Meltzer HY. Factors affecting outcome in Schizophrenia and their relevance for psychopharmacological treatment. International Clinical Psychopharmacology 2007; 22 : 249-267.

S-15
Brain-focussed treatments of depression

S-15-001
New data on the mode of action of electroconvulsive therapy

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Objectives: A review of new data on the mode of action of electroconvulsive therapy (ECT) in major depression, with particular reference to evidence from human beings and non-human primates.
Methods: An electronic search was conducted by the Library of the Royal College of Psychiatrists using the search strategy recommended by the Cochrane Collaboration, and covering the period from 1st January, 2004 to 31st December, 2008. Abstracts for all records were obtained, and read by the author. Full articles were obtained for all records that seemed of relevance to the objective of the study.
Results: The electronic search found 3,385 records from Embase and Medline databases. The full results will be presented at the Symposium, but preliminary conclusions can be drawn.
Conclusions: There is compelling evidence that generalized cerebral seizure activity is the crucial therapeutic ingredient of ECT, but brain imaging studies have challenged the belief that such seizures involve the whole brain homogeneously. Putative neuro-anatomical substrates for the mode of action of ECT are being identified.

S-15-002
New data on efficacy and safety of magnetic seizure therapy

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S-15-003
New methodological developments in transcranial magnetic stimulation

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Objectives: To explore new methods of using transcranial magnetic stimulation (TMS) to produce long lasting effects on human cerbral cortex, and to investigate their mechanisms of action.
Methods: I will review new methods of repetitive TMS (rTMS) including theta burst stimulation and explore how the effects are modulated by prior rTMS treatments and by prior administration of neuromodulatory drugs such as nicotine. Designs for sham coil stimulation that are effective controls for placebo effects will be presented.
Results: rTMS effects can be prolonged but not boosted in magnitude by prior TMS sessions and nicotine. Sham coil design has improved to the point where is can be indistinguishable from real stimulation.
Conclusions: Effects of rTMS can be enhanced and masked thus improving the possible therapeutic use treatment of depression and other conditions.

S-15-004
New data on deep brain stimulation

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Objectives: Deep Brain Stimulation is currently being researched actively for its as putative application in treatment resistant disorders like obsessive-compulsive disorder and major depression. Results from stimulation to different targets within the cortical–limbic–thalamic–striatal network have been presented in the last five years. The main focus of studies on the underlying neurobiology of major depression has focused on the description of biological differences between patients and healthy subjects such as alterations of monoaminergic or endocrine systems. The relative importance of the various biological changes has not been elucidated; correlation with specific symptoms of the disease has rarely been attempted. Psychotropic drugs work by altering neurochemistry to a large extent in widespread regions of the brain, many of which may be unrelated to depression.
We believe that more focused, targeted treatment approaches that modulate specific networks in the brain will prove a more effective approach to help treatment-resistant patients. In other words, whereas existing depression treatments approach this disease as a general brain dysfunction, a more complete and appropriate treatment will arise from thinking of depression as a dysfunction of specific brain networks that mediate mood and reward signals, in particular, the cortical–limbic–thalamic–striatal network. This conceptualization leads to novel ideas about targeted neuromodulatory treatments. Deep Brain Stimulation (DBS) allows the neuromodulation of sites in the brain known to be implicated in major depression.
Conclusions: Today it cannot be assumed that DBS will cure treatment refractory depression. Clinical usefulness of DBS approaches still needs to be demonstrated convincingly. Hypothesis guided Deep Brain Stimulation of different targets may reveal more information on the underlying neurobiology of depression and could be an interesting putative new antidepressant approach.

S-21
Social cognition in depression and suicide: A neuroimaging perspective

S-21-001
Self perception in depressed patients and subjects with high risk for depression

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Objectives: Emotional processing in depression is characterized by two biases. The first bias reflects the tendency of depressed patient to prioritize the processing of negative stimuli. Abnormal self-focus is a second emotional bias in major depression. Usually depressed patients tend to engage in self-reflection, self-evaluation spontaneously or after emotional perception. This persistent, increased self-focus may maintain negative mood and reinforce the activation of negative self-schema in depression. During this presentation we will present two fMRI studies evaluating the neural correlates of excessive self-focus in depressed patients and subjects with genetic risks for depression.
Methods: In a first study, we presented 15 depressed patients and 15 healthy controls with personality traits words during fMRI and asked subjects to judge whether each trait described them ('self' condition), or a generally desirable trait ('general' condition). We found that the activation of a dorsal part of the medial frontal gyrus (MPFC) in 'self' vs. 'general' condition was greater in patients than healthy subjects. Additionally, patients displayed an increased functional connectivity between the medial frontal gyrus, the dorsolateral prefrontal cortex and the dorsal anterior cingulate cortex.
Results: In a second study, we used functional magnetic resonance imaging to examine the effects of the serotonin-transporter-linked promoter region (5-HTTLPR) polymorphism on self-referential processing. Healthy never-depressed subjects were presented with emotional pictures and performed two cognitive tasks, either self-referential or not. The dorsal MPFC was less modulated in short allele carriers. In contrast with the amygdala, the effect of the genotype on this region was not affected by recent life stress. Additionally, the dorsal MPFC activity predicted the magnitude of the functional connectivity between the amygdala and the perigenual anterior cingulate, a brain circuit critically involved in emotion regulation and vulnerability for depression.
Conclusions: Overall these results suggest that self perception and the medial prefrontal cortex play a major role in depression.

S-21-002
Neural circuits underlying anhedonia in major depressive disorder

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Objectives: A mood-congruent processing bias toward negatively-valenced emotional stimuli is apparent in MDD, and may contribute to depressed mood and anhedonia. This bias is evident in the context of memory, attention and neurophysiological indices. The amygdala participates in evaluating the emotional salience of sensory stimuli both as part of distributed networks of subcortical structures that allow rapid, automatic assessment of stimulus features, and networks of cortical regions that allow conscious or explicit stimulus perception. We hypothesized that the negative processing bias associated with MDD is mediated by this rapid, automatic processing network involving the amygdala.
Methods: Using fMRI and a backward masking technique the amygdala responses to sad verus happy faces were assessed in depressed MDD (dMDD) subjects and healthy controls. Amygdala responses were compared also between dMDD and remitted MDD (rMDD) subjects, and in dMDD subjects before and following treatment. Similarly, amygdala responses to the anticipation and acquisition of reward versus punishment were assessed using the monetary incentive delay task (MID).
Results: The backward masking task data showed that emotional processing biases occur automatically in the amygdala, below conscious awareness, toward sad faces in dMDD and rMDD subjects and toward happy faces in healthy controls. This automatic negative bias resolved and a positive bias developed in MDD subjects following successful treatment. During the MID task dMDD subjects showed altered cortocolimbic activity in the amygdala, OFC, hippocampus and accumbens, as they anticipated initiating behavioral responses aimed at acquiring rewards or avoiding losses. These abnormalities were associated with impaired modulation of the behavioral response to changing incentive levels.
Conclusions: This bias away from positive and toward negative in MDD may relate to the risk for suicidal ideation, since attentional neglect toward positive stimuli may be underlie hopelessness, whereas pathological focus on negative may emphasize profoundly sad, and otherwise ignored, potential events such as death and suicide.

S-21-003
Is suicide a specific disorder of social cognition?

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Objectives: For long, it has been recognized that the social dimension of suicidal behavior is of major importance. For instance, suicide attempters or notes left by suicide completers frequently report relationship problems within the family, couple or at work or school to be precipitants of their act. Suicidal acts may be seen as means to escape from these unbearable situations but may also represent messages addressed by the patient to their entourage. It is therefore necessary to understand the specific cognitive processes implicated in social perception and interaction that may make the ground to the vulnerability to suicidal behavior.
Methods: A series of neuropsychological studies including the Iowa Gambling Task (IGT); an fMRI study using emotional faces and a modified version of the IGT.
Results: We will discuss here several results from our group and others showing that suicide attempters present cognitive deficits that may alter the adequate perception of their social environment and the possibility to respond advantageously to these situations.
Conclusions: We hypothesize that the vulnerability to suicidal acts may be understood and studied as a specific disorder of social cognition.

S-21-004
Emotional and social memory

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Objectives: In a series of studies we observed in healthy individuals that emotional expression influence memory for faces in terms of both accuracy (Pr) and also interestingly, in the memory response bias (Br; tendency to classify stimuli as previously seen or not, regardless of whether this was the case). The influence of emotion on memory in schizophrenia has been however little studied, with somewhat inconsistent results.
Methods: Twenty patients with schizophrenia and twenty matched healthy controls completed a fMRI study to investigate the recognition memory (old/new judgment) for happy, sad and neutral faces. The brain activity associated with the Br was obtained by correlating the behavioral response bias for happy and sad expressions with the contrast subjective old (i.e., when subject believed that the face is old; hit and false alarm) minus subjective new (miss and correct rejection) response.
Results: Although, patients exhibited an overall lower memory performance than controls, they showed the same effects of emotion on memory, both in terms of Pr and Br. For sad faces, the similar behavioral Br pattern between groups was mirrored by a largely overlapping neural network, mostly involved in familiarity-based judgments (e.g., parahippocampal gyrus). In contrast, controls activated a much larger set of regions for happy faces, including areas thought to underlie recollection-based memory retrieval (e.g., superior frontal gyrus and hippocampus) and in novelty detection (e.g., amygdala).
Conclusions: This study demonstrates that, despite an overall lower memory accuracy, emotional memory is intact in schizophrenia, although emotion-specific differences in brain activation exist, possibly reflecting different strategies.

S-28
Neurobiology of sleep regulation and sleep deprivation and consequences for depression and somatic health

S-28-001
Sleep and neuroendocrine biomarkers as predictors for psychic health and depressive illness course in children and adults

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Objectives: Sleep regulation and hypothalamic-pituitary-adrenocortical (HPA) system function are associated with psychiatric disorders such as depression. The predictive value of these alterations for long-term course of depression was assessed in a prospective long-term study over 8 years. However, most of the data available so far are from studies after the disorder's onset. Thus, we started an additional project in children aiming to investigate sleep regulation, HPA axis function, and psychological/behavioural variables in order to identify risk factors early in development.
Methods: 15 patients (4 men, 11 women; age 43–59) with depression were enrolled in the first study. HPA system assessment using the combined DEX/CRH test and sleep EEG studies were conducted at baseline, after a 6 week antidepressant treatment period (trimipramine), and 2 to 10 years after the index episode. In the second study, 67 pre-schoolers (35 boys and 32 girls) at the age of 5 years underwent sleep EEG-monitoring and baseline HPA activity assessment by the use of saliva morning cortisol measurements after awakening.
Results: In patients with depression it was shown that the amount of slow wave sleep and REM density were predictive for the long-term course of the disease. These identified sleep EEG markers correlated closely with HPA system regulation. In children boys showed significantly more REM sleep when compared to girls. Independent of gender, an unfavourable sleep profile was associated with an increased HPA axis activity. Furthermore, bad sleep regulation was related to more difficult behavioural / psychological dimensions.

Conclusions: Unfavourable sleep patterns associated with an increased HPA activity seem to reflect predictive markers for the long-term course of depression. Moreover, abnormalities in sleep regulation present in children are related to heightened HPA system activity as well. The longitudinal follow up of these children will demonstrate if these biological abnormalities are predictive for the onset of clinically relevant psychiatric problems.

S-28-002
Neuropeptidergic regulation of sleep and sleep deprivation

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Objectives: A bidirectional interaction exists between sleep electroencephalogram (EEG) and endocrine activity. A key role was shown for the reciprocal interaction between sleep promoting growth hormone releasing hormone (GHRH) and the sleep impairing corticotropin releasing hormone (CRH) in male subjects. A sexual dimorphism is suggested because in females the pulsatile administration of GHRH impairs sleep. Sleep deprivation (SD) is strongly promoting sleep by increasing slow wave sleep (SWS) and rapid eye movement sleep (REMS). Studies in rodents found a key role of GHRH in sleep promotion after SD.
Methods: 42 healthy subjects (age 19 - 69) were investigated during 4 consecutive nights. After one night of adaptation sleep EEG was recorded and hormone profiles of growth hormone (GH) and cortisol were collected simultaneously. This baseline night was followed by 40 hours of SD. In the recovery night sleep-endocrine activity was retested and the subjects received between 2200 and 0100 hourly bolus injections of either placebo, 50 ug CRH or 50 ug GHRH according to a randomized schedule.
Results: After placebo during the recovery night, non-rapid-eye-movement sleep (NREMS) and REMS increased and wakefulness decreased compared with the baseline night. After GHRH, the increase of NREMS and the decrease of wakefulness were more distinct than after placebo. Also, after CRH, NREMS increased more than after placebo, and a positive correlation was found between age and the baseline-related increase of slow-wave sleep. REMS increased after placebo and after GHRH, but not after CRH. Cortisol and GH did not differ between baseline and recovery night after placebo.
Conclusions: Our data suggest that GHRH augments the sleep promotion after sleep deprivation. The reduced stimulation of REMS after CRH during the recovery night is in line with the REMS suppression after CRH in young males. Differences appear to exist in peptidergic sleep regulation between spontaneous sleep and recovery sleep.

S-28-003
Neurotransmitter regulation of sleep deprivation in depression

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Objectives: The antidepressant efficacy of sleep deprivation (SD) in depressed patients can be prevented by early morning naps and the occurrence of microsleep (MS) episodes during SD. In addition, MS during SD reduces the intensity of NonREM sleep in the recovery night. Substances, such as the GABA-Benzodiazepine receptor antagonist flumazenil and modafinil augment vigilance and reduce NonREM-sleep pressure. In addition, flumazenil reduces NonREM sleep associated growth hormone secretion in early morning recovery sleep in healthy subjects. Therefore, flumazenil and also modafinil seemed to be promising candidates to reduce MS during SD, which may augment antidepressant response.
Methods: In two studies, each with 27 patients with major depression, a partial sleep deprivation (PSD) has been performed. In double blind randomized order either flumazenil/modafinil or placebo was orally applied during PSD. Sleep-EEG was registered continuously for 60 hours by a portable device.
Results: Both drugs significantly suppressed MS during SD, however in a different way. In addition, under flumazenil slow wave sleep was increased and stage 1 reduced in the recovery night. This was not observed under modafinil. Antidepressant efficacy of PSD was not substantially different between flumazenil or modafinil and placebo during PSD, but better after the recovery night in patients treated with flumazenil and after continuous mid-term treatment (2 further weeks) with modafinil.
Conclusions: From these findings it is concluded that GABAergic mechanisms and the orexin-receptor system are involved in the regulation of MS and NonREM-sleep during PSD. The association with the antidepressant efficacy of PSD has to be further determined.

S-28-004
The consequences of chronically disrupted and restricted sleep: Insights from experimental studies in animals and relevance for depression

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Objectives: Chronically restricted sleep is a widespread problem in our modern around-the-clock society. It is commonly believed that insufficient sleep, in the long run, may have repercussions for health and perhaps sensitizes individuals to psychiatric diseases. In this context, we applied an animal model of chronic sleep restriction to study effects of sleep loss on neurobiological and neuroendocrine systems that have been implied in the pathophysiology of depression.
Methods: Adult male rats were exposed to a schedule of chronic partial sleep deprivation allowing them about 4h of sleep per day. Sleep restriction was achieved by placing the animals in slowly rotating drums. Additional groups to control for stress and forced activity were included.
Results: While one day of restricted sleep had no major effects, a week of sleep restriction caused a reduction in adult hippocampal neurogenesis and altered HPA axis regulation and reactivity. These changes may in part be related to alterations in serotonergic signalling since sleep restricted rats displayed blunted physiological responses to direct serotonin-1A receptor stimulation. This desensitization of the serotonin-1A system persisted for many days even with unlimited recovery sleep.
Conclusions: While some effects of chronic sleep restriction may reflect adaptational processes to cope with persistent sleep curtailment, other changes may reflect maladaptation. The data show that chronic sleep restriction gradually causes changes in neurotransmitter receptor systems and neuroendocrine reactivity in a manner that is similar to what is seen in depression. This experimental study provides support for the hypothesis that disrupted and restricted sleep may contribute to the symptomatology of psychiatric diseases.

S-34
Identifying biomarkers of depression: New insights from animal models

S-34-001
Early environment shapes vulnerability to psychopathology in animal models of depression: Is altered metabolism a reliable biomarker?

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Objectives: Early postnatal experiences profoundly and permanently alter developmental trajectories, having long term influences on brain function and behaviour. Indeed, the impoverishment or deterioration of the early environment produces a number of long-term disrupting effects, including an increased vulnerability to psychiatric disorders, such as depression. Changes in metabolism have been hypothesized to be one of the possible factors mediating the effects of early experiences to adulthood. In order to investigate the association among early experiences, vulnerability to depression and metabolic profile, we exploited a novel experimental procedure: the mouse Communal Nest (CN).

Methods: CN consists in a single nest where three mouse mothers keep their pups together in the nest and share care-giving behavior from birth until weaning (postnatal day 25).
Results: Compared to mice reared in standard nesting laboratory condition (SN), CN pups experience higher levels of maternal care and peer interactions and with higher amounts of milk. At adulthood, CN mice show a reduced vulnerability to the depression-like phenotype. For instance, CN display higher levels of neural plasticity markers, such as BDNF levels and brain stem cell proliferation, have more elaborate social competences and show reduced anhedonia and neuroendocrine activation following social stress. These behavioural changes are associated with markers of increased metabolism. For instance, at baseline, CN tend to have higher levels of blood glucose but, after 24hrs food deprivation, their levels are significantly lower than those of SN mice. Furthermore, adult CN mice eat 15% more food, but they weigh only 5% more, corroborating the idea that CN mice have a higher metabolic activity.
Conclusions: Our findings corroborate the notion that the early rearing environment has a major impact on brain and behavior development, affecting the likelihood to develop selected symptoms of psychopathology. Such vulnerability appears to be associated with changes in the metabolic profile. Support contributed by EU, project INTELLIMAZE contract n 037965

S-34-002
Markers of neuronal network plasticity in mood disorders and antidepressant response

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Objectives: Early childhood events and adult stress predispose to mood disorders, presumably by producing structural and functional changes and impairing proper information processing in the critical neuronal networks regulating mood. Antidepressant treatments promote activity-dependent neuronal plasticity, however, it is not known how antidepressant treatments influence the structure and function of neuronal networks in brain.
Methods: In collaboration with Dr. Maffei's lab (Pisa, Italy),we have utilized the well-characterized developmental plasticity of the mammalian visual cortex as a model. We have also investigated the epigenetic effects of early life toxic stress on behavior and gene expression.
Results: We found that chronic antidepressant treatment reopens the critical period plasticity in the visual cortex adult rats. We further showed that the impaired vision brought about by a closure of one eye throughout development could be rescued in adult rats if adult antidepressant treatment was combined with the opening of the amblyopic eye and patching of the better eye in rats in adulthood. In other experiments, chronic antidepressant treatment reversed the epigenetic effects of early life toxic stress on BDNF gene expression and depression-like behavior.
Conclusions: These data suggest that antidepressant treatment, by reactivating developmental-type cortical plasticity, can help to repair malfunctioning neuronal networks brought about by imbalanced early experiences, when antidepressant treatment is combined with environmental rehabilitation. This hypothesis suggests a novel mechanism for the antidepressant action where the drug acts permissively to facilitate the functional recovery of neuronal networks in brain.

S-34-003
Novel strategies to discover susceptibility and resilience biomarkers for stress-induced diseases

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Objectives: Chronic stress is widely regarded as a key risk factor for a variety of diseases, among which are affective disorders. Genetic predispositions are thought to interact with environmental demands such as chronic stress. However, so far it was not possible to predict individual stress susceptibility or resilience.
Methods: Using a recently developed paradigm for chronic social stress in outbred mice we identified animals that are either resistant or susceptible to the persistent effects of chronic stress exposure based on their neuroendocrine phenotype. The stress-susceptible phenotype was stable over time under non-stress conditions and closely resembled core symptoms of affective disorders, including increased anxiety- and depression-like behaviour.
Results: A hippocampal microarray analysis revealed signature gene expression profiles within the AMPA receptor signalling pathway that were uniquely associated with stress susceptibility. Treatment with an AMPA receptor potentiator during stress attenuated the lasting effects of chronic social stress exposure on physiological, neuroendocrine and behavioural parameters. Based on these findings we could show that poor spatial short-term memory performance, a process that requires AMPA receptors, predicts high stress vulnerability later in life. Further, we identified single nucleotide polymorphisms that are associated with differences in stress susceptibility.
Conclusions: Our data suggest that differences in AMPA receptor function may underlie individual stress susceptibility and support AMPA receptor potentiators as potential therapeutic drugs in stress-related human disorders. Taken together, we can show that it is possible to identify behavioural and genetic susceptibility markers that are predictive for individual stress susceptibility.

S-34-004
From inflammation to depression: A role for indoleamine 2,3 dioxygenase

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Objectives: Although the relationship between inflammation and mood disorders in somatic patients is now well known, its mechanisms are still obscure. In laboratory rodents, acute or peripheral immune stimulation similarly induces behavioral signs of sickness that culminate in the development of depressive-like behavior, as measured by increased immobility in the forced swim and tail suspension tests and decreased preference for sucrose. These behavioral alterations can be prevented by chronic administration of antidepressant drugs. Depressive-like behavior is also associated with activation of the tryptophan degrading enzyme indoleamine 2.3 dioxygenase (IDO) in these animal models of inflammation-associated depression. Pretreatment with the tetracycline derivative minocycline that inhibits the production of proinflammatory cytokines blocks the development of both sickness behavior and depressive-like behavior. In contrast, pretreatment with a specific inhibitor of IDO, 1-methyl tryptophan, does not abrogate the production of proinflammatory cytokines nor the development of sickness behavior but blocks depressive-like behavior. IDO activation is mainly dependent on tumor necrosis factor-alpha and interferon-gamma. Chronic immune stimulation does not induce depressive-like behavior in mice deficient for the interferon-gamma receptor and in IDO-knock out mice. Although IDO activation potentially decreases the bioavailability of tryptophan for the synthesis of serotonin, blockade of IDO activation did not interfere with activation of serotoninergic neurotransmission. In addition, administration of the main IDO metabolite of tryptophan, kynurenine, to naïve mice mimicked the depressive-like effect of immune stimulation. These convergent clinical and experimental data point to the pivotal role of IDO in the development of depressive-like behavior and indicate that IDO-derived metabolites of tryptophan act as key players in the pathophysiology of depression. IDO and its downstream enzymes represent new targets for the treatment of inflammation-associated depression.

S-57
Depression, vitamin D and light

S-57-001
Vitamin D, light and parathyroid hormone in depression

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Objectives: About 13 percent of older individuals have symptoms of depression, and other researchers have speculated that vitamin D may be linked to depression. Underlying causes of vitamin D deficiency such as less sun exposure as a result of decreased outdoor activity, different housing or clothing habits and decreased vitamin intake may be secondary to depression, but depression may also be the consequence of poor vitamin D status. Moreover, poor vitamin D status causes an increase in serum parathyroid hormone levels. Overactive parathyroid glands are frequently accompanied by symptoms of depression that disappear after treatment of the condition.
Methods: We recently measured blood levels of vitamin D and parathyroid hormone and assessed symptoms of depression among 1,282 community residents age 65 to 95.
Results: We found a strong decrease in vitamin D level and increase in parathyroid hormone level (Hoogendijk et al., Arch Gen Psychiat 2008;65(5):508-512).
Conclusions: This finding may be important to patients because both low blood vitamin D levels and high parathyroid hormone levels can be treated with higher dietary intake of vitamin D or calcium and increased sunlight exposure. Vitamin D receptor is most abundant in the mood regulating hypothalamus. Sunlight may, therefore, have an antidepressant effect via the skin-vitamin D-hypothalamic tract.

S-57-002
Positive effect of bright light in non-seasonal depression

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Objectives: Background: The cause of depression is largely unknown, but several studies point to disturbances of biological rhythmicity. The functioning of the suprachiasmatic nucleus (SCN) is impaired, as evidenced by an increased prevalence of day-night rhythm perturbations, such as sleeping disorders. Moreover, the inhibitory SCN neurons on the hypothalamus-pituitary adrenocortical axis (HPA-axis) have decreased activity and HPA-activity is enhanced, when compared to non-depressed elderly. Using bright light therapy (BLT) the SCN can be stimulated. In addition, the beneficial effects of BLT on seasonal depression are well accepted. BLT is a potentially safe, nonexpensive and well accepted treatment option. But the current literature on BLT for depression is inconclusive.
Methods: RCT (ClinicalTrials.gov identifier: NCT00332670) in 89 subjects, of 60 years and older with a diagnosis of major depressive disorder. After inclusion subjects were randomly allocated to the active (BLT) vs. placebo (dim red light) condition. just before the start of light therapy, after completion of three weeks therapy period, and three weeks thereafter several endocrinological, psychophysiological, psychometrically, neuropsychological measures are performed:
Results: Main effect analyses on HADRS-17 scores revealed significant antidepressant effects from BLT after 3 weeks of BLT and an enhanced effect 3 weeks after ending the BLT. Effects are accompanied by changes in actometrical (circadian and sleep) variables, 24-hr cortisol urinary extretion and saliva cortisol and saliva melatonin curves. Primary results will be presented.
Conclusions: BLT reduces nonseasonal depression in elderly patients. Additional lightning may easily be implemented in the homes of patients to serve as add-on treatment to antidepressants or as a stand-alone treatment in elderly depressed patients. Our data support the role of a dysfunctional biological clock in depressed elderly subjects, such a finding may guide further development of novel chronobiological oriented treatment strategies.

S-57-003
Developmental vitamin D deficiency alters adult behaviour

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Objectives: It is now recognized that vitamin D is active in the brain and plays an important role in brain development. Guided by certain features of the epidemiology of schizophrenia, we have explored the role of vitamin D in the developing brain and behaviour in a rodent model of developmental vitamin D deficiency (DVD).
Methods: Sprague-Dawley rats were fed a vitamin D deficient diet or control diet six weeks prior to mating until birth when they were returned to a diet containing vitamin D until adulthood. The behavioural phenotype of the adult offspring rats was assessed in response to psychomimetic drugs, prepulse inhibition, social interaction, and tests of anxiety and depression.
Results: The behavioural phenotype of DVD rats included specific disruption in response to amphetamine in female rats and MK-801 in male rats, as well as altered social behaviour. There were no gross effects on development during postnatal life, the rats had normal functioning of the hypothalamic-pituitary axis and on the other behaviours measured.
Conclusions: In summary, low prenatal levels of vitamin D can influence critical components of orderly brain development which have long lasting effects on specific aspects of behaviour relevant to dopamine and glutamate signaling.

S-57-004
Vitamin D deficiency is associated with low mood and worse cognitive performance

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Objectives: Assess the relationship between cognitive performance, mood and vitamin D status in nondemented older adults.
Methods: Ninety-eight nondemented older adults at Washington University were assessed using a comprehensive clinical, physical, neurological and psychometric evaluation. A cognitive and behavioral assessment included the Mini-Mental State Examination (MMSE) and Short Blessed Test (SBT), and the 15-item Geriatric Depression Scale (GDS). The psychometric battery included 16 tests assessing primary, working episodic and semantic memory, mental control, visuospatial function, psychomotor speed, and language. Vitamin D status was determined using serum for 25-hydroxyvitamin D (25OH-D) levels. Subjects were considered vitamin D sufficient (25OH-D >30 ng/ml) and deficient (25OH-D < 30ng/ml).
Results: The sample (N = 98) included 57 women, 81 Caucasians and 17 African Americans. The mean age was 79.86 and mean educational level was 14.75 years. Mean 25OH-D level was 23.7ng/ml and 66% had vitamin D deficiency. Those with vitamin D deficiency had worse scores on the SBT 2.63 (SD-3.1) vs 1.29 (SD-1.9) p= 0.025 and on the GDS 1.91 (2.1) vs 1.0 (SD- 1.2) p=0.023 compared to those with sufficient vitamin D. Trends toward significance were noted in the overall psychometric factor score and logical memory. In regression models adjusting for the effects of age, education and race, vitamin D deficiency remained significantly associated with the SBT score.
Conclusions: Vitamin D deficiency is associated with worse cognitive performance and depressive symptoms in older adults. This is consistent with the previously reported association between vitamin D and cognitive performance; however, our data utilizes a group of well characterized healthy older adults without dementia. We also establish this finding using a higher threshold for vitamin D deficiency (30 ng/ml). This data provides additional support for the role of vitamin D in cognition and mood.

S-74
Chronobiological treatment combinations for major affective disorder: Clinical outcome and neurobiological correlates

S-74-001
Chronobiology as a paradigm for biological psychiatry

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Objectives: Biological psychiatry seeks to establish the genetic, neurochemical, and physiological basis of mental disorders and their treatments. Chronobiology, or biological rhythm research, has in recent years discovered a myriad of clock genes and their role in expressing the "day within"; the circadian pacemaker in the hypothalamus generating 24-hour rhythms, its CNS pathways and neurotransmitters; the link between time of day and sleep regulation, hormonal output, physiologic and psychological behaviour, performance and mood state; and the importance of synchronising agents (zeitgebers) to correctly entrain all these functions to the day-night cycle. Thus, rhythms underlie all behaviours -- and disturbances in rhythms can cause or result from psychiatric illness.
Methods: Periodicity in psychopathology is most striking in bipolar disorder. The illness is cyclic, and shifts in timing of the sleep-wake cycle accompany changes in clinical state. The switch out of depression is often accompanied by a spontaneous sleep deprivation; conversely, a prescribed sleep deprivation can be rapidly antidepressant. More strikingly, a phase advance of sleep timing can induce longer-lasting antidepressant effects.
Results: Light therapy (the strongest zeitgeber for synchronising the circadian clock) is the first treatment in psychiatry that was developed from an animal model (seasonality). Light is the treatment of choice for seasonal affective disorder, but has now been shown effective for major nonseasonal and even chronic depression, as well as in bulimia, sleep-wake disturbances in ageing and dementia, etc.
Conclusions: In contrast to depression, where there seems to be aetiologic links to clock function and even clock gene polymorphisms, many other psychiatric illnesses are accompanied by disrupted sleep-wake cycles. Evidence is accumulating that the worse the entrainment of the sleep-wake cycle, the worse the symptoms (independent of diagnosis, e.g. borderline, schizophrenia). Chronotherapeutics thus seeks to implement methods (light, melatonin) to improve entrainment and thereby clinical state, cognitive behaviour, and mood.

S-74-002
Nuts and bolts of chronotherapeutic interventions

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Objectives: Technical procedures inspire not only research ideas, but also new clinical thinking. Chronotherapeutics has honed the light and wake therapy procedures over 20 years, with refinements that maximize clinical response.
Methods: Light therapy has evolved into two basic modes: post-awakening exposure at constant high illuminance, and lower level simulation of dawn transitions toward the end of sleep. Bright light therapy is most effective when taken promptly after wake-up at the end of the "subjective" (circadian) night. The complementary dosing variables are light intensity (2000 to 10,000 lux) and exposure duration (10 minutes to 2 hours). Thirty minutes at 10,000 lux is usually sufficient. Morning exposure shifts the internal clock earlier relative to sleep, an effect that depends on internal time referencing. Subjective night differs by several hours from person to person. It can be diagnostically determined by salivary melatonin assay and approximated using a chronotype questionnaire. Naturalistic dawn simulation rises over hours, from darkness to an attenuated sunrise level of 50 to 300 lux (the dosing variable). Again, it is timed to the end of subjective night to promote circadian phase advances and ease of awakening.
For patients with extremely late subjective nights (delayed sleep phase disorder), bright light therapy and dawn simulation can be moved gradually earlier over days or weeks, thus anchoring the internal clock to solar time, with antidepressant benefit. Wake therapy is best administered with all-night sleep deprivation preceded and followed by days without napping. Since some patients do not respond on the first night, up to three repetitions within a week maximizes the effect. The transitory benefit of wake therapy can be sustained by initiating daily light therapy at the end of the first night awake and displacing recovery sleep earlier on the night following sleep deprivation.

S-74-003
Wake and light therapy in non-seasonal major depression

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Objectives: Sleep deprivation is known to induce a rapid amelioration of depressive symptoms. Recently techniques using bright light therapy and sleep time control have been developed to sustain the acute response of sleep deprivation. The aim of this study was to establish the efficacy of these methods and also to control for the placebo response by incorporating a suitable control group using daily exercise.
Methods: Thus, in the Chronos study, patients with an actual diagnosis of unipolar or bipolar major depression according to the DSM-IV, were randomized to either a (1) Chronotherapy group using a combination of three total sleep deprivations during one week, daily bright light treatment and sleep time control, or (2) an Exercise-group using a daily exercise program individually tailored to 30 minutes of moderate intensity. All patients were treated with duloxetine 60 mg daily. Patient were followed for 29 weeks.
Results: Depression scores on the Hamilton depression rating scale showed a statisticaly significant greater reduction in the Chronotherapy group, compared to the exercise group. This effect were seen from week one after sleep deprivation were performed and the difference between groups increased over the following weeks.
Conclusions: Thus the chronotherapeutic intervention induced a rapid and sustained response superior to the response seen in the exercise group.

S-74-004
Wake and light therapy in bipolar illness: fMRI correlates of response

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Objectives: There is still a high uncertainty about which biological changes are needed to recover from a major depressive episode. Changes of monoaminergic neurotransmission are often emphasized, but they are paralleled by profound changes in brain metabolism, neural responses to stimuli, sleep architecture, biological rhythms, and, at the intracellular level, neuronal signaling pathways regulating gene expression, neuroplasticity, and neurotrophic mechanisms. Sleep deprivation and light therapy target the biological mechanisms which are responsible of the possibility, unique to mood disorders, of rapid switching between depression, euthymia, and mania. Current knowledge suggests that multiple neurobiological effects of sleep deprivation are responsible for the clinical mood amelioration, suggesting a multi-target mechanism of action, and an impressive group of brain imaging studies using different brain imaging techniques (positron emission tomography, single photon emission tomography, functional magnetic resonance imaging, proton spectroscopy, arterial spin labeling) showed that clinical response is associated with changes in the functioning of specific brain areas. The combination of these new methodological acquisitions with the classical neurobiological and pharmacogenetic perspective provides an evolving knowledge about brain changes associated with antidepressant response, and will then help to identify the real targets of antidepressant treatment.

S-77
The emerging role of TMS in the treatment of psychiatric disorders

S-77-001
Transcranial magnetic stimulation of deep brain regions: An overview and ongoing studies in psychiatric patients and healthy subjects

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Objectives: The H-Coils are a new development in transcranial magnetic stimulation (TMS), designed to stimulate deeper neuronal pathways. The advantages and disadvantages of these coils will be discussed. Following our previous study evaluating safety and cognitive effects of the H-coil in healthy volunteers, we studied the antidepressive response induced by repeated, high-frequency deep TMS treatment using several H-coil versions over the prefrontal cortex (PFC).
Methods: We compared the effects of left (H1L coil), bilateral (H2 coil) and preferentially left (H1 coil) high frequency (20 Hz) stimulation of the PFC in medication free, drug-resistant depressive patients.
Results: Stimulation with the novel H-coils was well tolerated, with no major side effects. When using 120% of motor threshold to affect deep PFC regions, response rates (defined as at least 50% reduction in HDRS scores) were 60%, 30% and 47% for the H1L, H2 and H1 coil groups, respectively. On the other hand, when a more superficial stimulation was applied (using the H1L coil at 110% of motor threshold), response rate was 0%. The patients' subjective report using BDI showed a similar pattern of responses. Computerized cognitive tests (CANTAB) also indicated significant improvements induced by deep TMS over the PFC.
Conclusions: This study is the first evidence for the efficacy and safety of deep TMS in major depression and indicates that high frequency stimulation over the left PFC is more effective then bilateral stimulation. Additional studies using the H-coils in depressive and post-traumatic patients and in healthy subjects will be discussed.

S-77-002
Predictive factors and biomarkers for TMS in depression

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Objectives: Transcranial magnetic stimulation (TMS) is now an evidence-based treatment for major depression. As with any novel treatment, questions arise as to which, if any, patient characteristics can be utilized to predict antidepressant response in an individual patient. Furthermore, the identification of biomarkers associated with TMS response help elucidate its mechanism of action and may have clinical utility. Our objective is to review the scientific literature identifying biomarkers and predictive factors of outcome in TMS for depression.
Methods: We examine data looking at predictive factors for acute outcome in the largest sham-controlled trial of over 300 subjects. Additional findings from smaller studies and pooled data from multiple trials is also discussed. Studies examining biomarkers for clinical response to TMS are summarized.
Results: Studies have identified various predictive factors for clinical response in TMS for depression. Duration of depressive episode, degree of treatment-resistance and the presence or absence of psychiatric comorbidity are among the factors which may impact the likelihood of achieving clinical response. Potential biomarkers which have been identified include catecholamines, brain-derived neurotrophic factor and post-dexamethasone cortisol levels.
Conclusions: Analysis of trial outcome data aids in the identification of positive predictors of antidepressant response to TMS. Additional experience employing this treatment modality in much larger populations is needed to confirm these findings. Similarly, candidate biomarkers need to be studied more extensively before their utility can be confirmed.

S-77-003
TMS for other neuropsychiatric disorders

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Objectives: There is a growing consensus in the neuroscientific community that dysfunctional neuroplastic processes in the brain are involved in different neurological disorders. Repetitive transcranial magnetic stimulation (rTMS) is a potent tool for modifying neural activities both at the site of stimulation and at distant anatomically connected sites. Therapeutic application of rTMS can therefore be considered as being able to influence altered neural circuitry within a functional network.
Methods: This technique has been applied in different ways in different groups of patients with pain, chronic tinnitus, Parkinson's disease, and stroke. A single session of rTMS over appropriate cortical areas has a short term effect on cortical excitability, while daily sessions of rTMS seem to build to produce a long term therapeutic effect which in some cases could be predictive for treatment outcome of chronic epidural stimulation using implanted electrodes in a range of neurological disorders.
Results: Repeated sessions of low-frequency rTMS have an inhibitory effect and high frequency sessions of rTMS have an excitatory effect. Beneficial effects of this treatment have been demonstrated in several small controlled studies. However, results are characterized by high inter-individual variability. The optimization of the parameters of stimulation for each application is the key point before rTMS can be applied as a therapeutic tool in daily neurological practice. Well-controlled multicentre randomized trials in large series of patients are still necessary to confirm the potential of rTMS in neurological disease.
Conclusions: Although this is an stage of investigation, there is a reasonable evidence that rTMS is a promising tool for pathophysiological assessment and therapeutic management of certain neurological disorders. Further development of this technique will depend on a more detailed understanding of the neurobiological effects mediating the benefit of TMS and more clinical studies with larger sample sizes and longer follow-up periods are needed.

S-77-004
Efficacy of TMS for depression and review of large sham-controlled trial

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Objectives: While major depression is a leading cause of disability worldwide, a substantial proportion of patients do not adequately benefit from or tolerate existing therapies. An alternate treatment approach involves modulation of electrical activity in relevant neurocircuits. Electroconvulsive therapy (ECT) remains the prime example and gold standard for this approach; but issues regarding relapse rates, optimal administration, adverse cognitive effects, cost and access limit its role. Transcranial magnetic stimulation (TMS) produces intense, pulsed, localized magnetic fields which alter electrical current in cortical tissue. We will critically review the data to support TMS as an alternative therapy for major depression.
Methods: We summarize the literature for TMS as a monotherapy, augmentation strategy and as an alternative to ECT in the management of treatment-resistant depression. We focus on the results of the largest, multi-centered, sham-controlled trial involving over 300 subjects and the eight published studies comparing ECT with TMS for the treatment of depression.
Results: Several early trials, as well as meta-analyses of these data, concluded that there was a signal for clinical benefit with TMS and a good safety and tolerability profile. Since these trials were small (usually single-site) and outcomes were not always consistent, questions regarding clinical relevance arose. More recently, better-designed, sham-controlled trials have led to the approval of TMS for treatment of depression in several countries. Trials comparing TMS to ECT also indicate a potential benefit in a subgroup of patients referred for ECT.
Conclusions: The existing literature supports a role for TMS in depressed patients insufficiently benefited by standard approaches. There are, however, important questions that still require resolution before developing clinical algorithms that incorporate TMS. These include issues of study design; predictors of response; and strategies to enhance the efficacy of TMS.

S-09
Glutamate as a neurobiological target in anxiety disorders: Metabotropic or ionotropic receptors?

S-09-001
Role of the glutamate system in the neurobiology of anxiety and stress related disorders: How strong is the therapeutic rationale?

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Objectives: Interest in specific pharmacological approaches to glutamatergic modulation has emerged from the translational literature in stress models of psychopathology, as well as from experimental therapeutic trials of glutamatergic agents combined with neuroimaging techniques such as proton magnetic resonance spectroscopy (1H MRS).
Methods: Inasmuch as glutamate is a key contributor to stress-induced impairments in neuroplasticity, several glutamatergic-based mechanisms for human anxiety disorders have been explored in proof-of-concept and early phase II trials, in addition to the ionotropic and metabotropic glutamate receptor studies detailed in this symposium.
Results: An early study assessing in vivo glutamate function in anxiety patients used high-field 1H MRS in patients with generalized social phobia, reporting a 13% higher glutamate/creatine ratio in the anterior cingulate cortex (ACC) compared to healthy controls, with glutamate levels correlating with the intensity of phobic symptoms and with activation of rostral ACC in response to aversive faces with functional MRI. Subsequent studies in patients with social phobia replicated and extended these findings to identify regional increases in steady-state levels of glutamate and glutamine, with post-treatment normalization using an anticonvulsant medication (levetiracetam) that modulates GABA and/or glutamate activity. Riluzole, a drug that attenuates glutamate release and increases expression of glutamate transporters, has shown preliminary efficacy in a number of mood and anxiety disorders, beyond its established utility in amyotrophic lateral sclerosis. Chronic administration of riluzole decreased ruminative worry and anxiety sensitivity in an open-label investigation for patients with GAD; responders showed regionally specific increases in the neural viability marker N-acetylaspartate in hippocampus.
Conclusions: While significant challenges remain in translating group-level data to the individual patient and in enhancing sensitivity and specificity of imaging biomarkers, these reports provide rationale for research exploring glutamate modulating agents as anxiolytics.

S-09-002
Role of animal models in the development of current and novel therapeutic strategies for anxiety disorders

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Objectives: Anxiety disorders are serious, growing medical problems that remain poorly understood and inadequately treated. The complex interaction between stress and genetics that leads to the manifestation of such disorders in certain susceptible individuals is one of prime interest in neuroscience. This is paralleled with efforts to develop pharmacological strategies to counteract the deleterious effects of stress. However, psychiatry has proven to be among the least penetrable clinical disciplines for the development of satisfactory in vivo model systems for evaluating novel treatment approaches. In recent years, there has been an accumulation of evidence that selective targeting of glutamate receptors may be a useful strategy for the treatment of anxiety disorders. Such evidence has been contingent on the availability of predictive animal models, and is largely driven by the development of selective, potent and orally bioavailable tools for distinct glutamate receptors and receptor binding sites in the brain. Moreover, the availability of genetically modified mice is also adding to the armamentarium researchers have to dissect the role of glutamate in brain circuits relevant to anxiety. There are key issues facing drug discovery as it endeavors to identify "translational models" for anxiety. Popular tests for anxiety-like behaviors are often based on ethologically relevant behaviors, such as aversion to exposed, well-lit spaces. The use of cognitive-based tasks that involve Pavlovian fear conditioning is one approach that is being used in both mouse and human situations to illuminate the neural substrates of fear and learning and memory in the brain. Moreover, recent emphasis has also been placed on developing mouse models of the early-life origins of anxiety as childhood trauma and neglect exert a profound and pervasive influence on risk for anxiety disorders. How such approaches have been applied to understanding the role of the glutamate system in anxiety will be discussed.

S-09-003
Targeting metabotropic glutamate receptors: Evidence to support pharmacological validation in anxiety and stress disorders

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Objectives: As glutamatergic system may play an important role in pathophysiology of both depression and anxiety, it is important to show the recent data on possible anxiolytic and/or antidepressant effects of metabotropic glutamate (mGlu) receptor ligands. Preclinical data indicated that antagonists of group I mGlu receptors, particularly antagonists of mGlu5 receptors, produced both anxiolytic-like and antidepressant-like effects. Several lines of evidence suggest that mGlu5 receptor antagonists reduce NMDA receptor function in the brain. The inhibition of mGlu5 receptors may lead to a decrease in NMDA receptor-mediated neurotransmission, producing a final effect similar to that evoked by NMDA receptor antagonists, which are known to display antidepressant-like activity at the preclinical and the clinical (ketamine) level. Clinical data also demonstrated that mGlu5 receptor antagonist, fenobam, was an active anxiolytic drug. Among all mGlu receptor ligands, group II mGlu receptor agonists seem to be drugs with promising therapeutic potential and good safety profile. Animal studies showed anxiolytic-like effects of group II mGlu receptor agonists. Currently, group II mGlu receptor agonists are in phase II clinical trials for potential treatment of anxiety disorders. On the other hand, data have been accumulated indicating that antagonists of group II mGlu receptors have an antidepressant potential. Group III mGlu receptor ligands represent the least investigated group of mGlu receptors. However, preclinical data also indicated that ligands of these receptors, both agonists and antagonists, may have an anxiolytic- and antidepressant-like potential. For the group III mGlu receptor agonists, reduced glutamate release might account for the biological effects of these agent. Also clinically used antidepressant drugs have been shown to reduce glutamate release in the brain. However, other mechanisms of group III mGlu receptors activation, including heterosynaptic inhibition of GABAergic neurotransmission and control of serotonin release cannot be ruled out as mechanisms of their antidepressant/anxiolytic effects.

S-09-004
Targeting ionotropic glutamate receptors: Therapeutic rationale in anxiety and stress disorders

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Objectives: Current pharmacological therapy of anxiety includes benzodiazepines (BDZ) affecting GABAA receptors or selective serotonin reuptake inhibitors (SSRI), which are also widely used for depression. This diversity does not ensure freedom of side-effects during treatment of these disorders. The main problem with BDZ are tolerance, sedation and abuse potential. SSRI produce. weight gain and sexual dysfunction, shortcomings in efficacy as well as a delayed onset of action. These shortcomings justify the search for new treatments for anxiety and stress-related disorders like PTSD and depression. Antagonism of NMDA receptors has gained interest after finding that central administration of AP7 produces anxliolytic-like effects. Similarly, the use of NMDA antagonists for depression has been proposed two decades ago, but so far no treatment has reached the market.
Results: Anxiolytic effects of NMDA antagonists, acting at different recognition sites, such as the competitive site, glycineB site, channel blockers or polyamine site, have been studies, mostly showing a positive action. However, our own experience rather points out to an inconsistency of the results For AMPA modulators, the available data are even more limited. In the case of depression, our preclinical date provide modest, test dependent support for antidepressive effect of NMDA antagonists only, and in fact clinical trials with memantine have shown conflicting results.

Conclusions: Taken together, these results will be discussed, as well as the potential value of ionotropic receptor modulators in depression and PTSD. In the author's opinion there is little convincing evidence that ionotropic glutamate receptor modulators display therapeutically useful anxiolytic or antidepressive properties in man. In fact, such activity has not been consistently described so far for NMDA or AMPA antagonists in clinical use, such as memantine or topiramate respectively. In the case of PTSD, pre-clinical and clinical data has been encouraging albeit limited.

S-17
Translational neuroscience may inform treatment development for posttraumatic stress disorder

S-17-001
Early postnatal stress: Impact on neural circuits and relevance to psychophysiology

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Objectives: Traumatic events during early life may precipitate long-lasting alterations in the functional properties underlying emotional expression that are attributable to the pathophysiology of stress-related disorders. In this symposium, we summarize our recent work elucidating whether early postnatal stress alters the neural circuits associated with fear memory, using electrophysiological approaches combined with behavioral analysis.
Methods: Rats exposed to footshock (FS) stress during the second (2W) or the third (3W) postnatal week were subjected to contextual fear conditioning (CFC), an animal model of anxiety, at the postadolescent period (10 to 12 weeks).
Results: Fear-related freezing behavior during exposure to CFC was markedly attenuated in the 2W-FS group, presumably due to disturbance of the retention and/or consolidation of fear memory, an effect that was attributable to synaptic transmission in the hippocampal CA1 field. Aversive stress exposure at the third postnatal week (3W-FS) impaired extinction of context-dependent fear memory evaluating by expression of freezing, which appears to be associated with dysfunction of hippocampal-medial prefrontal cortex circuits. Thus, the altered behavior observed at the postadolescent period seems to be the result of neurodevelopmental perturbations elicited by early life stress, in turn, a "critical period" exists in development of neural system underlying emotional expression. Furthermore, the decreased attenuation of freezing behavior observed in 3W-FS was abolished by repeated treatment with either the partial N-methyl-D-aspartate receptor agonist D-cycloserine or the serotonin 1A receptor agonist tandospirone.
Conclusions: Considering similarity between fear extinction training in animals and exposure psychotherapy in humans, these pharmacological interventions may have clinical significance in the treatment of anxiety-related disorders, such as posttraumatic stress disorder (PTSD). In other words, a better understanding of the neural mechanisms of extinction deficits caused by early postnatal stress could help to clarify the pathophysiology of PTSD in which fear extinction is compromised.

S-17-002
Long term alterations in brain and neurobiology in PTSD

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Objectives: Brain areas involved in the stress response include the medial prefrontal cortex, hippocampus and amygdala. Neurohormonal systems that act on brain areas to modulate PTSD symptoms and memory include glucocorticoids and norepinephrine. Dysfunction of these brain areas is responsible for symptoms of PTSD.
Methods: Brain imaging studies show that PTSD patients have increased amygdala reactivity during fear acquisition. Other studies show smaller hippocampal volume. A failure of medial prefrontal/anterior cingulate activation with re-experiencing of the trauma is hypothesized to represent a neural correlate of the failure of extinction seen in PTSD.
Results: The brain has the capacity for plasticity in the aftermath of traumatic stress. Antidepressant treatments and changes in environment can reverse the effects of stress on hippocampal neurogenesis. In humans with PTSD paroxetine increases hippocampal volume and improves memory function in conjunction with improving PTSD symptoms. Phenytoin, which blocks the effects of stress on the hippocampus in animal studies, also increases hippocampal volume in PTSD patients.
Conclusions: Future studies should use brain imaging and neurobiology to assess plasticity in PTSD, preferrably in true prospective designs, or in relation to treatment. These can include both functional neuroimaging and neuroreceptor imaging to track the course of change during treatment, or to predict which traumatized individuals will develop (chronic) PTSD. The information from such studies will provide valuable information that will guide the development of new treatments.

S-17-003
Mechanisms of resilience: Lessons from PET imaging

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Objectives: There exists an increasing body of research on psychosocial factors associated with resistance to severe trauma. The neurobiological mechanisms that contribute to the ability of many people to adapt with minimal life disruption after the exposure to sever trauma is yet not fully understood. Even though animal studies suggest an important role for the serotonin (5-HT) type 1B receptor in the response to severe inescapable stress it is not clear at all whether such models constitute relevant models for stress response in humans. The selective 5-HT1B receptor radioligand, [11C]P943, a selective, high affinity 5-HT1B receptor antagonist, permits for the first time in vivo assessment of central 5-HT1B receptor binding using positron emission tomography (PET).
Methods: We studied healthy controls without trauma exposure and healthy controls who had experienced severe trauma but did not develop psychiatric symptoms. Following a transmission scan, [11C]P943 was injected by pump over one min and high resolution research tomograph (HRRT) list mode data were acquired for 120 minutes.
Results: Trauma-exposed healthy controls relative to non-traumatized controls show a downregulation of 5-HT1B receptor expression in a cortico-striatal-limbic circuit that has been consistently implicated in PTSD.
Conclusions: Compensatory downregulation of 5-HT1B receptors among trauma-exposed healthy controls leads to improved 5-HT transmission which allows the chemical signal (5-HT) to restore the affective/anxiety circuitry and prevents symptom development after severe trauma. Serotonergic and non-serotonergic mechanisms mediate these effects.

S-17-004
Neurobiology of suicidal behavior in PTSD and implications for suicide prevention

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Objectives: To review and discuss the role of neurobiological factors in the pathophysiology of suicidal behavior in posttraumatic stress disorder (PTSD).
Methods: A comprehensive review of the scientific literature on the neurobiology of suicidal behavior in PTSD and the role of biological treatments in suicide prevention in patients with PTSD has been carried out. A new concept related to the comorbidity of PTSD and major depressive disorder (MDD) has been developed.

Results: Multiple neurobiological factors including serotonin, glutamate, gamma-aminobutyric acid, norepinephrine, neuropeptide Y, corticotrophin-releasing hormone, dopamine, opioids, and thyroid hormones are involved in the pathophysiology of PTSD. PTSD is associated with suicidal behavior. Serotonergic and hypothalamic-pituitary adrenal (HPA) axis abnormalities are associated with both PTSD and suicidal behavior and may underlie both conditions. PTSD is frequently comorbid with MDD. I have previously proposed that some or all individuals diagnosed with comorbid PTSD and MDD have a separate psychobiological condition that can be termed "post-traumatic mood disorder" (PTMD) (Sher L. The concept of post-traumatic mood disorder. Medical Hypotheses, 2005;65(2):205-210). PTMD (i.e., a combination of PTSD and MDD) is associated with higher suicidality compared to PTSD alone or MDD alone. This increased suicidality may be related to neurobiological differences between PTMD and PTSD alone or MDD alone.
Conclusions: Prevention of suicidal behavior in individuals with PTSD should include biological treatments of both PTSD and comorbid conditions. Medications affecting the serotonergic system may reduce symptoms of PTSD, treat comorbid conditions, such as MDD, and reduce suicidality. Medications affecting the HPA system might potentially have a beneficial effect on individuals with PTSD and suicidal behavior. Suicidal behavior in patients with PTSD is an underestimated and understudied problem. Studies of the neurobiology, treatment and prevention of suicidal ideation and behavior in PTSD are merited.

S-25
Peripheral and central mechanisms involved in post-traumatic stress disorder and its treatment

S-25-001
Translational research in the neuroscience of fear extinction: Implications to PTSD and other anxiety disorders

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Some people adapt well in the aftermath of traumatic events and are quickly able to inhibit their fear responses to trauma-associated stimuli. Fear responses, however, persist for longer periods of time for others to the point where they reach a pathological state. Why are some people more resilient to trauma while others are not? What are the neural substrates that underlie fear inhibition and extinction? Are these circuits deficient in patients with anxiety disorders? In my talk, I will focus on presenting translational data from the rat and human brains with the objective of trying to provide some preliminary answers to the above stated questions. Specifically, I will review human studies indicating that prefrontal areas homologous to those critical for extinction in rats. Furthermore, I will present some data to show that those brain regions in the rat brain appear to be structurally and functionally homologous to specific brain regions in the human brain. I will also show some data suggesting that these brain regions, the ventromedial prefrontal cortex (vmPFC) and the dorsal anterior cingulate cortex (dACC), appear to be deficient in patients with posttraumatic stress disorder (PTSD). I will present some structural and functional neuroimaging and psychophysiological studies done in our lab that focused on the neural mechanisms of fear extinction, particularly extinction recall and the contextual modulation of extinction recall. These recent studies suggest that: 1) human vmPFC is involved in the recall of extinction memory; 2) the size of the vmPFC might explain individual differences in the ability to modulate fear among humans; 3) hippocampal activation is observed during the recall of extinction memory in a context where extinction training took place but not in the initial conditioning context; 4) and the dACC may be involved in the expression of fear responses. I will also present recent neuroimaging and psychophysiological data from PTSD patients suggesting that 1) the retention of extinction memory is impaired in PTSD, and 2) the function of the vmPFC and dACC (measured by fMRI) appears to be impaired in PTSD in the context of fear extinction. Implications of these findings to the pathophysiology of anxiety disorders such as PTSD and current extinction-based behavioral therapies for anxiety disorders will be discussed.

S-25-002
Variability of symptoms in daily life of patients with PTSD

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Objectives: Posttraumatic stress disorder (PTSD) is characterized by recurrent phases of acute anxiety, including bodily symptoms of anxiety (BSA). Thus, variability of BSA is a core feature of PTSD. Previous research has almost exclusively focused on the assessment of symptom severity, while a systematic assessment regarding variability of BSA is lacking. The aim of the present study was to validate the diagnostic criterion of recurrent BSA and to quantify variability of BSA in PTSD in comparison to a panic disorder control group in the daily life of patients. Furthermore, we attempted to determine the degree to which symptom variability differs from the concept of symptom severity.
Methods: Using electronic diaries we examined BSA variability (i.e. RMSSD of BSA) and severity (i.e. the average number of BSA) in the daily life of 17 PTSD patients, 26 PD patients, and 28 healthy controls (HC) during one week.
Results: Compared to HC, patient groups exhibited elevated variability of BSA, which was more pronounced in PTSD than PD ($p<0.005$). The same pattern was found for symptom severity. In PTSD, severity was unrelated to variability of BSA and in PD, BSA variability and severity were only loosely coupled. Additionally, we found that in PTSD and PD, numbers of symptomatic episodes were comparable but the duration of symptom-free episodes was shorter in PTSD than PD.
Conclusions: The results confirm the need for distinguishing between the concepts of symptom variability and severity. Further, they indicate that in daily life, PTSD patients are particularly burdened by somatic symptoms of anxiety. It has been demonstrated that ecological momentary assessment of symptom variability is a useful approach, which provides new insights into the phenomenology of PTSD.

S-25-003
Update on biopsychological correlates and predispositions of PTSD and its successful CBT treatment

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Objectives: Current models of PTSD postulate that biopsychological factors are involved in the aetiology and maintenance of the disorder. There is also an accumulating body of research that there may also be predisposing biopsychological factors such as volume reductions in corticolimbic brain areas. The aim of this talk is to outline how these can interact with PTSD severity and successful treatment.
Methods: In 110 treatment-seeking survivors of motor vehicle accidents (MVAs), the association between psychophysiological correlates of PTSD, of its CBT treatment and genetic polymorphisms that indicate altered serotonergic (5HTTLPR, 5HT1A) and dopaminergic (DAT) neurotransmission or that are associated with impaired memory function and fear retention (BDNF ValMet) have been assessed. Associations were investigated in a cross-sectional between-group design and a randomized controlled CBT vs. waitlist trial.
Results: The results point to a pattern of increased heart rate, frontal P300 amplitude and EEG alpha asymmetry to trauma-related stimuli which was closely associated with the PTSD severity and thus the treatment outcome. Also, there was no evidence for a higher percentage of s allele carriers in the PTSD group. On the other hand, contrary to our hypothesis, startle EMG and ERP (P200) were not related to PTSD and treatment outcome but to the short variant of the 5HTTLPR. Interindividual differences in ERP components to the startle sound (N100, P200, P300) were also observed for the 5HT1A, DAT and BDNF ValMet polymorphisms whereas these polymorphisms were not associated with PTSD. Only for the 5HTTLPR there was a significant treatment effect: carriers of the s-allele responded significantly less well to CBT than l-allele carriers.
Conclusions: Some physiological variables may indicate acquired aversive responses (e.g. conditioned fear) which are no longer present after successful CBT, whereas others may represent a biopsychological predisposition for generally increased physiological reactivity and response to treatment.

S-25-004
Fear conditioning/extinction in PTSD before and after treatment

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Objectives: The post traumatic stress disorder (PTSD) is an anxiety disorder that occurs after exposure to a trauma: usually involving actual or threatened death or serious injury to self or others, and provoking feelings of intense fear, helplessness or horror. It has high prevalence lifetime rates (8-10% in the USA) and important comorbidities (87% associated depression, anxiety, addictions…). The prevailing hypothesis is that PTSD patients have a deficiency in their capability to extinguish fear after conditioning to a fearful stimulus (Francati et al., 2007; Blechert et al., 2007). The fear conditioning and extinction model seems a suitable one to mimic the PTSD dysfunctions. Our study aims at exploring the peripheral mechanisms involved in fear Conditioning/Extinction paradigm in PTSD, both before and after one of its treatment options PTSD (Eye Movement Desensitization and Reprocessing (EMDR)).
Methods: 20 PTSD patients and 20 controls (matched for age, sex and educational level) were evaluated, both before and after therapy, for their PTSD symptoms. They also performed the classical fear conditioning/extinction task. Two-way repeated measures ANOVAs with Population as a between factor and Treatment as a within factor were used to analyze these data.
Results: Our results show that after EMDR therapy, patients' scores on all PTSD scales significantly decreased from pathological to normal standards. Most comorbid disorders faded. As expected, before therapy, patients more easily conditioned to fearful stimulus and resisted its extinction as evidenced by electrodermal conductance responses and subjects ratings. After therapy PTSD responses to fear conditioning/extinction paradigm were comparable to those of controls.
Conclusions: Psychophysiological impairments in PTSD patients might be represented as such by atypical peripheral responses to the fear Conditioning/Extinction paradigm that disappear after therapy. The mechanisms involved in this paradigm might thus be at the core of PTSD symptoms and should be further explored at the central level.

S-40
New insight into panic disorder

S-40-001
Perspectives in research and treatment of panic disorder

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S-40-002
Challenge tests

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Objectives: Challenge tests with panic-inducing agents offer unique opportunities to reproduce the phenomena of panic attacks for scientific scrutiny. The criteria for optimal panicogenic properties were formulated to set standards for such agents in respect to their safety, reliability, specificity and clinical predictive value. The key lessons from panic challenge studies and directions in their use will be summarized.
Methods: A review of effective challenge agents and trends in their applications to human research on panic attacks and related markers was conducted. The examined panicogens were clustered by their putative principal mode of action as metabolic (sodium lactate and hyperosmotics), respiratory (carbon dioxide, doxapram) and other (caffeine) stimulants, noradrenergic (yohimbine, isoproterenol), serotonergic (fenfluramine, mCPP), GABA-ergic (flumazenil) and CCK-ergic (CCK-4, pentagastrin).
Results: Use of challenge tests surged in 1980-ies, peaked in 1990-ies and plateaued in current decade. The emphasis on ideal panic replication model has shifted to searching for meaningful correlates and validation of anxiolytics, including investigational and novel treatments. Several concepts, such as respiratory sensitivity, suffocation alarm, serotonin dysregulation and CCK hypothesis of panic disorder have emerged largely based on challenge data. Brain metabolic and activation responses to laboratory panic have advanced the knowledge on neuronal circuitry of panic attacks. Combined challenge methods have been used to test specific hypotheses. Genetic and psychological susceptibility to panic induction are also being explored.
Conclusions: Three decades of panic challenge studies have contributed rich data on neurochemical, behavioural, physiological and endocrine facets of panic attacks. However, some of the findings are contradictory and difficult to replicate. Research on healthy volunteers may not fully reflect patogenetic and treatment aspects of panic disorder. The promises of challenge tests as diagnostic and assessment tools or aids in antipanic drug development remain hindered by their heterogeneity and methodological issues.

S-40-003
Genetics of panic disorder: New evidences

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Objectives: Panic disorder is a common, heritable psychiatric disorder whose genetic basis has remained elusive. Genetic linkage and candidate gene studies have provided some leads, but without any widely-accepted findings. Genome-wide association studies offer the promise of identifying genetic risk factors without many of the limitations of linkage or candidate gene studies. We are performing a genome-wide association study of panic disorder using DNA samples previously collected by 14 collaborating groups.
Methods: Participants were recruited either as cases, when they had been diagnosed with panic disorder or related conditions, or as healthy controls, when they did not carry such a diagnosis. Equimolar aliquots of DNA from each subject have been combined in pools of 30-50 subjects each, on the basis of contributing site, case/control status, and gender, and are being genotyped on an array containing approximately 610,000 single-nucleotide polymorphisms. Data will be analyzed using meta-analytic methods that consider site and gender to identify relatively consistent association signals. After analysis, a set of 50-100 of the best markers will be genotyped on the individual samples.
Results: We will present the results of our initial analyses in European and European-American samples.
Conclusions: At the conclusion of the study, allele frequency data from the DNA pools will be published and made available to interested investigators, along with information on the summary allele frequencies and statistical results on individually-genotyped markers.

S-40-004
Neuroimaging of panic disorder

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Objectives: There is a pressing need to specify the neurobiological substrate underlying the onset and development of panic disorder (PD). The brain imaging studies have provided further evidence of neuroanatomical substrates involved in PD. The structural brain abnormalities observed in patients with PD include increased ventricle-brain ratios in computed tomography, and focal abnormalities in the temporal area with an increased atrophy in magnetic resonance imaging (Fontaine et al., 1990; Vythilingam et al., 2000). The positron emission tomography (PET) and the single photon emission computed tomography (SPECT) studies in PD have demonstrated variations of functional activity in the various brain structures (Eren et al., 2003; Fischer et al., 1998; Meyer et al., 2000). Several SPECT and PET studies showed also reduced 5-HT1A receptor and benzodiazepine receptor binding in several brain regions in PD patients (Kuikka et al., 1995; Malizia et al., 1998; Nash et al, 2008). Recently, we performed a SPECT study of the functional activity of 5-HT transporter (5-HTT) in PD using radioligand [123I]nor-β-CIT (Maron et al, 2004a).

The results of this study showed that the patients with current PD had significantly lower 5-HTT binding in the midbrain raphe, in the temporal lobes, and in the thalamus than the healthy controls. The patients with PD in remission had normal 5-HTT-binding properties in the midbrain and in the temporal regions, but still a significantly lower thalamic 5-HTT binding. In order to replicate our findings we aimed to investigate of brain 5-HTT bindings, using PET scans and highly selective and specific tracer for 5-HTT, [11C]MADAM, in new sample of PD patients of both genders. Secondly, we examined the possible predicative effect of 5-HTT bindings on the treatment response to 12 weeks medication with escitalopram. The results of this PET study and its possible implication could be presented.

S-53
Neurobiological correlates of dissociation and influence on information processing in stress-related disorders

S-53-001
Neural correlates of dissociation in patients with posttraumatic stress disorder

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Objectives: The neural mechanisms underlying dissociation have become an increasing focus in the neuropsychiatric literature. It is crucial that we achieve greater understanding of the neural networks underlying dissociation in order to help develop more precise diagnostic categories in trauma-related disorders as well as to permit the development of more sophisticated treatment strategies. Dissociation typically involves a disruption in the usually integrated function of consciousness, memory, identity, body awareness, and/or perception of the environment.
Methods: We reviewed the literature on the neurobiology of dissociation and trauma disorders obtained through a PubMed search dating back to 1950. In addition, we reviewed primary book sources on the topic of dissociation.
Results: Neuroimaging studies demonstrate altered levels of brain activation during dissociative phenomena that play an essential role in emotion and autonomic nervous system regulation, sensory processing, attention and memory. In particular, dissociation reflects frontal inhibition of limbic and other temporal lobe structures. Also, studies have shown unique brain activation patterns in PTSD patients with and without major dissociative symptoms. Moreover, dissociative states can be triggered by several classes of neurochemicals, including serotonergic hallucinogens, NMDA antagonists, and opioid agonists, acting through the hippocampus and other brain areas involved in memory and emotion. Studies of soldiers undergoing high stress military training show that those with high levels of dissociative symptoms differ in levels of neuropeptide Y and DHEA from those with low levels of dissociative symptoms. The literature suggests a pattern of HPA-axis dysregulation in dissociative disorders as compared to non-dissociative PTSD that involves tonic hyperactivation of cortisol, reduced feedback inhibition and reduced phasic secretion of cortisol under conditions of acute stress.
Conclusions: Recently, there have been major advances in our understanding of the neural underpinnings of dissociative responses in PTSD and dissociative disorders, the nature of pharmacologically-induced dissociation, and as well as the regulation of the HPA axis in disorders involving dissociative symptomatology.

S-53-002
The neural correlates of emotional distraction during working memory performance in traumatized patients with borderline personality disorder

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Objectives: Emotional dysregulation is a core problem in Borderline Personality Disorder (BPD), including emotional hyperreactivity (Linehan et al., 2007), which has been associated with amygdala hyperresponsiveness. Whereas current theories of BPD emphasize the disruptive potential of negative emotions on cognition (Fertuck et al. 2006), behavioral and neuro-biological data on the impact of emotion on cognitive functioning in BPD patients are still lacking.
Methods: Using functional magnetic resonance imaging (fMRI, 3T) neural activity was assessed in BPD patients and healthy control subjects (HC) performing a Sternberg working memory task, while being distracted by task-irrelevant emotional and neutral pictures (see Oei et al., submitted). Participants included 18 unmedicated BPD patients (with a history of interpersonal trauma) and 18 HC matched for age, education and IQ.
Results: rm ANOVAs on behavioural pilot data showed longer reaction times on working memory performance when emotional distractors are presented compared to neutral distractors. This was specified by a significant group x condition interaction, indicating that the slowing effect on working memory performance by emotional distractors was more pronounced for BPD patients compared to controls, especially in BPD patients with dissociative symptoms. The neural correlates associated with the presentation of emotional distractors during WM in BPD patients will be analysed in the next few months.
Conclusions: These findings are in line with the hypothesis that hyperresponsiveness to emotional distracting stimuli negatively affects cognitive functioning in BPD patients. Knowledge about brain structures involved in the inability to inhibit emotional distraction may help to tailor interventions aimed at reducing emotional hyperresponsiveness in BPD patients.

S-53-003
Influence of dissociation on information processing in stress-related disorders

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Objectives: We recently conducted two aversive differential delay conditioning studies in unmedicated patients with borderline personality disorder (BPD) and healthy controls to examine learning processes and impact of acute dissociation. A significant reduction of emotional learning processes during dissociation in BPD (skin conductance response and valence ratings) as well as altered neurobiological activation patterns could be shown. As these were post-hoc analyses, further studies will focus on alterations in learning during induced dissociative states by the script-driven imagery technique. The current study therefore aimed to investigate the validity of this technique to induce dissociation in BPD as well as neurobiological activation pattern during induced dissociation in BPD.
Methods: To investigate dissociative states under experimental conditions, we used the script-driven imagery technique. 15 unmedicated BPD patients were investigated during fMRI. Neutral and dissociation-associated autobiographic scripts were both presented three times. We had three main outcome measures: 1.) intensity of the dissociative states and aversive inner tension experienced during the script-presentations, 2.) pain sensitivity after script-presentations and 3.) fMRI signal changes.
Results: After the dissociation-associated scripts, dissociation scores were significantly higher as compared to the neutral scripts and pain sensitivity was significantly lower. On a neural level, we found increased inferior frontal activity during the dissociation-associated as compared to the neutral script. In a regression analysis we found a positive correlation between dissociation and activation of the superior frontal gyrus and a negative correlation with the inferior and middle temporal gyrus. Regression analyses of patients with comorbid posttraumatic stress disorder revealed a negative correlation in the right parahippocampal gyrus. Measures of stress had no influence on these results.

Conclusions: Script-driven imagery reliably induced dissociation in BPD patients. Our data support previous neural models of dissociation as well as our own findings. Further studies will focus on alterations in learning and memory processes during induced dissociative states.

S-53-004
Neural correlates of dissociation in patients with borderline personality disorder

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S-60
Disaster follow-up: International perspectives

S-60-001
9/11 – American insights

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S-60-002
1999 earthquake in Turkey – the lessons from a seven year follow-up

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Objectives: To follow-up 564 earthquake victims longitidunally for PTSD
Methods: Subjects were rated by a PTSD scale 1-3 months, 6-8 months, 18-20 months and 9 years after the event.
Results: PTSD prevalance was 31 % after 1-3 months, 26.5 % after 6-8 months, 9.5 % after 18-20 months and 8.5 % after 9 years. PTSD criteria were met at least once by 50.1 % of females and by 37.3 % of male subjects. 4 subjects presented PTSD as late onset 9 years after the at the 4th time point. There was large increase in missing data at the 4th time as expected.
Conclusions: PTSD is a chronic disorder which continues for a long time. Effective intervention studies are needed for treatmnet.

S-60-003
Tsunami 2004 – retrospective introspection

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Objectives: We know about the implications of the events that follow disasters but Tsunami is a very rare experience. So, we wanted to know the sequences and the consequences that follow this disaster.
Methods: The events thay happened following this disaster is explained from our experience and from other sources. The reported and experienced PTSDs are discussed. Of late we have been seeing sporadic cases of psychological and psychiatric problems.The post-tsunami life style and living conditions of the affected are described.
Results: The PTSD following the Tsunami is not very glaring. Life style and attitude are definitely different. More of substance abuse were reported. More absenteeism was noted. For some, life style improved. Schooling increased. Depressive cases are now reporting with difficulties in management.
Conclusions: Occurrence of PTSD immediately after the tsunami is not alarming. The relief measures and hopes given by the international and national agencies influenced the outcome and has a bearing on the recovery. Some peculiar cultural values are influencing the recent reported cases.

S-60-004
Can PTSD be prevented?

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Objectives: The concept of "golden hours" in internal medicine highlights the "window of opportunity" that exists immediately after trauma for preventing further damage. Since PTSD develops after a specific trauma, there may be a window of opportunity to intervene and prevent its development.
Methods: The challenge is to find out if and what type of early intervention during the ‚window of opportunity' – the time from exposure until PTSD develops – is effective for those at a high risk of developing PTSD.
Results: Cortisol – the "stress hormone" is a cornerstone in the normal response to traumatic events. An animal model using rats with hyper-reactive HPA axis (the Fischer strain), or hypo-reactive (the Lewis strain), showed that plasticity of the HPA axis is critical for recovery from a traumatic event. It was also found that the normal hyper-secretion of cortisol following exposure to a traumatic event was associated with a reduction in the amplitude of the memory-fear associated with the exposure. This could explain why benzodiazepines, which decrease cortisol secretion, might be associated with less recovery compared to individuals who did not get BNZ. Early administration of BNZ was associated with exaggerated response to traumatic cues in rats. Moreover, it is also suggested that early administration of cortisol might be a potential prevention strategy in individuals exposed to traumatic events. A PTSD animal model of early administration of SSRI suggests that it is useful in reducing prevalence of PTSD later on. These studies led to a human PTSD prevention study, in which SSRI administration is started right after the exposure.
Conclusions: The complex interaction between memory, PTSD, intervention during the "window of opportunity" and long-term consequences could be explored systematically in an animal model, and then be implemented clinically. There are currently a couple of clinical studies examining innovative interventions based on insight gained from animal studies.

S-68
The cortical-striatal network in obsessive-compulsive disorder and depression

S-68-001
Limbic-prefrontal control is improved in paroxetine responders, but the ventral striatum is also involved in SSRI-response

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Objectives: Dysregulations within the cortico-striatal and cortico-limbic networks may be important in the pathophysiology of major depressive disorder (MDD). Amygdala hyperactivation has often been demonstrated in MDD and this is altered in response to treatment. Additionally, Deep Brain Stimulation of the ventral striatum has been reported to improve depressive symptoms and anhedonia. To explore the role of these networks in MDD, we will discuss results from our functional Magnetic Resonance Imaging (fMRI) study on brain activity in response to pharmacological treatment.
Methods: In an event-related fMRI study 22 patients with MDD were scanned before, during and after 12 weeks of paroxetine treatment. The fMRI paradigm consisted of sex-judgments of fearful, angry, happy and neutral faces, relative to scrambled (baseline) faces. Twenty-one age- and sex-matched healthy controls (HC) were scanned once as reference. Correlations were calculated between changes in brain activity and changes on the Hamilton Depression Rating Scale (HDRS17).
Results: At study-entry, MDD-patients showed increased limbic (amygdala and insula) and decreased cortical activations relative to HC. With all and angry/fearful faces contrasts, treatment response was associated with decreased activations in amygdala, right insula and orbitofrontal cortex, and increased activation in dorsolateral prefrontal cortex, parietal cortex and ventral striatum. With happy faces, no difference in VS was observed. Amygdala activation was inversely correlated with increased pregenual cingulate and dorsolateral prefrontal cortex activation and with improvement using the HDRS17.

Conclusions: Improvement of MDD by paroxetine is associated with increased fronto-limbic control. Decreased amygdala activation by negative faces could be a biomarker for clinical response to antidepressants, but needs further exploration in other MDD-treatments. The ventral striatum might be deactivated less in treatment responders, indicative of improved resilience to expected loss. Reward processing in MDD needs further investigation.

S-68-002
The effects of ventral capsule/ventral striatum stimulation in depression

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Objectives: The ventral capsule/ventral striatum is a potential site for neuromodulation given its important role in the cortico-striatal-thalamo-cortical (CSTC) network. Evidence suggests a role for this network in obsessive-compulsive disorder (OCD) and major depressive disorder (MDD). Studies of deep brain stimulation (DBS) in this area for severe OCD by our group, and others, found significant benefit. In addition to improved OCD symptoms, patients also had significant improvement in mood. A study of DBS utilizing the VC/VS was then undertaken in highly treatment refractory patients.
Methods: 17 patients at three collaborating centers underwent DBS of the VC/VS. All patients were refractory to multiple medication trials, psychotherapy, and bilateral ECT. Stimulation was titrated to therapeutic benefit and the absence of adverse effects. DBS was continuous and delivered in an open-label fashion. Outcomes were measured using multiple scales including the Montgomery-Asberg Depression Rating Scale (MADRS), the Hamilton Depression Rating Scale (HDRS-24), and the Global Assessment of Function Scale (GAF).
Results: Patients enrolled were highly refractory with over 6 trials of antidepressants and an additional 6 augmentation/combination trials in their current episode. 15 of 17 received and adequate trial of bilateral ECT in the current episode. Average age at implant was 46.3 years with a 21.0 year mean duration of illness. All were followed for over a year. MADRS scores were reduced by 52.7% at 3 months, 48.8% at 6 months, 54.8% at 1 year, and 59.2% at last follow-up. Responder rates at the same time points were 53%, 47%, 53%, and 71% respectively. Functionality showed significant improvement in the group. Neuropsychological testing showed no differences at 6 months. Suicidality measures improved at 1 month. Overall, DBS was well tolerated. There was one completed suicide during the course of the study.
Conclusions: DBS of the VC/VS demonstrated some initial promise for the treatment of highly refractory MDD.

S-68-003
Imaging neurotransmission in the cortical-striatal network of OCD

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Objectives: It is well accepted that the cortico-striatal-thalamo-cortical (CSTC) circuit plays a pivotal role in the pathophysiology of obsessive-compulsive disorder (OCD). The CSTC is heavily endowed with serotonin, dopamine, noradrenalin, glutamate and GABA neurotransmitters, which have been shown to be involved in the therapeutic efficacy of OCD as well. The aim of this presentation is to explore the involvement of serotonergic, dopaminergic and glutaminergic neurotransmission of the CSTC circuit in OCD.
Methods: A systematic literature search was carried out for all imaging studies on neurotransmission in OCD, that have used single photon emission computed tomography (SPECT), positron emission tomography (PET) and magnetic resonance spectroscopy (MRS). Results of new studies will be presented, combining PET imaging and dopaminergic modulation in OCD patients. Findings will be combined into a pathophysiological model for dysfunctional neurotransmission in OCD.
Results: Results from SPECT and PET studies suggest that OCD is related to diminished serotonergic input into the frontosubcortical circuits, along with dopaminergic hyperactivity in striatum. MRS studies demonstrate an association between OCD and elevated striatal caudate levels. Improvement of obsessions and compulsions in response to serotonin reuptake blockade is related to normalization of dopaminergic and glutaminergic hyperactivity. Amphetamine-induced dopamine release in striatum was not different between OCD patients and healthy controls.
Conclusions: Serotonergic deficits may be primary to OCD, causing secondary dopaminergic and glutaminergic abnormalities that can be successfully targeted in OCD treatment.

S-68-004
Disinhibition of frontal-striatal circuits in the compulsive-impulsive spectrum

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Objectives: Dysfunction of the cortico-striatal-thalamo-cortical (CSTC) circuit is involved in mediating the symptoms and cognitive deficits associated with the obsessive-compulsive disorder (OCD). However, this seems to be partly nonspecific. Many related disorders in the compulsive-impulsive spectrum show overlapping neuropsychological and neuronal features. In order to elucidate the function of the CSTC, we will bring together the psychiatric, neurological and addiction perspectives on the compulsive-impulsive spectrum of disorders.
Methods: Results from our own functional imaging studies will be discussed, examining important neuropsychological functions, such as emotion regulation, executive functioning, cognitive flexibility, and response inhibition in patients with OCD. Both functional and structural imaging studies will be presented. In order to describe the overlapping and differentiating features, I will also review neuroimaging research on other neuropsychiatric disorders within the impulse-compulsive spectrum, i.e., hypochondriasis, impulse control disorders in Parkinson's disease, pathological gambling and cocaine seeking behaviour.
Results: The most striking functional overlap between these related disorders is the inability to inhibit an urge or prepared response. This 'disinhibition' might be explained by an increased activation of the direct (relative to indirect) pathway of the 'limbic' or ventral frontal-striatal circuits in combination with decreased activation of the indirect (relative to direct) pathway in the dorsal frontal-striatal circuits.
Conclusions: Whereas there are large differences between disorders within the impulse-compulsive spectrum they share the focus on an imbalance within and between the CSTC as underlying substrate for the repetitive behaviours. I will discuss possibilities to modulate the function of the CSTC circuits using transcranial magnetic stimulation.

S-87
Recent advances in neuropharmacology of stress

S-87-001
Early life stress modifies the effects of 5-HT1A agonist, 8-OH-DPAT in animal tests of anxiety and depression

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Objectives: The purposes of the experiments were to investigate the effects of early life stress (social isolation from weaning) on anxiety and depression and to compare the behavior effects of the selective 5-HT1A receptor agonist, 8-hydroxy-2-(di-n-propylamino) tetralin (8-OH-DPAT) in isolation and socially reared rats.
Methods: Male Wistar rats (21 days of age) were reared either alone (isolation rearing) or in groups of six rats/cage (social rearing). After four weeks, these rats were tested for their sensitivity to 8-OH-DPAT using the rat elevated plus-maze and the forced swimming tests.

Results: The results from the plus-maze test showed that pretreatment of 8-OH-DPAT (0.05, 0.1 and 0.5 mg/kg s.c.) in both isolation and socially reared rats dose-dependently produced an anxiogenic profile, indicated by a decrease in the percentage of open arm entries and the percentage of time spent on the open arms. These effects of 8-0H-DPAT were more pronounced in isolation than socially reared rats ($P<0.05$). The results from the forced swimming test demonstrated that pretreatment with 8-OH-DPAT (0.1, 0.25, 0.5 and 1 mg/kg s.c., 24 h and 1 h before a 5 min test) in socially reared rats produced a dose-dependent reduction of immobility and elevation in struggling compared to the saline controls. Sub chronic administration of 8-OH-DPAT (0.5 mg/kg s.c. 24 h and 1 h before a 5 min test) significantly decreased immobility and increased struggling ($P<0.01$) in both isolation and socially reared rats compared to saline treated group. These effects were greater in isolation reared rats than socially reared rats.
Conclusions: These results indicate that social isolation stress from weaning modifies the behavioral effects of 5-HT1A agonist, 8-OH-DPAT, and that 5-HT1A receptors may be involved in anxiety and depression.

S-87-002
Early postnatal stress disturbs normal development of the serotonergic neurons in the raphe nuclei

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Objectives: Postnatal stresses such as maternal separation or inappropriate handling alter the serotonergic systems by regulating 5-HT receptors. Given the association with early postnatal stress and serotonergic systems, early life adversity might cause persistent changes in the 5-HT neurotransmission underlying emotional regulation. The aim of the present study was to assess whether traumatic events during the early postnatal period would affect the rat brain development of the serotonergic system underlying regulation of emotional expressions.
Methods: Pups were exposed to aversive footshock (FS) stimuli, at early postnatal period during the second week and the third week. At postadolescent period (10–12 weeks old), a behavioral study was undertaken to analyze the fear-related behavior. Immunohistochemical study was carried out to determine the 5-HT- and parvalbumin-immunoreactive cells in the rapne nuclei.
Results: Rats that had received aversive stimuli FS at the postnatal period of the third week, but not the second week, produced an abnormal behavior in open field test; the probability of central appearances was higher than that in control group. The number of 5-HT and GABA co-localized neurons in the raphe nuclei was significantly decreased by FS at 3 weeks old. Fluvoxamine treatment (10 mg/kg, p.o.) for 14 days immediately after the aversive stress normalized the behavioral patterns in open field test and the reduction of 5-HT/GABA contained neurons in the raphe nuclei.
Conclusions: These data suggest that aversive stress exposed at the third week disturbs normal development of the serotonergic neurons, and is attributable to the serotonergic function in the raphe nuclei underlying regulation of fear stress.

S-87-003
Pros and cons of stress on the development of social behavior

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Objectives: Among various stress, social one is crucial for an environmental factor leading to psychiatric disorders. However, it is very difficult to extract social stress effect on the disorder development. We, thus, wish to develop animal model and quantitative behavior analysis method tracking down the molecular and neuronal basis of the disorders.
Methods: 1) Rearing conditions; Domestic chickens were hatched in house and reared as a single or a group until the day of behavior test. Common marmosets were raised by their parents (as a single young (P1) or two peers (P2)), or a single by human (H1). 2) Behavior test (Fig.1);The behavior was video-recorded, analyzed on each behavior parameter, and correlated with its rearing condition by principle component analysis (PCA).
Results: 1) Among various behavior parameters, a combination of call-type (T-like,E-like, and ph in Fig. 2) and physical movements revealed the difference of social interaction of single young marmoset (P1 or H1) from P2 based on PCA. P2, P1, and H1 shared the area (Fig.2 area ⊖) in the space defined by PCA (10-dimensional), but P1 and H1 occupied also unique area (Fig. 2 area ⊜) not containing P2 behavior (white square). 2) Socially isolated chicks showed freeze or escape, but the grouped ones approaching behavior. Quantitative analysis showed the importance of mutual interaction. This point was investigated by 10-min interaction experience on food per day with socially isolated chicks. These chicks obtained social affiliation with no exception, but without any food the experience had no effect.
Conclusions: 1) Multi-dimensional behavior parameter analysis based on PCA was effective to extract the social trait related to social rearing conditions. This method can be applied to reveal the developmental difference of social interaction of psychiatric disorders especially in preschool children. 2) Social party was very effective to develop social affiliation in peer-relation. Furthermore SSRI treatment was effective even after critical period.

Fig.1 Context-dependent social interaction revealed importance of peer relationship

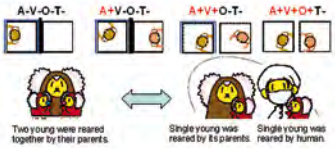
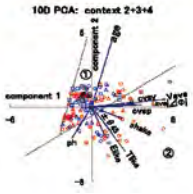


Fig.2 Principle component analysis (PCA) revealed unique behavior trait of young marmoset reared without peer relationship



S-87-004
Behavior recognition technology application in neuropharmacology of stress

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S-24
The possible role of Oxytocin as a key molecule in the new treatment and in the pathogenesis of autism-spectrum disorder

S-24-001
Introduction

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Objectives: The recent literature has showed an increasing attention on autism spectrum disorder (ASD). The number of individuals diagnosed with ASD has dramatically incresed as much as several times during the past decade, although the pathogenesis and treatment of disorder have not been clarified.
Methods: ASD is characterized in common by the dysfunctions of social reciprocity which is more evident among males to females (extreme male brain theory). ASD is much more common in males. Recently oxytocin, a female hormone, is proposed to act in enhancing social ability in human adults as well as in prairie vole.
Results: In this Symposium, clinical, basic and neuroimaging studies will substantiate the hypothesis that sexually dimorphic factors such as oxytocin may imply the dysfunctions in social reciprocity, abnormality of social brain regions and low probability in females, all seen in ASD individuals.
Conclusions: Taken together, the accumulating evidence suggests that oxytocin deserves to be examined as a candidate that causes the sexually dimorphic aspect of human social reciprocity, social brain development and the pathogenesis of ASD.

S-24-002
Possible animal model of autism

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Objectives: Oxytocin (OT), a neurohormone involved in reproduction, also plays a critical role in social behavior from rodents to humans. The role of CD38 in regulating OT secretion for social behavior has been demonstrated in adult mice, but not examined in infants or during development.
Methods: We examined separation stress-induced motor activity and ultrasonic vocalization (USV) in pups of both genotypes. We also measured plasma OT levels and demonstrated that postnatal 21-day (weaning time for mice) is a time window of differentiating plasma OT in CD38 control and knockout mice. We determined ADP-ribosyl cyclase activity in the developing brain (in the hypothalamus and posterior pituitary) and discuss its relationship with plasma OT level.
Results: Separation from the mouse dam induces stress in 7-day old pups. During such isolation, locomotor activity was higher in CD38 knockout (CD38-/-) pups than in wild-type controls (CD38+/+). The number of ultrasonic vocalization was lower in CD38-/- pups than in CD38+/+ pups. However, the difference between the two genotypes seems to be less severe than those in OT knockout or OT receptor knockout mice. To explain this, we measured plasma OT levels. The level was not lower in CD38-/- pups during the period from 1–3 weeks after birth, but was significantly reduced after weaning (≤3 weeks). ADP-ribosyl cyclase activities in the hypothalamus and pituitary were markedly lower from 1 week after birth in CD38-/- mice and were consistently lower thereafter to the adult stage (2 months old).
Conclusions: These results showed that the reduced severity of behavioral abnormalities in CD38-/- pups was due to partial compensation by the high level of plasma OT.

S-24-003
Neuroimage of autism: Neural basis of oxytocin

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Objectives: Since recent literature has argued to give up a single explanation covering diverse symptom defining autism-spectrum disorder (ASD), our study focuses on deficits in social cognition as the target of phenotype in searching cause for ASD.
Methods: First study revealed that the gray matter volume reductions in several regions important for social cognition were common to monozygotic twins with Asperger's syndrome as compared with healthy matched controls. The findings suggest a contribution of shared genetic factors to underlying the structural abnormalities in ASD. Second study showed that the young healthy females showed greater Cooperativeness as well as larger relative global and regional gray matter volumes than the matched males, particularly in the social-brain regions including posterior inferior frontal and anterior medial prefrontal cortices. Moreover, specifically in females, higher cooperativeness was tightly coupled with the larger relative total gray matter volume and more specifically with the regional gray matter volume in most of the regions revealing larger in female sex-dimorphism. These results suggest that sexually-dimorphic factors may affect the neurodevelopment of these "social-brain" regions, leading to higher cooperativeness in females. The findings may also have an implication for the pathophysiology of autism; characterized by severe dysfunction in social reciprocity, abnormalities in social-brain, and disproportionately low probability in females. Third study showed a gender specific relationship between a polymorphism of oxytocin-receptor gene and regional gray matter volume of inferior frontal gyrus in healthy young adults. Forth study demonstrates the correlation between smaller-than normal volume of posterior inferior frontal gyrus and worse function of social communication in the males with ASD compared with matched controls.
Conclusions: Furthermore, we would like to discuss the possibility of future study examining the relationship between oxytocin-induced enhancement of social cognition and polymorphisms of genes encoding oxytocin-related molecules using neuroimaging as endophenotypes.

S-24-004
Neural correlates of social cognition

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Objectives: Recent research has demonstrated that oxytocin is a key neurochemical mechanism for social behavior. In particular, oxytocin generally modulates social relationships through increasing the bonds between self and other (e.g., pair-bonding, trust). Oxytocin also has the effect of increasing mentalizing ability. Therefore, the neural systems underlying shared mentalizing representations between self and other are likely to be some of the targets where oxytocin modulates social behavior. We review the neural systems underlying shared representations of self and other and illustrate how such shared representations of self and other are integrated throughout the brain. Furthermore, we present data on autism spectrum conditions (ASC), showing that such neural systems are disrupted.
Methods: Functional neuroimaging (fMRI) and a functional connectivity approach was undertaken on 33 healthy adult males and 30 age, gender, and IQ matched adults with autism spectrum conditions (ASC). We assessed the whether shared neural systems for self- and other-mentalizing interact with the rest of the brain in a similar or different fashion.
Results: Both activation and connectivity results converge on the observation that mentalizing about the self and other recruits identical neural circuitry. Furthermore, the distribution of neural circuits for shared mentalizing overlaps with low level embodied/simulation-based neural circuits. Such results were not apparent in individuals with ASC. In particular, individuals with ASC had broad impairments in self-referential cognitive processing linked to ventromedial prefrontal cortex.
Conclusions: Mentalizing about the self and other recruit identical neural circuitry and such circuitry integrates low level embodied information with high level inference-based mechanisms. The disruption of such processes in ASC highlights the possible cause of social dysfunction in such individuals. Given the role of oxytocin as facilitating similar types of social processes, it is like that the neural circuits identified here are some of the circuits oxytocin is likely to work on.

S-31
ADHD in adults: Comorbidity aspects and the therapeutic issues

S-31-001
The 5-HTTLPR-S/s Genotype increases the risk for depression and anxiety disorders in youth with ADHD when exposed to parental depression: A gene-environment interaction study

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Objectives: Multiple studies have documented gene-environment interaction between the 5-HTTLPR short allele and psychosocial adversity in which individuals with the risk allele exposed to adversity had an increased risk for depression. Dr. Biederman's study examined whether similar gene-environment interaction can predict the development of depression in the context of attention-deficit/hyperactivity disorder (ADHD). We also investigated whether this gene-environment interaction was specific to depression or extended to other forms of psychopathology.
Methods: We compared rates of major depressive disorder (MDD) in children with ADHD stratified by the 5-HTTLPR genotype and psychosocial adversity. Psychosocial adversity was defined by low socioeconomic status, large family size, family conflict, exposure to maternal psychopathology, and exposure to parental major depression.
Results: Exposure to parental MDD selectively increased the risk for mood and anxiety disorders only in children with ADHD homozygous for the short risk allele (S/S) compared to offspring with the L/S and L/L genotypes (S/S=61%, S/L=32%, L/L=31%). In contrast, offspring with no exposure to parental MDD had no differences in rates of MDD by genotype (S/S=15%, S/L=23%, L/L=16%)
Conclusions: The 5-HTTLPR-S/S genotype appears to mediate the risk for mood and anxiety disorders in ADHD in youth when exposed to parental MDD.

S-31-002
Gender effect in response to methylphenidate treatment in adults with ADHD

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Objectives: This study evaluated sex effects in response to OROS- methylphenidate (MPH) for the treatment of adult ADHD in males and females.
Methods: Subjects were outpatient adults satisfying full diagnostic criteria for DSM-IV ADHD between 19 and 60 years of age participating in a 6-week placebo controlled, randomized clinical trial of OROS-MPH: Placebo (N=109) and OROS-MPH (N=102).
Results: There were no baseline differences between males and female on AISRS symptom severity scores (29.6±6.4 in 119 males versus 30.6±5.4 in 92 females, p=0.2). Total daily doses at endpoint were 1.1±0.3 mg/kg in males and 1.1±0.3 mg/kg in females (p=0.5) with the majority of both males and females completing the study (75% vs. 78%, p=0.6). Improvement associated with OROS-MPH relative to placebo was similar for males and females (-5.2±2.0 vs. -5.5±2.2, p=0.9) and there was no impact of sex on OROS-MPH associated changes in pulse (p=0.4), systolic blood pressure (p=0.7) or diastolic blood pressure (p=0.1).
Conclusions: Efficacy and tolerability data was similar in male and female adult subjects with ADHD enrolled in a large, randomized, placebo-controlled, trial of OROS-MPH. Trial Registration. The trial of OROS-MPH was registered at clinicaltrials.gov (identifier #NCT00181571) but the trial of IR-MPH was funded by the NIH and was conducted before registration was required or available.

S-31-003
Cigarette smoking and ADHD: A review and new pharmacotherapies perspectives

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Objectives: ADHD, one of the most prevalent disorders in children, persists in 60 to 80% of the cases though adulthood. Although ADHD-like symptoms have been described for more than 300 years (e.g. Moliere in is play entitled "The Blunderer" in 1653), Paul Wender conducted the first study aimed at treating adults with ADHD in 1976. Still this condition is under-diagnosed in adults and much of our knowledge on the pathophysiology has been deduced from the effects of stimulants, the mainstay of pharmacological treatment for the last 50 years. Although stimulants domine the market new molecules were approved recently for ADHD: atomoxetine, a non-stimulant treatment, in 2002 and guanfacine, a central $\alpha 2$-agonist as a second-line treatment, in 2007. Other neurotransmitters are involved in certain features of ADHD. A "nicotinic hypothesis" was proposed since (1) acetylcholine is involved cognition (on the basis of anatomical, pharmacological and animal studies), (2) a number of studies reported that nicotine exposure during pregnancy is a risk factor for externalized disorders including ADHD and, conversely, that (3) ADHD is an independent risk factor for cigarette smoking (ADHD patients reporting an earlier initiation, a heavier consumption and a stronger difficulty to quit compared to the general population). For the last twenty years, a huge number of molecules aimed at activating the $\alpha 4\beta 2$ and $\alpha 7$ central nicotinic receptors were synthesized. Some of them are being tested for cognitive impairment in Alzheimer disease, schizophrenia and ADHD. The first study on a sample of 200 adults with ADHD was completed in June last year; it compared the efficacy and tolerability of ABT-894, placebo and atomoxetine. To date, the magnitude of effects of these nicotinic agonists is not clearly stated and it cannot be concluded whether they would be used primarily or secondarily.

S-31-004
Impulsivity in adult ADHD clinical subtypes

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Objectives: Impulsivity is a main clinical feature in adult Attention Deficit/Hyperactivity Disorder (ADHD) and has led to a wide range of techniques for measuring but with still discussion on better operant methodology for various neuropsychological components in distinct behaviours in ADHD. The aim of the study was to assess impulsivity in adults ADHD with regards to lifetime prevalence of impulse control disorders and behavioural impulsivity measures.
Methods: We therefore conducted a retrospective study in 50 adults in an adult ADHD program. Patients were assessed within components of impulsive behaviour and completed Gostop and time paradigme tasks.
Results: High prevalence for Intermittent Explosive disorder (IED) were found using the IED integrated research criteria (24% for lifetime and 16% for the last 12 months) and within this group, anxiety and depression were found more frequent. No significant past history of conduct disorder was found in patients with more emotional outbursts. But behavioural impulsivity tests results may be more dependent on ADHD symptoms severity.
Conclusions: Relationship between angry without hostile cognition, emotional dysregulation and impulsivity found in ADHD may share common neuropsychological basis with IED, may overlap but may underlyie ADHD endophenotypes.

S-73
Biological child and adolescent psychiatry

S-73-001
Neurobiology of child and adolescent ADHD

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Objectives: Attention-deficit/hyperactivity disorder (ADHD) is a complex multifactorial disorder of high prevalence throughout childhood, adolescence and adulthood. Diagnosis is generally met based on clinical symptom ratings, however, no reliable objective measures have been found to date.
Methods: Here recent efforts to clarify the neurobiological underpinnings of ADHD are presented including neurophysiological and genetic studies as well as investigations in regard to presumptive biological markers.
Results: ADHD is a highly heterogeneous dimensional diagnostic construct displaying abberrant brain morphology, disturbed neurophysiological function and dysfunctional neurotransmitter systems.Pharmacological mechanism and genetic studies indicate that monoaminergic systems are involved in the etiology of ADHD. Several genetic variants with small contribution have been identified.
Conclusions: The integration of different methods is required to elucidate the neurobiology of ADHD. New approaches may deliver promising biological markers.

S-73-002
Proteomic research in autism

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S-73-003
Genetics of early-onset obsessive compulsive disorders

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Objectives: Obsessive-Compulsive Disorders (OCD) are characterized by recurrent, intrusive and disturbing thoughts as well as by repetitive stereotypic behaviour. Epidemiological data are similar in children and adults: Up to 3% of the general population suffered from OCD and children with OCD are often seriously impaired in their development. OCD has been shown to be familial, especially in early onset OCD up to 20% of the first degree relatives are also affected with OCD or OCD like symptoms.
Methods: Only three genome scans were done until now: The first genome scan was done in seven families ascertained through pediatric OCD probands. The highest LOD score was found on 9p24 (Hanna et al., 2002). Evidence for the linkage to 9p24 was supported also using microsatellite markers spanning the 9p-region (Willour et al., 2004). Hanna and collegues (2007) conducted a second genome-wide linkage scan in 121 subjects with early onset OCD from 26 families. The maximum nonparametric log of odds (NLOD) score was 2.43 on chromosome 10p15. Evidence for association in the linkage region was found with three markers in the 3' end of ADAR3. Studying of 219 families revealed by multipoint analysis suggestive linkage signals on chromosomes 3q, 6q, 7p, 1q, and 15q. Covariate-linkage analyses implicated a possible role of gene(s) on chromosome 1 in increasing the risk for an earlier onset form of OCD (Shugart et al., 2006).
Conclusions: Finally, candidate gene studies, are not yet associated with linkage regions, except in the case of the glutamate transporter gene SLC1A1 in 9p24. Genomwide linkage analyses are in progress and the results will promote further independent replication studies.

S-73-004
Potential biological markers of early-onset schizophrenia

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Regina Huennerkopf, Johannes Thome, Manfred Gerlach

Objectives: Diagnosis of schizophrenia is mainly based on symptomatic aspects. However a biological marker could support early differential diagnosis, follow-up and potentially the detection of relapse. Potential markers of schizophrenia have been investigated in the field of biochemistry, neuroimaging and neuropsychology. A brief overview of previous studies in the neurochemistry domain will be given and own results on mitochondrial complex I will be presented.
Methods: As for biochemical parameters, several studies in adults (Ben-Shachar et al. 1999; Dror et al. 2002) suggested increased platelet mitochondrial complex I expression and activity as potential peripheral markers of schizophrenia. The assessment of complex I mRNA expression in the peripheral blood cells of the rare population of early-onset schizophrenic (EOS) patients will be presented. To investigate the specificity of this possible marker, for the first time also children with autism spectrum disorder (ASD) were investigated. Both – schizophrenia and autism – are suggested to be neurodevelopmental disorders with mitochondrial dysfunction and increased oxidative stress.
Results: We were able to reproduce the recently found elevated complex I mRNA levels in our previous sample of 10 EOS patients compared to 10 controls, and furthermore in our independet new sample of 12 EOS patients compared to 18 controls. In the ASD group we were not able to observe altered expression of the complex I 75-kDa subunit.
Conclusions: Our results on the mitochondrial complex I mRNA expression in early-onset schizophrenic children and adolescents suggest the platelet mitochondrial complex I as a potential inherent peripheral marker of this disease. Further studies are warranted to investigate the state-dependency of this potential marker of schizophrenia and to elucidate how this parameter might interact with other pathological factors associated with schizo¬phrenia.

S-83
Acute neuropsychiatric states in autism

S-83-001
Acute behavioral states in adolescent with autism hospitalized in a psychiatric intensive care unit

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Objectives: During adolescence, few individuals with autism experiment severe disruptive behaviours such as violence, agitation, tantrums or self-injurious behaviours. We aimed to describe possible etiologic factors in a series of consecutive inpatients.
Methods: We reviewed the chart of all adolescents (12-17 years) with autism hospitalised for severe disruptive behaviours in a Psychiatric Intensive Care Unit located in a University setting in Paris during the period 2001-2005. We systematically collected socio-demographic characteristics, clinical variables (severity, presence of language, cognitive level), associated organic conditions, etiologic diagnosis of the episode, and treatments.
Results: All the patients (N=29, mean age=14.8 years, 79% of males) exhibited severe autistic symptoms (mean CARS score=41.9) and mental retardation. Two third had no functional oral language. Fifteen subjects exhibited epilepsy, including 3 cases for which epilepsy was unknown before the acute episode. For 6 (21%) subjects, epilepsy was considered as the main cause of the disruptive behaviours since adequate diagnosis and treatment during hospitalisation led to significant behavioural improvement. Other suspected causes included adjustment disorder (N=7), lack of adequate therapeutic or educational management (N=6), depression (N=2), catatonia (N=2) and non-specific comorbid organic condition (N=3).

Conclusions: Disruptive behaviours among autistic adolescents may rely on diverse causes including environmental problems, comorbid acute psychiatric condition, or somatic disease such as epilepsy. The management of these behavioural changes requires a multidisciplinary approach.

S-83-002
Catatonia in autism: Implications across the life span

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Objectives: There is increasing evidence that catatonia is an important source of impairment in adolescents and adults with autism. Aim is to review the evaluation, diagnosis, differential diagnosis, and treatment of catatonia in autism.
Methods: Presentation and discussion of a case-vignette spanning early childhood to adulthood.
Results: Autistic and catatonic symptoms overlap, yet catatonia is diagnosable in about one of seven adolescents and young adults with autism. Case-reports suggest that benzodiazepines and electroconvulsive therapy are effective treatments in the acute and maintenance phase for people with autism who develop catatonia.
Conclusions: Catatonia should be assessed in people with autism when there is an obvious and marked deterioration in movement, vocalizations, pattern of activities, self-care, and practical skills. Benzodiazepines and electroconvulsive therapy are favored options for acute and maintenance treatment in these cases. Further studies on the possible biological-genetic overlap between autism and catatonia would be helpful.

S-83-003
Self-injurious behavior in autism: Etiology, assessment and treatment

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Lee Wachtel

Objectives: Classically defined as self-directed acts that result in tissue damage, self-injury occurs within a wide range of frequency and intensity in individuals with autism. Self-injury in autism may seriously impair physical health and global functioning, and requires prompt, comprehensive treatment. This paper aims to review the incidence, etiology, assessment and treatment of self-injury in autism.
Methods: Review of the current literature on self-injury in autism and presentation of case examples, both pediatric and adult. Video footage will be included.
Results: Estimated prevalence rates of self-injury in autism range from 5-66%, with various etiologies proposed. These include neurotransmitter and neuroendocrine dysfunction, association with affective, psychotic or catatonic psychopathology, as well as discrete operant functions. Comprehensive assessment requires a multidisciplinary approach. Treatment options are myriad, and rely largely upon pharmacological, behavioral and combined interventions. Electroconvulsive therapy may also be effective in severe cases.
Conclusions: Self-injury may present a significant challenge for individuals with autism, with multiple factors implicated in its pathogenesis. Appropriate assessment, diagnosis and treatment allows for reduction of self-injury with improved patient safety and functioning.

S-83-004
The role of epilepsy in children and adolescents with autism spectrum disorders

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Objectives: The association between autism and epilepsy has been extensively documented and a conservative estimate is about 20-25%. A prospective study of seizure disorders in autism has been carried out in a clinical population of children and adolescents with autism. The aim of this research was to investigate the outcome of epilepsy and its putative role on clinical course of autism. the term autism herein comprehends the whole autism spectrum.
Methods: Subjects: 129 children were first evaluated in 2001 and followed up to 2008 at the Division of Child Neuropsychiatry of the University Hospital of Siena. The study group was made up of 103 Males and 26 Females, mean age 7,8 ys; SD +/- 2.7. All subjects met the DSM-IV criteria for Autistic disorder, Asperger disorder or Pervasive Developmental Disorder Not otherwise specified. Childhood Autism Rating Scale (CARS) was used to confirm the clinical diagnosis. The subjects were first evaluated in 2001 and subsequently followed up with six months or at least once per year control. Seizures types were classified according to ILAE classification. The assessment of adaptive level of patients was conducted using the Vineland Adaptive Behavior Scales.
Results: 51 (40%) children had Epileptic Paroxysmal Abnormalities (PA), 18 (14%) were suffering from Epilepsy. 40 (31%) had PA without seizures. Different types of seizures were observed and the majority of patients suffered from partial epilepsy.
Conclusions: In this study the prevalence of epilepsy was in the low range of current reported rates. Age, sample characteristics and other unknown factors may be implicated in this finding. Epileptiform activity without seizures was found rather frequently and it is important to emphasize its potential negative effect on cognition and behavior. Seizures seemed to have only minor effects on core symptoms of autism.

S-19
Early diagnosis of Alzheimers disease

S-19-001
Clinical and prognostic heterogeneity of mild cognitive impairment

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Objectives: To determine the cognitive outcome after one year, and the diagnostic transitions after up to 4 years of follow-up, in a cohort of older adults with MCI.
Methods: Prospective study, with baseline and 12-month assessments in a cohort of 139 older adults (78% women, mean age 68.5 years; mean educational level, 11.7), classified at baseline as cognitively unimpaired or MCI according to Petersen's criteria.
Results: At baseline, 29.6% of patients had amnestic MCI, 57.4% had multiple-domain MCI, and 13.0% had non-amnestic MCI. The 1-year rate of progression from MCI to AD was 3.7%. Of the patients diagnosed as MCI at baseline, 20.4% resumed normal cognitive function upon one-year follow-up (all but one previously diagnosed with aMCI or mdMCI); the proportion of recovery for patients with pure amnestic deficits was higher (37.5%) than for those with multiple-domain (13%) or non-amnestic (14%) impairment. Patients diagnosed with MCI on both assessments were older (p=0.002) and had a worse global cognitive performance (p=0.014), as compared to MCI patients who were considered normal after 12 months. In stepwise backward logistic regression, older age was the strongest predictor of MCI diagnostic stability after one year (OR=1.19, CI95%1.01–1.40, p=0.037). According to the Markov chain model, the patterns of cognitive state transitions from baseline to up to 4 years of follow-up varied greatly between the MCI subtypes. Single-domain MCI (amnestic and non-amnestic) showed a greater rate of recovery upon reassessments (22.5% and 21%). Among subjects who progressed to AD, the most common diagnosis prior conversion was multiple-domain MCI (85%).
Conclusions: The cross-sectional diagnosis of MCI has limited prognostic relevance, as compared to the longitudinal reassessment. Patients who maintain the MCI status are older, have worse baseline cognitive performance, and multiple cognitive deficits.

S-19-002
The role CSF biomarkers in the identification of AD at pre-dementia stages

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Objectives: Background: The pathophysiological process of Alzheimer's disease (AD) is thought to begin long before clinical symptoms develop. Existing therapeutics improve symptoms, but increasing efforts are being directed toward the development of therapies to impede the pathologic progression. Although these medications must ultimately demonstrate efficacy in slowing clinical decline, there is a critical need for biological markers that will aid early preclinical and clinical detection and patient characterisation, stratify pre-clinical and clinical patient populations for trials, indicate whether a candidate disease-modifying therapeutic agent is actually altering the underlying degenerative process. Objectives: In this presentation in vivo neurobiological measures closely related to pathophysiological, neuropathological and clinical data, such as hyperphosphorylation of tau protein and tangle formation, and the amyloidogenic pathway will be reviewed and discussed. As this work has considerably matured, it has become clear that biological measures may serve a variety of important clinical functions in an early clinical, pre-clinical and potentially pre-symptomatic detection of patients.
Results: Knowledge of AD is rapidly advancing, thus the NINCDS-ADRDA criteria diagnostic criteria currently used may need revision and updating. Whereas sensitivity has been shown very good to excellent, specificity has been much lower. Revised criteria are being suggested by the field and discussed in the APA DSM-V and WHO ICD-11 working groups. In particular, the potential implementation of additional operationalised neurobiological criteria to the classical descriptive clinically symptomatic criteria within the diagnostic process may aid to an earlier and more accurate characterisation of AD patients.
Conclusions: There is an urgent need for a harmonized collaborative effort between stakeholders in academic research, industry and regulatory authorities for the establishment of worldwide standards and networks for the identification and qualification of biological marker candidates. Biomarkers in clinical trials are needed to monitor safety, enrich the population of responders and provide presymptomatic efficacy measures for labeling as "disease modifiers".

S-19-003
Imaging of amyloid-beta in Alzheimers disease

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Objectives: Beta-amyloid (Aβ) targeted PET tracers may shift the timepoint for accurate diagnosis of Alzheimer's disease (AD) from postmortem to antemortem. BAY 94-9172 is an 18F-labeled stilbene derivative currently in clinical development as an Aβ marker for PET.
Methods: In a proof of mechanism study we investigated the ability of BAY 94-9172 brain PET to differentiate AD-patients from healthy controls (HC). 10 AD-patients and 10 age-matched HC underwent dynamic brain PET, and images at 70-90 min p.i. were analyzed visually and semi-quantitatively after co-registering the PET data with individual MRI (cerebellar reference region).
Results: Visual analysis (3 blinded experts) revealed 9 of the 10 AD, but only 1 of the 10 HC brains to be positive for Aβ (p<0.001). Compared with HC, the standardized uptake value ratios in AD subjects were significantly higher in frontal (1.73±0.37 vs. 1.35±0.18, p=0.01), anterior cingulate (1.72±0.36 vs. 1.41±0.15, p=0.02), posterior cingulate (1.79±0.48 vs. 1.36±0.13, p=0.01), and lateral temporal (1.49±0.30 vs. 1.24±0.10, p=0.02) cortices, as well as in the caudate (1.49±0.30 vs. 1.19±0.13, p=0.01). Voxel-based analyses by single-case comparisons confirmed these differences. An Aβ load index combining information on extent and severity of pathological tracer uptake was negatively correlated to the Mini-Mental State Examination score (r=-0.609, p=0.004).
Conclusions: These results indicate that [18F]BAY 94-9172 PET has the potential to provide accurate and quantitative non-invasive, in vivo determination of Aβ load and may facilitate an antemortem diagnosis of AD. This offers disease prediction at early stages, monitoring the course of Aβ deposits and the effects of new anti-amyloid therapies. Further evaluation of the diagnostic efficacy of this promising radiotracer in global multicenter trials is ongoing.

S-19-004
For a new concept and new criteria for the diagnosis of Alzheimer's disease

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Objectives: FOR A NEW CONCEPT AND NEW CRITERIA FOR THE DIAGNOSIS OF ALZHEIMER'S DISEASE Bruno Dubois INSERM-UPMC UMRS 610, Federation of Neurology, Salpetriere Hospital; University of Paris6, Paris, France bruno.dubois@psl.aphp.fr The criteria of the NINCDS-ADRDA for AD represent the prevailing diagnostic standards in research. While these sets of criteria represented an important step forward following their publication, they have now fallen behind the unprecedented growth of scientific knowledge of the disease from its earliest clinical manifestations through postmortem histopathology. Distinctive and reliable biomarkers of AD are now available through structural brain imaging with Magnetic Resonance Imaging (MRI), molecular neuroimaging with Positron Emission Tomography (PET) and cerebrospinal fluid (CSF) analyses. This progress provides the impetus for the revised research diagnostic criteria for AD. Our proposed diagnostic framework was developed through an international working group 2005, who determined by consensus that a set of revised AD criteria could be developed to capture both the earliest stages, prior to full-blown dementia, as well as the full spectrum of the illness. These new criteria are centered around a clinical core of early and significant episodic memory impairment. They stipulate that in addition there must also be at least one or more abnormal biomarkers amongst structural neuroimaging with MRI, molecular neuroimaging with PET and CSF analysis of amyloid beta/tau proteins.

The timeliness of these criteria is underscored by the myriad of drugs currently under development that are directed at altering the disease pathogenesis. Validation studies within both existing and prospective cohort studies will be needed to advance these criteria and optimize their sensitivity, specificity and accuracy. The strength of these proposed research criteria is the introduction of neurobiological measures onto the clinically based criteria.

S-32
Depression and dementia: Stress hormones and neuroprotection

S-32-001
Role of neurosteroids and oxidative stress in neurodegeneration

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Objectives: Oxidative stress caused by reactive oxygen species plays a decisive role in the pathogenesis of neurodegenerative disorders such as Alzheimer's disease (AD). Early defects in glucose utilization in the brains of AD patients suggest possible abnormalities in mitochondrial function in AD. Several studies performed in animals suggest neurosteroid involvement in neuroprotection. However in humans, the role of neurosteroidogenesis in the regulation of degenerative processes is unknown.
Methods: Different methods were used to identify oxidative stress and mitochondria malfunction in brains from transgenic mice or cell culture models as well as neogenesis of neurosteroids.
Results: In our own studies, we could clearly demonstrate that Aß causes oxidative stress and mitochondrial malfunction in a cell culture model as well as in APP transgenic mice. Using transgenic mice overexpressing the P301L mutant human tau protein, we could demonstrate mitochondrial dysfunction by proteomic and functional analyses in these mice. Thus, we can speculate that tau and Aß accumulation probably act in synergy on oxidative stress and mitochondrial dysfunction. Of note, Ginkgo biloba extract at therapeutically relevant in vitro and in vivo concentrations is able to improve mitochondrial dysfunction associated with oxidative stress and/or aging. Furthermore, recent results demonstrate an amino-acid sequence dependent action of Aß on neurosteroidogenic pathways. The data also indicate that, unlike progesterone neosynthesis, regulation of endogenous estradiol formation by pathogenic factors may be a deciding process controlling cell death mechanisms. Targeting estradiol biosynthetic pathways in nerve cells may therefore be interesting to develop neuroprotective strategies.
Conclusions: In summary, protection against mitochondrial dysfunction, improved ATP production, and prevention of cell death signals may be important features of antidementive drugs. Since mitochondrial failure and reduced energy metabolism seem to be very early events during the course of AD, the stabilization of mitochondrial function represents an emerging preclinical concept of age-related memory disorders and dementia.

S-32-002
Neuropeptide regulation and sleep in aging and depression

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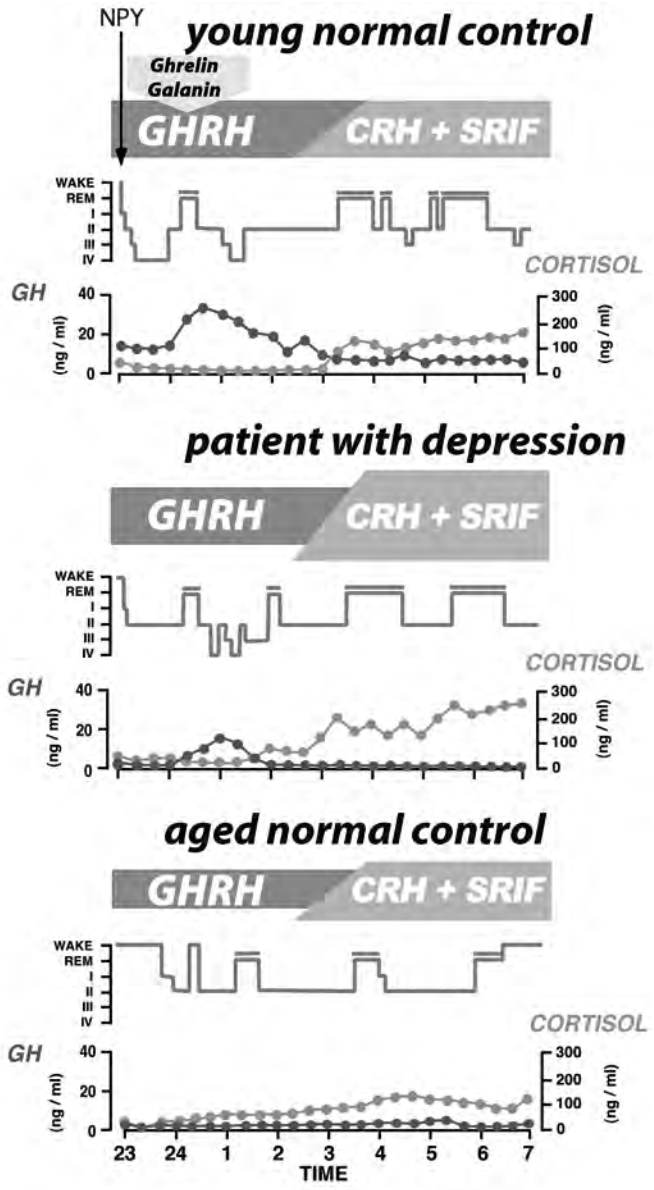
Objectives: Sleep is characterized by electrophysiological activity and by distinct patterns of hormone secretion. In patients with depression sleep-endocrine activity is changed as slow wave sleep (SWS) and growth hormone (GH) decrease, cortisol increases and REM sleep is desinhibited. During ageing similar changes occur.
Methods: In a series of studies we investigated the role of various peptides in normal and pathological sleep-endocrine regulation. The peptides or placebo were injected, in most studies in pulsatile fashion during the first few hours of the night via long catheter to normal subjects and patients with depression.
Results: After GH-releasing hormone (GHRH) SWS and GH increased and cortisol decreased in young men, whereas corticotropin-releasing hormone (CRH) had opposite effects. The sleep-promoting effect of GHRH was reduced in elderly subjects and in young men during early morning hours. In patients and controls (19-76yrs) a sexual dimorphism of the effects of GHRH was found. GHRH increased NonREM sleep and decreased wakefulness in men, but impaired sleep in women. After ghrelin GH, cortisol and ACTH increased in young and elderly subjects regardless of gender, whereas sleep was promoted in males only. Somatostatin impaired sleep in elderly subjects. Galanin enhanced SWS in young men. After morning administration of galanin to depressed patients REM latency was increased and the Hamilton score decreased. Neuropeptide Y prolonged sleep latency in depressed patients and normal controls. After four weeks of treatment of patients with depression with a CRH-1-receptor antagonist SWS increased and wakefulness and REM density (amount of rapid eye movements) decreased.
Conclusions: A reciprocal interaction of GHRH and CRH appears to play a key role in sleep regulation, at least in male subjects (see figure). Changes in the GHRH/CRH ratio in favour of CRH contribute to sleep-endocrine changes during depression (CRH overactivity) and normal ageing (reduced GHRH activity). Besides of GHRH, ghrelin, galanin and NPY promote sleep, whereas somatostatin impairs sleep.



S-32-003
Can hormones provide natural neuroprotectivity: Melatonin and estrogen in neurodegeneration?

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Objectives: Alzheimer's disease (AD) is a progressive neurodegenerative disorder and a major health problem. The two major neuropathological findings in the AD brain are the presence of neuritic plaques containing the neurotoxic β-amyloid-peptide (Aβ) and neurofibrillary tangles.
Methods: That oxidative stress may be a culprit in neuronal loss in AD has been emphasized in recent years and the evidence is becoming progressively stronger that the excessive generation of free radicals and inefficient anti-oxidative mechanisms are involved in the neuronal pathogenesis of the disease. The free radicals that have been incriminated as causing neuronal loss are believed to be generated by Aβ.
Results: Today, it is well established that some natural substances may help to counteract the oxidative stress caused by free radicals and some human hormones have obvious anti-oxidative capacity.
Conclusions: These hormones play an important role in the functioning of the central and peripheral nervous system, have behavioural, physiological and neuroprotective effects, and their levels decrease markedly with age and in AD. They may provide a natural source of neuroprotection in neurodegenerative disorders. Two of them, melatonin and estrogen, respectively, will be discussed in detail.

S-32-004
Antidepressants, age related sleep alterations and depression

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Objectives: To a certain extent, sleep alterations observed in major depression such as sleep fragmentation, deficit of slow wave sleep and REM sleep disinhibition mirror age-related alterations in sleep EEG. The present paper focus on the relationships between age, mood, sleep and the effects of antidepressant therapies
Methods: Recent sleep-wake electrophysiological and neurobiological findings in major depression will be presented and integrated with our present knowledge of sleep-wake mechanisms. Original data illustrating how different sleep/wake regulating mechanisms are implicated in the sleep effects of age, depression and antidepressant therapies will be discussed. Polysomnographic data on the effects of age on human models mimicking hyperarousal (first night effect) and S deficiency (post-nap sleep) will also be presented
Results: Strong evidence suggest the implication of wake-promoting mechanisms in depression linked to a stress-related hyperarousal reaction implicating the CRH system and the locus coeruleus-autonomous nervous systems. Other mechanisms that could be involved are an impairment of NREM sleep propensity (S deficiency) and an aminergic/cholinergic imbalance leading to REM disinhibition. In our models, older subjects only differentiate from younger subjects in terms of NREM propensity; wake-propensity and REM propensity were not differently affected in the two groups.
Conclusions: There is a probable coexistence at various degree of hyperarousal, process S deficiency and aminergic/cholinergic imbalance in major depression. It is suggested that the age-related lower NREM sleep propensity would be a pejorative factor for counteracting the effects of hyperarousal on sleep.

S-42
Neurobiology of Alzheimer's disease: Beyond the amyloid hypothesis

S-42-001
Alzheimer's disease, vascular dementia, or both?

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Objectives: Clinically diagnosed "Alzheimer's Disease (AD)" is characterized by mixed pathologies at autopsy, including AD-related neurodegenerative changes [i.e., the neurofibrillary tangles (NFT) and neuritic plaques (NP)], ischemic changes, and, less commonly, hippocampal sclerosis and cortical Lewy Bodies. Their relative contributions and specificity for the dementia of AD (DAD) remain unclear.
Methods: Literature Review.
Results: Prior studies suggest that the location(s) in which pathological lesions are measured contributes independently of their global severity to clinical diagnosis. Specifically, frontal circuit lesions capable of disrupting executive control function (ECF) may be most relevant to dementia case finding. In particular, frontal circuit ischemic pathology may commonly convert pre-clinical limbic AD pathology to clinical "AD", as opposed to DAD. Alternatively, ischemia may set pre-clinical limbic AD pathology in motion towards DAD conversion.
Conclusions: The distinction between mixed pathologies and DAD has implications for the prospective evolution of "AD"'s clinical features and their response to treatment.

S-42-002
The GSK-3 hypothesis of Alzheimer's disease

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S-42-003
Phospholipids, phospholipase A2 and membrane abnormalities in Alzheimer's disease

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Objectives: The objective of this study is to compile cumulative research data on the evidence of PLA2 and membrane phospholipid abnormalities in the pathophysiology of Alzheimer's disease (AD).
Methods: Translational research including: (1) in vitro studies (membrane phospholipid content and anisotropy, radio-enzymatic determination of phospholipase A2 activity/subtypes, modulation of PLA2 in primary cultures of cortical and hippocampal neurons), (2) animal models (memory and behavior in adult rats; regional brain PLA2 expression and activity; PLA2 modulation), and (3) clinical and pathological studies with patients with cognitive impairment and AD (PLA2 activity in brain homogenates and peripheral tissues, intracerebral phospholipid metabolism with 31P-Magnetic Resonance Spectroscopy, longitudinal determination of platelet PLA2 activity).
Results: PLA2 is superfamily of enzymes that include key modulators of cerebral phospholipid metabolism. Preliminary post-mortem studies have shown that PLA2 activity is decreased in frontal and parietal areas of the AD brain, which is in accordance with spectroscopic evidence of reduced phospholipid turnover in the pre-frontal cortex of AD patients. Such abnormality may also be observed in peripheral cells, and reduced PLA2 activity in platelet membranes of AD patients correlates with the severity of dementia. In rat hippocampal slices, PLA2 has been implicated in mechanisms of synaptic plasticity. In adult rats, stereotaxic injection of PLA2 inhibitors in the CA1 hippocampus impairs short- and long-term memory and reduces the fluidity of neuronal membranes. In primary cultures of cortical and hippocampal neurons, the inhibition of PLA2 precludes neurite outgrowth, and the sustained inhibition of the enzyme in mature cultures leads to loss of viability.
Conclusions: Taken together, these findings reinforce the involvement of PLA2 enzymes in neurodevelopment and neurodegeneration processes, and further suggest that reduced PLA2 activity, probably reducing membrane phospholipids breakdown, may contribute to the memory impairment and to the pathogenesis of dementia in AD.

S-42-004
Is aging part of Alzheimer's disease, or is Alzheimer's disease part of aging?

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Objectives: Alzheimer's disease (AD) was originally described as a cause of presenile dementia, and advanced age was actually an exclusion criterion. Decades later the AD definition was changed to include senile dementia cases. Under the revised definition AD became strongly age-related and in some demographics over 50% may be affected. The question of whether presenile and senile AD cases are similar enough to qualify as a single disease was previously raised although not conclusively settled. Recent advances in AD and aging-related molecular, biochemical, and clinical knowledge are particularly relevant to this ongoing debate. Because presenile and senile AD may not be etiologically equivalent, and most AD drug development efforts are based on the rare presenile forms, an etiologic hypothesis that specifically pertains to senile AD was recently proposed. This hypothesis, the Mitochondrial Cascade Hypothesis, incorporates aging theory and data showing mitochondrial function is reduced in both aging and AD. The Mitochondrial Cascade Hypothesis asserts: (1) inheritance determines mitochondrial baseline function and durability; (2) mitochondrial durability influences how mitochondria change with age; and (3) when mitochondrial change reaches a threshold, AD histopathology and symptoms ensue. This hypothesis views late-onset AD and aging as convergent rather than divergent events. If correct, treatments that mitigate or reverse brain aging will likely benefit late-onset AD subjects more than beta amyloid reduction will.

S-52
Clinical and biological aspect of apathy in neuropsychiatry

S-52-001
The concept of apathy in Alzheimer's disease

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Objectives: Apathy is increasingly recognized as a common behavioral syndrome in neuropsychiatric disorders, but it is conceptually ill defined. The aim of this contribution is to review the history and the current use of the concept of apathy in neurology and psychiatry.
Methods: Review of literature and conceptual analysis
Results: There is no consensus on diagnostic criteria for apathy as a syndrome. Apathy is mostly defined as a disorder of motivation and operationalized as diminished goal-oriented behavior and cognitions. Disagreement exists about whether an emotional dimension should be part of the definition of apathy. A proposal for diagnostic criteria for apathy, that did include such an emotional component, has recently been published (Starkstein & Leentjens, JNNP 2008;79:1088-92). A slightly revised version of these criteria have recently been endorsed by the European Psychiatric Association (EPA) and the European Alzheimers' Disease Consortium (EADC) (Robert Ph. et al. Eur Psychiat, in press). There are several reliable scales to measure the severity of apathy in patients with neuropsychiatric disorders. In the absence of a gold standard, proper validation of these scales is not possible
Conclusions: Apathy is increasingly recognized as a common behavioral syndrome and as a potential target for treatment in neuropsychiatric disorders. Research is hampered by the lack of generally accepted diagnostic criteria. From a nosological perspective, future studies should examine the overlap with other psychiatric and neurodegenerative conditions and further validate specific diagnostic and assessment tools.

S-52-002
Apathy in other neurodegenerative diseases

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Objectives: Apathy is defined as a lack of motivation leading to reduced interest and participation in various activities as well as blunting of emotions. It reflects a dysfunction of the frontal lobes, following either direct lesion of the frontal cortex or damage to regions tightly connected to the latter. The frontal-subcortical circuits often seem to be involved. Apathy is a common behavioral syndrome in neurodegenerative disorders.
Methods: Review of the literature.
Results: In Alzheimer's disease (AD), apathy is the most frequent and the most persistent neuropsychiatric disorder. It is present at all stages of the disease. After cognitive decline, it is one of the main factors explaining functional decline in AD. Moreover, apathy is frequent in "mild cognitive impairment" (MCI) and it has been shown that conversion to dementia is more frequent in MCI patients with than without apathy. Apathy is also common in Parkinson's disease (PD) where its frequency ranges from 17 to 70%. It is generally not related to motor symptoms severity. It may occur as a syndrome in itself or in association with depression or dementia. In PD patients treated by bilateral subthalamic nucleus stimulation, it may occur as an adverse effect. Apathy is also a frequent behavioural symptom in other movement disorders (progressive supranuclear palsy and Huntington's disease). In frontotemporal dementia (FTD), apathy is a highly prevalent behavioural symptom, even in patients with mild dementia. It is more severe in late-onset patients. Apathy is more frequent and more severe in the frontal variant of FTD where its severity significantly correlates with the extent of frontal atrophy.
Conclusions: Apathy is an important behavioural disorder in most of the neurodegenerative disorders. It is accompanied by heightened functional disability and by greater carer burden. The recent definition of consensus diagnosis criteria would help in its detection and facilitate the research of treatment.

S-52-003
Ambulatory actigraphy for the evaluation of apathy in Alzheimer's disease

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Alice RIVET, Philippe ROBERT, Jerome YESAVAGE

Objectives: to assess the relationship between apathy and locomotor activity using ambulatory actigraphy in Alzheimer's disease (AD).
Methods: Thirty AD subjects and fifteen healthy controls were recruited from the Nice Memory Center. Apathy was assessed with the Apathy Inventory (AI). Patients with a score greater than three on the AI caregiver version are considered in this report as having apathy. Locomotor activity was assessed using a wrist-worn actigraph for 75 minutes, during which a neuropsychological and behavioral examination were performed (60 minutes) followed by 15 minutes of free activity.
Results: AD patients show lower motor activity than healthy subjects. AD patients with apathy have lower motor activity than AD patients without apathy. Apathy total score correlated negatively with mean motor activity. Most of the total score correlation was accounted for by correlations between the apathy dimensions lack of initiative and lack of interest, with mean motor activity.
Conclusions: Ambulatory actigraphy could be a simple technique to assess apathy objectively as part of routine assessment of AD patients

S-52-004
Discussion

Philippe Robert
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S-54
Aß Immunotherapy of Alzheimer's disease

S-54-001
Selection of efficacy outcomes in disease-modifying trials that are meaningful to clinicians, patients and payers

Serge Gauthier
Canada

Objectives: Immunotherapy against amyloid deposition can be tested in patients at different stages of Alzheimer's disease (AD).
Methods: Review of literature and speaker's experience with clinical trials at different stages of Alzheimer's disease.
Results: The selection of stage of disease will influence the clinical trial design and outcomes. For instance in the pre-dementia stage of AD, time to diagnosable dementia may be a very meaningful outcome, supplemented by time to loss of a percentage of instrumental activities of daily living (ADL). In mild AD (with dementia already present) decline over 18 months in cognition, global impression of change and ADL is the traditional approach. In moderate stage AD where the slope of decline on these outcomes is faster, these outcomes could be measured over 12 months. Background therapy with cholinesterase inhibitors and memantine is required once dementia caused by AD has been diagnosed; this would not be required in pre-dementia AD. ApoE genotype is an important factor in progression from amnestic mild cognitive impairment (aMCI) to dementia, and stratification for ApoE status is required in clinical trials with aMCI and pre-dementia AD; responder analysis based on apoE genotype is to be done at all stages of the disease. Patients with familial early onset AD should be considered for proof-of-concept studies with anti-amyloid drugs; the availability of the Dominantly Inherited Alzheimer Network (DEAN) in the USA-England-Australia and an equivalent network between Québec and France will facilitate access to such patients who are currently excluded from clinical trials for AD because of their age of onset before 50, despite their predominantly amyloid pathology.
Conclusions: New opportunities are now available to increase the changes of positive results in clinical trials using immunotherapy and other potential disease-modifying therapies in Alzeimer's disease.

S-54-002
Biomarkers in Alzheimer's disease: Use for clinical trials

Anton Alvarez
Spain

Objectives: Pharmacology research in Alzheimer's disease (AD) is currently focusing on the development of disease-modifying treatments able to slow down AD progression. Such a kind of therapeutic agents has to reduce the rate of functional decline in AD patients, and must also influence relevant AD-related pathogenic events like neuronal and synaptic loss, amyloid deposition, tau pathology, neuroinflammation, and alterations in brain metabolism and trophic activity.
Methods: Therefore, the identification and validation of surrogate biomarkers is essential for the optimization of future clinical trials (CTs) with drugs having potential disease modification activity. Biomarkers have to be selected according to the mechanism of action and the main effects of a given drug in experimental models, and drug-placebo differences should be demonstrable for the surrogate marker. This implies the biomarker must be reliable (reproducibly measured) and sensitive to changes in the progression of the disease. Ideally, a surrogate biomarker should respond to the therapeutic intervention, correlate with and predict the clinical response, and reflect the AD pathophysiology mechanism targeted by the treatment. However, biological markers can also be used as secondary outcome measures (biological correlates of drug effects) and to enrich CTs.
Results: The quantification of the levels of amyloid-beta and related molecules in cerebrospinal fluid (CSF) and probably in plasma, and the determination of the brain amyloid load by PET scanning are measures of potential utility for clinical trials with anti-amyloid agents like the vaccines. Changes in CSF tau, brain metabolic and volumetric measurements through different techniques, imaging markers of activated microglia, serum measures of inflammation and oxidation, DNA markers, and determinations of other biological parameters have also been proposed as biomarkers for AD CTs. To date, none of them has been validated.
Conclusions: Applicability, limitations and future directions in the use of biomarkers in CTs will be discussed.

S-54-003
AD vaccines: The new generation – successes and challenges on its way into clinical practice

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Objectives: The concept of active Aβ immunotherapy of AD was introduced in 1999 by Schenk and colleagues when they showed that applying Aβ with the adjuvant QS21 to APP transgenic mice reduces cerebral Aβ load, ameliorates their neuropathology, and, improves their cognitive function. The effects were corroborated by other investigators and appeared to be mediated by vaccination-induced antibodies.
Methods: As a next step, Elan/Wyeth took this approach into the clinics. When the vaccine's (AN1792) formulation was changed to include PS-80, known to promote TH1 polarization, cases of meningoencephalitis (ME) occurred. Research into the pathogenesis of ME cases identified Aβ-specific, CD4+ TH1 lymphocytes as the causative agent. Noteworthy, despite the fact that, on average, only 2 rather than the projected 6 vaccinations were applied, the study generated evidence for the proposed activity, that is reduction of cerebral Aβ as well as a clinical benefit.
Results: The AN1792 example stresses the importance of considering autoimmunity when immunizing with self-proteins. As the therapeutic effect of AD vaccines is mediated by Aβ-specific Abs, the task is to build vaccines eliciting such Abs without activating Aβ-reactive T cells. A possible solution, adopted by most vaccine developers (Elan/Wyeth, Novartis/Cytos, AFFiRiS) is the use of short Aβ-derived peptides. AFFiRiS takes this a step further. Rather than relying on fragments of Aβ, AFFITOPE vaccines use short synthetic peptides, mimicking neoepitopes of the native Aβ, as their antigenic component. The AFFITOME platform technology to was used to generate a pool of peptides allowing to control such that the specificity of the vaccine-induced antibody response is focusing exclusively on Aβ and preventing crossreactivity with APP.
Conclusions: The availability of second generation vaccines enables us to address the most thrilling question in AD research: Is the reduction of cerebral Aβ concentrations in and of itself sufficient to modify the course of the disease?

S-54-004
AFFITOPES of Aß as active vaccines in the treatment of AD: results of a phase I study with AFFITOPE AD02

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Objectives: Active immunotherapy has been shown to reduce Amyloid-beta (Aß), a protein that accumulates in Alzheimer brains. As human use of the first Aß-vaccine AN1792 was afflicted with the occurrence of meningoencephalitis (most likely caused by the activation of Aß-specific T-cells), a new technology for Aß-vaccines was developed. Using Aß-AFFITOPES to induce Aß-neoepitope targeting antibodies likely offers several advantages. The short length of the peptides prevents the activation of Aß-specific T-cells. Furthermore, the antibody response exclusively targets Aß but not its precursor APP.
Methods: 24 patients who fulfilled the NINCDS-ADRDA criteria for probable AD of mild to moderate degree (MMSE 16-26) were included into a single-center, randomized, Phase I clinical trial with the active Aß-vaccine AFFITOPE AD02. Patients were randomized in a 1:1 ratio into two groups, one group receiving a peptide/carrier protein conjugate alone, the second group receiving the same conjugate adsorbed to aluminiumhydroxide as adjuvant. The vaccine´s safety and tolerability, primary objectives of the study, were assessed weekly in a standardized manner. The vaccine's immunological and clinical activities, both secondary parameters, will be analyzed in an explorative manner only.

Results: So far, a total of 290 adverse events have been reported; two were serious adverse events, which were both classified as having no causal relationship to AD02. Injection site reactions made up 55% of all adverse events. With the exception of granulomas, all local reactions were short lived (lasting several hours to a few days). Regarding the systemic adverse events, all were of mild to moderate degree. Up to now, none of the patients presented with symptoms that would be reminiscent of meningoencephalitis. The vaccines' immunological and clinical activity will be assessed at the end of the study.
Conclusions: Safe and effective Alzheimer treatments are urgently needed. Preliminary analysis of Phase I data indicate an acceptable toxicity- and tolerability profile for AD02.

S-62
Lithium, neuroprotection and dementia

S-62-001
Neuroprotective effects of lithium: in vitro and in vivo models

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S-62-002
Does lithium protect against dementia? Evidence from clinical and genetic studies.

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Objectives: (1) To investigate the association between cognitive state and a set of clinical and treatment-related variables in the search for risk and protective factors for cognitive impairment and dementia in a cross-section of elderly individuals with long-standing bipolar disorder (BD) and (2) to determine the effect of lithium treatment on the expression of GSK3 alpha and beta in cultured neurons, adult rats and human leukocytes.
Methods: (1) Sample: 114 elderly patients with BD (DSM-IV), euthymic upon assessment (CAMDEX / IQcode), undergoing long-term lithium therapy (n=66) or treatment with other mood-stabilizing drugs (n=48); 70 subjects were cognitively unimpaired, 25 had MCI and 19 had dementia (AD). (2) RT-PCR determination of GSK3 transcription (mRNA) in primary cultures of hippocampal neurons, adult Wistar rats brains, and humans leukocytes.
Results: (1) The prevalence of dementia (19.4%) was higher than expected in age-comparable general population (7.1%). Factors associated with cognitive impairment were: older age (p=0,002), longer history of BD (p=0,021), and the number of previous depressive episodes (p=0,039). The prevalence of AD among lithium users was 4.5% as compared to 33.3% among non-users. After controlling for age and sex distribution the effect of lithium on decreased AD prevalence remained significant (OR=0.079; p<0.001). (2) lithium treatment resulted in a significant inhibition of GSK3b transcription in hippocampal, but not in cortical neurons, suggesting a dose-dependent and regional-specific effect, and in human cells.
Conclusions: There was a higher prevalence of AD in bipolar patients. Lithium treatment reduced the prevalence of AD to the levels of the general elderly population. This putative neuroprotective effect may result from the modulation of GSK3beta activity and transcription, which reinforces its therapeutic value inhibiting important pathways in the pathophysiology of AD.

S-62-003
Epidemiological evidence on the effects of lithium on the prevalence of dementia

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Objectives: To investigate whether continued treatment with lithium reduces the risk of dementia in a nationwide study.
Methods: An observational cohort study with linkage of registers of all prescribed lithium and diagnoses of dementia in Denmark during a period from 1995 to 2005 and a random sample of 30 % of the general population.
Results: Persons who purchased lithium once had an increased rate of dementia compared to persons unexposed to lithium (RR=1.47 (95% CI: 1.22-1.76). For persons who continued taking lithium the rate of dementia decreased to the same level as the rate for the general population. The rate of dementia decreased early following consumption of lithium tablets corresponding to one prescription (typically 100 tablets) and stayed at a low level, although with a slight increase with the number of subsequent prescriptions. The association between the number of prescriptions with lithium and dementia was unique and different from the association between the number of prescriptions of anticonvulsants and dementia. All findings were replicated in sub-analyses with Alzheimer's disease as outcome.
Conclusions: Continued lithium treatment was associated with a reduced rate of dementia to the same level as the rate for the general population. Methodological reasons for this finding cannot be excluded due to the non-randomised nature of data.

S-62-004
Lithium for the treatment of mild cognitive impairment: Preliminary results of a double-blind, placebo controlled trial

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Objectives: To evaluate the safety, tolerability and efficacy of long-term, low dose, lithium treatment on cognitive and biological outcomes in sample of patients with MCI.
Methods: 77 elderly patients with MCI (Petersen's criteria) recruited for a two-year RCT; 51 signed informed consent (6 excluded through baseline assessment); 45 subjects randomized to receive lithium (n-24) or placebo (n=21). Both groups received non-pharmacological treatment (memory training protocol). Lithium carbonate administered in doses sufficient to achieve sub-therapeutic plasma levels (0.25-0.50mEq/L). Primary outcome: conversion from MCI to AD; secondary outcomes: modification of cognitive and functional scores (ADAS-COG, CDR, neuropsychological battery) and/or biological parameters (CSF Abeta42, total Tau, phospho-Tau; platelet APP ratio; platelet GSK3 and PLA2 activity).
Results: Between April 2007 and December 2008, 41 patients completed at least a 12-month follow-up. One patient (lithium) was excluded from the study, and 1 patient (placebo group) died due to medical complications not related with the study drug (stroke and septic shock, respectively); 2 patients withdrew consent (unavailability to attend follow-up visits). Outcome data to be presented at the WFSBP: one-year clinical and cognitive outcome; safety and tolerability data according to the UKU scale and laboratory screening; modification of CSF and platelet biomarkers from baseline to one year outcome.
Conclusions: Overall tolerability of lithium was acceptable, and compliance to this study was good. Preliminary data from this study will be interpreted in the light of potential methodological limitations, including the possibly short duration of treatment (1 year) to yield significant changes, and lack of statistical power due to the relatively small sample size. Efforts have already been started to increase sample size through collaboration with other institutions, and to extend follow-up to up to four years in a single-blind regimen.

S-03
Serotonin receptors in endophenotypic variations and treatment of schizophrenia: Genetic, neurocognitive, and pharmacological perspectives

S-03-001
Multimodal imaging genetics on serotonin receptor polymorphisms in schizophrenia

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Objectives: Recent genetic evidence indicates that polymorphisms of 5-HT1A, 5-HT2A receptor and 5-HT transporter (SERT) are related to psychotic symptoms, cognitive disturbances, and treatment response in schizophrenia. The aim of our study was to determine the effect of variations in functional candidate genes involved in 5-HT activity on phenotypic measures in subjects with schizophrenia.
Methods: In the group of 63 cases and 55 controls we studied the influence of the polymorphisms of 5-HT1A receptor (rs6295), 5-HT2A (rs6313) and SERT (rs479554) on brain morphometry (VBM), cognitive activation (fMRI) and regional metabolism (18FDG PET). Statistical parametric mapping (SPM5) with genetic variants as factors was applied to structural and functional images.
Results: Full factorial three-way ANOVA indicated that the G allele of 5-HT1A receptors was associated with a smaller volume of parahippocampal gyrus in S allele carriers for SERT polymorphism (rs479554). The G allele of 5-HT1A allele was also shown to decrease brain metabolism in prefrontal cortex as demonstrated by 18FDG-PET. A significant interaction between the 5-HT2A receptor-T and SERT-S alleles was noted for performance on the 2-back task (fMRI).
Conclusions: Parahippocampal gyrus and prefrontal cortex have been shown to play an important role in cognitive function. Our findings suggest the polymorphism in the 5-HT1A receptor predicts structural and functional characteristics in cortical regions receiving projection of 5-HT neurons. The effect of G allele of 5-HT1A receptor on cell differentiation in neurodevelopment would be modulated by 5-HT extracellular level influenced by SERT gene variants.

S-03-002
Improving cognitive function in animal models of schizophrenia: Focus on serotonin receptors

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Objectives: Spatial working memory, short-term place memory and information processing are impaired in schizophrenia. The efficiency of antipsychotic drugs, particularly of typical antipsychotics, on cognitive deficit in schizophrenia is disputed. The inhibition of serotonin-2A/2C receptors (5-HT2A/2C R) or activation of 5-HT1A R is important for cognitive improvement in schizophrenic patients treated with anti-psychotics. The objective of this presentation is provide data from animal experiments in determining the effect of the antagonists at 5-HT2A/2C R and full/partial agonists at 5-HT1A R on behavioral performance in animal models of schizophrenia based on the glutamatergic hypothesis.
Methods: We investigated the effect of full/partial agonists at 5-HT1A R and antagonists at 5-HT2A/2C R on MK-801 (0.1mg/kg)-induced sensorimotor gating and memory in rats
Results: We found that high doses of partial agonist (tandospirone) and full agonist (8-OH-DPAT) at 5-HT1A R potentiated a sensorimotor gating deficit induced by MK-801. The antagonist of 5-HT2A/2C R ameliorated the memory deficit and deficit in sensorimotor gating induced by MK-801
Conclusions: Our findings are in accordance with the published results that antagonist of 5-HT2A/2C R and partial 5-HT1AR agonists could be effective in schizophrenia treatment. However, the high activation of 5-HT1A R could exacerbate psychotic symptoms. This research was supported by grant MZ0PCP2005 from the MZCR and by the projects 1M0517 from the MSMT

S-03-003
Learning and memory in 5-HT1A-receptor mutant mice

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Objectives: In most patients schizophrenia is accompanied by cognitive dysfunctions. Post-mortem and PET-studies revealed an increase in cortical 5-HT1A-receptor density and it was found that partial 5-HT1A-receptor agonists positively influenced verbal memory in schizophrenic patients, suggesting that cognitive deficits could be ameliorated by 5-HT1A-receptor active drugs. However, the role of the 5-HT1A-receptor for cognitive processes has not yet been clarified to its full extend. Recently, we introduced a mouse line with a postsynaptic overexpression of the 5-HT1A-receptor in cortex and hippocampus. The aim of this study was to further investigate the role of the postsynaptic 5-HT1A-receptor for learning and memory.
Methods: Wildtype and transgenic mice were tested in the inhibitory avoidance task, the Morris water-maze test, the hole-board test for habituation, and the social recognition test. Moreover, pre- and posttraining effects of 8-OH-DPAT (0.03-0.3 mg/kg) on the inhibitory avoidance performance were examined.
Results: Transgenic mice display no overall cognitive deficit: Untreated wildtype and transgenic mice showed a comparable performance in the inhibitory avoidance task and Morris water-maze test, and both genotypes habituated to the hole-board in a similar manner. However, anterograde amnesia induced by 8-OH-DPAT was only apparent in transgenic mice at a dose of 0.3 mg/kg. In both genotypes retrograde amnesia was not observed after the administration of 0.3 mg/kg 8-OH-DPAT.
Conclusions: Since the 5-HT1A-receptor overexpressing mice show untreated a rather normal behaviour likewise to wildtype mice, we assume that transgenic mice possess compensatory mechanisms. However, after activation of the postsynaptic 5-HT1A-receptors the differences between wildtype and transgenic mice became more visible. Hence, our findings suggest that postsynaptic 5-HT1A-receptors in cortex and hippocampus play rather a modulatory than a pivotal role in learning.

S-03-004
Serotonin-1A receptors and cognitive enhancement in schizophrenia: Evidence from translational research

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Objectives: Postmortem and PET studies indicate increased serotonin (5-HT)-5-HT1A receptor density in several brain areas mediating cognition, e.g. prefrontal cortex, in subjects with schizophrenia. This is consistent with neurochemical and behavioral data from animal studies in which both perospirone and aripiprazole, second generation antipsychotic drugs (SGAs) with 5HT1A agonist actions, ameliorate phencyclidine-induced learning memory deficits, an effect blocked by pretreatment with 5HT1A antagonists. The objective of this presentation is to provide some of the recent views on the role of 5HT1A receptors in cognitive remediation in schizophrenia.
Methods: The author will provide a review of clinical studies on the effect of 5-HT1A partial agonists, such as tandospirone and buspirone, on cognitive domains relevant to outcome in patients with schizophrenia. These studies were conducted with a randomized, placebo-controlled, double-blind fashion. To understand the neural basis for cognitive benefits of 5-HT1A agonists, data from three-dimensional brain imaging of P300 electrophysiological activity in patients treated with perospirone will be presented.
Results: The addition of small to moderate dose tandospirone, but not placebo in patients treated with first generation antipsychotic drugs was found to improve executive function and verbal learning and memory. On the other hand, buspirone outperformed placebo in improving performance on a measure of attention/speeded motor performance in subjects treated with SGAs. Standardized low-resolution brain electromagnetic tomography (sLORETA) images of P300 indicate 6-month treatment with perospirone was associated with enhancement of P300 activity in the left prefrontal cortex, one of the brain regions showing an increase in 5-HT1A receptor density in subjects with schizophrenia (e.g. Sumiyoshi et al. 1996).

Conclusions: These clinical observations indicate 5-HT1A receptors are a promising target for the treatment of cognitive disturbances of schizophrenia. This concept may concur with other presenters of this symposium who will provide genetic, neurocognitive, and pharmacological findings concerning these receptors.

S-10
Disturbed synaptic plasticity in schizophrenia? The evidence, visualisation and modulation.

S-10-001
How good is the evidence from post-mortem studies?

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Objectives: To review the post-mortem research evidence for disturbed synaptic plasticity in schizophrenia.
Methods: The focus will be on studies evaluating the integrity of synaptic terminals using markers for presynaptic complexes. These include the SNARE proteins SNAP-25, syntaxin and VAMP, as well as proteins which interact with members of the SNARE complex (synaptotagmin, complexin, sept5, synaptophysin). Relevant animal studies investigating the possible effects of antipsychotic drugs and the role of these proteins in cognitive function will be examined.
Results: Animal studies indicate measuring the amount and distribution of SNARE and modulator proteins can be informative concerning disruptions to neural connectivity. SNARE and modifier proteins are altered in amount and distribution in schizophrenia. In 14/18 studies, individual presynaptic proteins or the coding mRNAs were differentially affected in schizophrenia compared with control samples. In 11 of these studies, there was discordance between schizophrenia-related effects on synaptophysin, and schizophrenia-related effects on other presynaptic proteins, indicating not all proteins or all terminal types were equally affected. In 17 studies, all indicated the effects of schizophrenia on presynaptic proteins or the coding mRNAs were different in at least one brain region compared with other regions, indicating the effects of schizophrenia on neural connectivity may be more pronounced in specific circuits. New data also indicates that in addition to differences in amount of these proteins in schizophrenia, protein-protein interactions are also disturbed.
Conclusions: Studies of SNARE and other proteins enriched in presynaptic terminals indicate abnormalities are present in schizophrenia. These may affect specific sets of proteins and specific neural circuits differently. Studies of SNARE proteins forming into complexes, and of interactions between SNARE and modulator proteins may provide new insights into the mechanism of illness.

S-10-002
Using in-vivo imaging: Can we see synaptic processes directly?

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Gunther Helms

S-10-003
NRG-1, synaptic processes and schizophrenia

Stephen Lawrie
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S-10-004
Enhancing synaptic processes via exercise? Is there evidence for schizophrenia?

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Objectives: Physical exercise may change brain function and structure and increase grey matter volume in humans. In patients with schizophrenia the volume of certain brain regions, i.e. the hippocampus, is reduced. We investigated the effects of physical training on brain morphology and clinical features in a randomized, controlled trial.
Methods: Sixteen male patients with schizophrenia were either randomized to perform cycle ergometry (SP) or tabletop football (CP) for 30 minutes three times a week for 3 months. Eight healthy volunteers (SV) matched for age, socio-demographic variables and Body Mass Index also underwent physical exercise. Before and after the intervention incremental exercise testing, MRI scanning, and psychopathological rating, including Positive and Negative Syndrome Scale (PANNS) were performed. Results were controlled for a variety of clinical parameters.
Results: The left (LH) and right (RH) hippocampus volume increased significantly in both exercise groups (SP: LH +12.8%, RH +11.3%, $p<0.001$; SV: LH +17.1%, RH +16.0%, $p\leq0.01$) but not in the CP group. The increase was correlated with the training intensity. In the SP group a significant reduction in the PANSS cognition subscore was found (18.0±6.6 pts. vs. 13.8±5.5 pts; $p<0.05$). Differences in the changes from baseline to endpoint between the SP and CP group were significant in the PANSS total score, negative, cognition, and agitation subscores in favor of the SP group.
Conclusions: Physical exercise in patients with schizophrenia was found to increase the hippocampus volume and to improve psychopathology.

S-36
Psychophysiological endophenotypic makers in prodromal and first-episode schizophrenia patients

S-36-001
Endophenotype candidacy of key psychophysiological disturbances in schizophrenia

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Objectives: A bidirectional effort – laboratory to large-scale studies – may enhance translational research in schizophrenia. The application of neurobehavioral probes in functional imaging enables to examine the underlying brain circuitry in relation to task performance. When such tasks are applied in family studies, their suitability as endophenotypic measures can be assessed. Emotion processing was examined with fMRI showing deficits in patients with schizophrenia. The test was included in the Penn computerized neurocognitive battery (CNB) in large-scale genetic studies, demonstrating its utility as an endophenotypic measure. Both patients and first-degree relatives have deficits in affect recognition and these are associated with abnormal amygdala response to fearful faces. Amygdla over-reactivity in patients is associated with flat affect. Thus, elucidating a specific physiological disturbance may yield insight into pathophysiology that can be linked to genetics.

S-36-002
Deficits in prepulse Inhibition in the prodrome of schizophrenia

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Objectives: Schizophrenia patients exhibit impairments in prepulse inhibition (PPI) of the acoustic startle response (ASR). PPI is commonly used as an index of sensorimotor gating. Results of animal studies and some human data suggest that PPI deficits are in part genetically determined, such that PPI could be an endophenotypic indicator of risk for schizophrenia. Thus, PPI deficits should already be present prior to onset of psychosis. To test this assumption, we investigated PPI in individuals with prodromal symptoms of schizophrenia and patients with first-episode schizophrenia.
Methods: Startle reactivity, habituation, and PPI of ASR were assessed in 54 subjects with prodromal symptoms of schizophrenia (35 at an early prodromal stage, 19 at a late prodromal stage), 31 first episode schizophrenic patients (14 unmedicated, 17 medicated), and 28 healthy controls. Patients were also examined with the Positive and Negative Symptom Scale and the Global Assessment of Functioning Scale.

Results: Prodromal subjects and unmedicated patients with first episode schizophrenia showed significant PPI deficits, whereas schizophrenic patients treated with risperidone had almost normal PPI. In contrast, startle reactivity decreased with severity of symptoms but was relatively unimpaired in the medicated patients. With respect to habituation, prodromal subjects and schizophrenic patients did not differ from healthy controls.
Conclusions: PPI disruption is present in subjects in a prodromal state likely to proceed to schizophrenia, supporting the hypothesis that PPI disruption is an endophenotype of schizophrenia. In contrast, startle reactivity and habituation deficits were not evident in the prodromal subjects, but only in unmedicated patients with a diagnosis of schizophrenia.

S-36-003
Effects of a six month antipsychotic treatment on sensory(motor) gating and its neural generators: A longitudinal study of antipsychotic-naive first-episode schizophrenic patients

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Objectives: Evidence is accumulating that cognitive deficits form core features in schizophrenia. It has been suggested that treatment with atypical antipsychotics can ameliorate these deficits. However, studies have often been confounded by medication or chronicity of the disease, making it hard to differentiate between the features related to schizophrenia itself, and those caused by medication effects and/or progress of the disease. In the present study the influence of six months treatment with quetiapine was investigated on psychophysiological parameters of sensory gating in a large group of first-episode, antipsychotic-naïve schizophrenia patients and age and gender matched healthy controls.
Methods: Thirty-four antipsychotic-naïve patients with first-episode schizophrenia and 34 age and sex matched healthy controls were tested in both a P50 suppression and a prepulse inhibition of the startle reflex (PPI) paradigm both at baseline and after a period of 6 months. The patients were treated with quetiapine during the period between baseline and follow-up, the controls received no treatment.
Results: At baseline, patients showed significant reductions in both P50 suppression and PPI, at follow-up only the P50 suppression deficits remained. Source localization of the P50 amplitude revealed two bilateral sources located in the temporal cortex, two bilateral sources located near the eyes, and one source in a fronto-central location. Only the last source was positively correlated with the P50 amplitudes of both patients and controls.
Conclusions: The results indicate that deficits in P50 suppression and PPI are present at an early stage in the development of schizophrenia. Furthermore, where PPI of the patients improved to such a level that it was not significantly different from the controls anymore, P50 suppression did not respond to a 6 months treatment period with quetiapine. Furthermore, a generator with a fronto-central origin in the brain (possibly the anterior cingulate) was found to be the principal source of the P50 amplitude.

S-36-004
Vulnerability markers in the prodrome in early psychosis: Predicting outcome and understanding the mechanism

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Objectives: Schizophrenia emerges during a period of active brain development. A greater understanding of early neuropathological changes in the prodrome and first episode of schizophrenia can lead to earlier identification, informed treatment and perhaps prevention of this devastating illness. Electrophysiological measures that index early sensory processing, including P50 event related potential sensory gating, mismatch negativity (MMN) and prepulse inhibition (PPI) of the startle response, have been shown to be deficient in individuals with schizophrenia, their first degree relatives and schizotypal personality disorder. Translational studies that include developmental models suggest that that these paradigms may be useful markers for understanding the early stages of psychosis, providing insight into neural and genetic substrates.
Methods: Individuals at risk for psychosis (N=72), FE patients (N=43) and normals (N=56) ages 12 to 33 were assessed as part of a clinical, neurocognitive and electrophysiologic battery at at 6 months intervals.
Results: The pattern of results varies across time and measures. FE and AR subjects have deficits in MMN as well as N100 gating in the paired click ERP paradigm. PPI deficits are most prominent in FE subjects with an earlier age of onset and appear to worsen over time. In addition, measures of PPI asymmetry suggest neurodevelopmental differences in the early psychosis group. Interestingly, performance across measures is not significantly correlated.
Conclusions: Prodromal and FE subjects show a range of early sensory processing deficits that can provide insight into the early stages of psychosis. While early evoked responses and MMN may specifically index those deficits that are present before the onset of illness, PPI appears to be sensitive to developmental changes early in the course of illness. The lack of a correlational relationship between measures suggests separable underlying neural substrates that may help to tease out different aspects of risk and neuropathological.

S-37
Psychoses at the interface between neurology and psychiatry

S-37-001
Epilepsy and psychosis – an epidemiological view

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Objectives: Epilepsy is comorbid with schizophrenia and other psychosis, but most studies are conducted in select populations of people with severe forms of epilepsy and few assess time order. We evaluate the epidemiological evidence for the observed comorbidity, the potential contribution of febrile seizures, and whether particular types of epilepsy are more likely to be comorbid with schizophrenia and other psychosis.
Methods: A literature review of studies evaluating the comorbidity of epilepsy and schizophrenia and other psychosis and the comorbidity of febrile seizures and schizophrenia.
Results: In a Danish population-based cohort, individuals with newly diagnosed epilepsy were 2.5 times more likely to develop schizophrenia than those without epilepsy and 2.9 times more likely to develop schizophrenia-like psychosis. This association was not restricted to complex partial epilepsy or to other focal epilepsies. First degree family history of epilepsy and of psychosis contributed to the increased risk for schizophrenia. In contrast, a case-control study from Rochester, Minnesota found that schizophrenia was protective for the development of epilepsy. These intriguing findings suggest that epilepsy or its correlates may increase the risk for schizophrenia. Febrile seizures are associated with a 1.7-fold increased risk for schizophrenia in the Danish cohort. This finding has recently been replicated in a US cohort. Interestingly, a Japanese study reported an association between febrile status epilepticus and interictal psychosis in temporal lobe epilepsy. This may provide a hypothesis to explain the association between FS and psychosis as hippocampal pathology develops in about 12% of children with febrile status epilepticus. Most clinical studies of comorbidity of epilepsy and psychosis find a stronger association for temporal lobe epilepsy, but selection factors may contribute to this finding.
Conclusions: Epilepsy or its correlates appears to increase the risk for schizophrenia and sequelae of febrile seizures may contribute to this association.

S-37-002
Psychosis, neurological soft signs and their meaning

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Objectives: An excess of neurological signs is present in psychosis, particularly in primary and motor coordination signs. It remains unclear whether these signs progress over the course of the illness, and it has never been investigated whether any progression is associated with changes in brain structure.

Methods: We evaluated 49 individuals (mean age 27 years +-8; 59% males; 45% DSM IV schizophrenia) at the time of the first psychotic episode and 6 years later. We investigated neurological function using the Neurological Evaluation Scale, and grey matter volume using Magnetic Resonance Imaging, with a 1.5 T GE scanner. We estimated grey matter volume with automated segmentation methods.
Results: Rates of primary and motor coordination signs remained stable over the follow up period, as did motor sequencing signs. In contrast, sensory integration signs increased over the follow up period (p=0.007). Higher rates of primary signs (at baseline) and higher rates of motor coordination signs (at follow up) were correlated with more grey matter loss over follow up (p=0.05 and p=0.072 respectively).
Conclusions: Primary and motor coordination deficits may represent trait markers of psychosis and their presence may be predictive of a more progressive illness course. Further work will investigate whether these signs are also associated with regional brain changes.

S-37-003
Epilepsy and psychosis – anatomy and physiology

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Objectives: To compare the similarities and differences between schizophrenia and the schizophrenia-like psychoses of epilepsy.
Methods: The phenomenological data and the brain imaging data of people with the schizophrenia-like psychoses of epilepsy will be presented and compared with those from schizophrenia.
Results: The data show some important differences which reveal that people with the epileptic psychoses retain affective responses and have recurrent affective episodes in contrast to the flat affect reported in schizophrenia. Further the prognosis of the former appears to be better. Data reveal that in contrast to schizoprhenia in the epileptic psychoses the amygdala are increased in size and there is less alteration of cognitive function and less alteration of cortical structure.
Conclusions: These results will be discussed in the context of trying to understand the biolgoical bases of psychoses through neurological models.

S-37-004
On the question of the lateralization of epilepsy in the manic-depressive syndrome and depression

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Reviewing the evidence published in the last 40 years on the lateralization of the epilepsy in cases associated with depression, the majority of studies show that depression relates to right sided temporal lobe epilepsies (and generalized epilepsies). However, some reports link depression to left hemisphere epilepsies, especially when associated with structural lesions of the left hemisphere and frontal lobe impairment, whereas, with intact frontal lobe function depressions are related to right hemisphere epilepsies. In the case of mania there are fewer reports, but strikingly the association is with the right hemisphere, importantly this is also true after right temporal lobectomies. It will be argued that these apparently contradictory findings can be explained by taking into consideration transcallosal disinhibition: both mania and depression originate in the right hemisphere, mania is evoked by contralateral dysfunctional activation of the left hemisphere and depression arises either by ipsilateral ictal right hemisphere activation or by abnormal activation of that hemisphere in the case of structural lesions where the brain damage effect overrides the epileptic aspect, shifting the brain state to right hemisphere preponderance.

S-48
New findings on the neurobiological basis of language abnormalities in schizophrenia

S-48-001
Contribution of gene-brain interaction to language abnormalities in schizophrenia

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Objectives: The D-amino acid oxidase activator gene (DAOA or G72) has been found associated with several psychiatric disorders such as schizophrenia, major depression and bipolar disorder. Impaired performance in verbal fluency tasks is an often replicated finding in the mentioned disorders. In functional neuroimaging studies, this dysfunction has been linked to signal changes in prefrontal and lateral temporal areas and could possibly constitute an endophenotype. Therefore, it is of interest whether genes associated with the disorders, such as G72, modulate verbal fluency performance and its neural correlates.
Methods: 84 healthy individuals performed a semantic verbal fluency task while brain activation was measured with functional MRI. All subjects were genotyped for two single nucleotide polymorphisms (SNP) in the G72 gene, M23 (rs3918342) and M24 (rs1421292), that have previously shown association with the above mentioned disorders. The effect of genotype on brain activation was assessed with fMRI during a semantic verbal fluency task.
Results: While there were no differences in performance, brain activation in the right superior temporal gyrus (BA 22) was positively correlated with the number of M24 risk alleles in the G72 gene.
Conclusions: G72 genotype does modulate brain activation during language production on a semantic level in a key language area. These findings are in line with structural and functional imaging studies in schizophrenia, which showed alterations in the superior temporal gyri bilaterally.

S-48-002
Disordered thought and impaired connectivity of language regions in schizophrenia

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Objectives: To use 3T fMRI to study the interplay between the anterior (frontal) and posterior (sylvian-parietal-temporal, SPT) language systems in verbal working memory in schizophrenia. The theoretical basis was the left SPT region acting as the interface between phonological networks in the bilateral superior temporal sulcus (STS) and gyrus (STG) and the anterior articulatory networks.
Methods: Subjects were 14 chronic schizophrenic patients and 14 demographically matched healthy controls performing 12 runs each of these auditory and visual verbal working memory protocols: a) 3 sec encoding phase, three different words to be memorized are sequentially presented 1/sec; b) 15 sec rehearsal phase with instructions silently to rehearse one word each time a 1/sec crosshair signal occurred (to control rehearsal rate); c) Retrieval with 1/sec sequential presentation of 3 words with instruction to indicate if order was the same or different than in encoding phase. Two analyses were done separately for each memory stage in each modality: (i) regional analysis specifically targeted the posterior language system and (ii) analysis of functional connectivity between the anterior and posterior language systems.
Results: In the regional analysis, the left SPT region showed consistently reduced activation during encoding and retrieval stages in schizophrenia. Magnitudes of activation in the bilateral posterior STS were positively and significantly correlated with severity of delusions at every memory stage. Stage-specific functional connectivity analysis revealed reduced temporal correlations of activation between the left SPT and the left anterior insula during encoding of auditory words, the degree of which was correlated with severity of auditory hallucinations.
Conclusions: These findings implicate SPT/STS and the connection with anterior insula as a neural substrate of delusions and auditory hallucinations in schizophrenia. They are highly congruent with our and others' structural MRI findings of abnormally reduced STG/STP and anterior insula volumes and with DTI findings of an abnormal arcuate fasciculus.

S-48-003
Abnormalities of the language circuitry in schizophrenic thought disorders and hallucinations

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Objectives: To understand the pathophysiology of psychotic thought disorders; possible common structural and neurophysiological mechanisms shared with auditory verbal hallucinations
Methods: Patient groups selected for the actual presence of the specific schizophrenic symptoms of auditory verbal hallucinations and formal thought disorders. Arterial spin labeling and structural imaging
Results: A functional imbalance of the language system was found, correlated with the severity of formal thought disorders. In particular, a hyperactivation at rest in frontal and temporal language related areas along with a structural deficit in the involved left temporal regions was found.
Conclusions: A structural deficit in left temporal regions was associated with hyperexcitation of regions involved in the left fronto-temporal language system, and formal thought disorders. A complex imbalance of the language system on the basis of regional developmental deficits might be the neurophysiological basis of typical, language related core symptoms of schizophrenia

S-48-004
Language deficits in schizophrenia: Evidence from behavioral, functional and connectivity studies

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Raquel Gur, Monica Calkins, David Leitman, Christian Kohler

S-50
Microglia in psychiatric disorders

S-50-001
Microglia as an immune source: The possible role in schizophrenia and depression

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Objectives: Microglia is the primary component of the intrinsic immune defence in the CNS, this cell type constitutes ~ 15% of the total CNS cells. Microglia provides the first line of defense whenever injury or disease occurs. It can sense a wide range of stimuli that disrupt physiological homeostasis including CNS trauma, ischemia, infection, toxic insult and autoimmune injury. An acute insult to the CNS triggers rapid microglia activation, the principal component of neuroinflammation. Once activated, microglia show a series of changes on morphology, gene expression, and number: resident microglia shows an increased proliferation and infiltrating precursors are increasingly recruited. Moreover, activated microglia cells show increased phagocytosis and produce and secrete a spectrum of inflammatory mediators, such as pro-inflammatory cytokines, chemokines, reactive free radicals and eicosanoids. These inflammatory mediators can not only further modulate immunologic actions but also act on neurons to alter their function. Microglia cells become quickly activated in response to CNS injuries or immunologic stimuli. Activated microglia functions similarly to macrophages by undergoing phagocytosis, antigen presentation, and rapid proliferation. Compared to macrophages, microglial reaction is more tightly regulated spatially and temporally to maintain a precise immune response and thereby to protect the vulnerable nervous tissue, but a variety of substances secreted from activated microglia can damage neighbouring healthy tissue and maintain the vitious circle of CNS inflammation.
Since microglia can be activated both, by cytokines or other inflammatory mediators which are transported from the peripheral blood into the CNS and from stimuli released from other CNS-cells, an inflammatory microglia activating CNS process can be either blood-borne or CNS-borne.

S-50-002
Glial Cell Changes and Gene expression in the Brain and Blood in Schizophrenia

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Objectives: Schizophrenia is devastating disorder characterized by intermittent episodes of psychosis and cognitive impairment affecting executive functioning. Neuropathologically, the most robust findings are ventricular enlargement and microscopically diminution of synaptic and dendritic markers. Traditionally the pathological process is proposed to encompass neuronal dysconnectivity whereas; the putative role of other glial cell populations has been largely ignored.
Methods: Thus, in this presentation I will review our neuropathological and gene expression work suggesting involvement of the immune system in schizophrenia and related psychiatric disorders and how potential microglial dysregulation can affect neuronal function. First, I will discuss previous work in which we have demonstrated that glial cell abnormalities, such as reduction in glial cell cortical density exist in schizophrenia and that this is shared with affective disorders. I will then present our observations of significantly up regulated microglial markers such as calprotectin, in the schizophrenia brain.
Results: I will also discuss our observations of abnormalities in the expression of glycogen synthase kinase-3 beta, which has roles in maintenance of the cytoskeleton as well as an emerging role in modifying signaling in the innate immune system. Finally, I will present our recent results in a comparative gene expression study of the brain and blood compartments in schizophrenia in which we noted three MHC Class II genes were deregulated in both compartments.
Conclusions: I will conclude with a description of current analysis of a novel blood based dataset in which genes involved in the immune development, function and response are over-represented.

S-50-003
The distribution of microglia in post-mortem brains of patients with schizophrenia and depression

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Objectives: One of our recent postmortem studies [Steiner J, Mawrin C, Ziegeler A, Bielau H, Ullrich O, Bernstein HG, Bogerts B. Distribution of HLA-DR-positive microglia in schizophrenia reflects impaired cerebral lateralization. Acta Neuropathologica 2006;112:305–16.] revealed increased microglial densities in two schizophrenic patients who had committed suicide. Therefore, the hypothesis of microglial activation in schizophrenia and depression is dicussed in the context of previous publications on this topic.
Methods: Microglial HLA-DR expression was analyzed by immunohistochemistry in the dorsolateral prefrontal cortex (DLPFC), anterior cingulate cortex (ACC), mediodorsal thalamus (MD) and hippocampus of 16 schizophrenics, 14 depressed patients with affective disorder and 10 matched controls. A subgroup of six schizophrenics and seven patients with affective disorder who committed suicide was included.
Results: No diagnosis-dependent changes in microglial density were observed (DLPFC: $P = 0.469$; ACC: $P = 0.349$; MD: $P = 0.569$; hippocampus: $P = 0.497$). However, significant microgliosis was detected in the DLPFC ($P = 0.004$), ACC ($P = 0.012$) and MD ($P = 0.004$) of suicide patients. A similar trend was seen in the hippocampus ($P = 0.057$).
Conclusions: In conclusion, immunological factors may play a hitherto underestimated role in suicide. First, microglial activation might be interpreted as a consequence of presuicidal stress. Second, one might speculate a causal link between microglial activation and suicidal behaviour, such as cytokines and nitric oxide, which are released from microglial cells are known to modulate noradrenergic or serotonergic neurotransmission and thus may trigger suicidality.

S-50-004
Ultrastructural abnormalities of microglial cells in post-mortem brains in schizophrenia

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Objectives: The results of postmortem immunohistochemical studies of microglial density in schizophrenia (SZ) brain are controversial. Deficit of oligodendrocytes, ultrastructural alterations of oligodendrocytes and myelinated fibers, degeneration of oligodendrocytes and their close apposition with microglial cells have been described in SZ brain. We performed quantitative electron microscopic study of microglial cells, including those located in close apposition to oligodendrocytes, in SZ and control brains.
Methods: Microglial cells were studied in prefrontal cortex (PFC, BA10, layer V), head of the caudate nucleus (CN) and CA3 hippocampus (pyramidal layer) in 40 chronic SZ cases and 40 normal matched controls. Volume fraction (Vv) and cross-sectional areas of nucleus and cytoplasm of microglial cells were estimated.
Results: ANCOVA followed by post hoc revealed the effect of diagnosis but not age or postmortem delay on Vv and area of nucleus of microglial cells and decrease of the parameters in CN in SZ group vs. controls (-40%, $p<0.01$; -10%, $p<0.05$). The changes were found only in the subgroup of cases with predominantly negative symptoms (20 cases, $p<0.05$). In this subgroup area of nucleus of microglial cells correlated positively with onset of disease ($r= 0.51$, $p<0.05$) but not with age ($r=0.35$, $p=0.16$). The parameters did not differ significantly in PFC and hippocampus in SZ compared to controls. Vv of microglia apposed total oligodendrocytes and degenerating oligodendrocytes significantly decreased in CN but increased in PFC in SZ group vs. controls. Vv of microglia correlated negatively with the proportion of pathological of myelinated fibers in CN in SZ group ($r = -0.42$, $p<0.01$) and positive in control group ($r=0.33$, $p<0.05$).
Conclusions: Region specific decreased size of nucleus and deficit of microglia in CN are present in SZ cases with predominantly negative symptoms. Reactivity of microglia in SZ is associated with the pathology of oligodendrocytes and myelinated fibers. Supported by Stanley Medical Research Institute.

S-55
EEG and MEG response to mismatch stimuli as an index of schizophrenia neurobiology and genetics

S-55-001
Mismatch negativity from the prodrome to chronicity: Relationships with functional status, generator sources and grey matter loss

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Objectives: To explore whether mismatch negativity (MMN) is reduced in prodromal schizophrenia, and determine the relationship of MMN in schizophrenia patients to functional status, grey matter loss and generator sources. Three separate studies are reported.
Methods: Study 1: MMN to duration deviants was recorded from 72 individuals at ultra-high risk (UHR) of developing schizophrenia (13 met criteria for first episode psychosis at baseline - FEP, 6 made a subsequent transition within one year) and 20 healthy subjects. Study 2: MMN was recorded in response to duration, frequency and intensity deviants in 18 schizophrenia patients with an established illness and 18 healthy subjects. Functional status was assessed using the SOFAS. High-resolution structural magnetic resonance scans were acquired to generate average cerebral cortex models using cortical pattern matching and provided grey matter estimates. Study 3: Cortically constrained LORETA source analysis of duration MMN in 16 recent-onset patients, 19 chronic patients and 35 matched controls.
Results: Study 1: duration MMN was significantly reduced in both FEP and UHR groups, and a non-significant reduction in MMN in 6 UHR individuals making a subsequent transition to schizophrenia compared to 19 UHR individuals who did not. Study 2: MMN amplitude to all deviants was reduced in schizophrenia patients but only frequency and duration MMN correlated with SOFAS. However, only frequency MMN in patients was correlated with fronto-temporal grey matter reduction. Study 3; LORETA analysis revealed strong duration MMN sources in temporal cortex and weak sources in frontal regions. Both sources were reduced in schizophrenia but more marked in recent-onset patients.
Conclusions: Our findings suggest a close association between frequency MMN with cerebral pathology and daily functioning in established schizophrenia while reduced MMN to duration deviants appears to be associated with the prodrome and first-episode phase of the disorder.

S-55-002
Deficits in primary auditory cortex circuits in subjects with schizophrenia: Matching up with mismatch negativity

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Objectives: Schizophrenia is associated with auditory processing and event related potential impairments which localize to layer 3 of primary auditory cortex. We have undertaken a series of studies of this region in subjects with schizophrenia to identify abnormalities in auditory circuits which may contribute to these deficits.
Methods: Single and multiple label immunohistochemistry was used to determine densities of dendritic spines and populations of axon boutons in deep layer 3 of primary auditory cortex of subjects with schizophrenia and comparison subjects.
Results: We have found a 27% reduction in density of dendritic spines within deep layer 3 of primary auditory cortex which is correlated within subjects with densities of axon boutons. Preliminary data indicates that the reduction in bouton density arises from decreases of intracortical but not thalamocortical axon boutons.
Conclusions: The results suggest that dendritic spines and their primary inputs, corticocortical excitatory boutons, undergo correlated reductions in primary auditory cortex of subjects with schizophrenia. The restriction of findings to intracortical bouton densities suggests an intracortical, rather than thalamocortical, pathology underlies the observed functional and electrophysiologic impairments in auditory sensory processing.

S-55-003
MEG mismatch abnormalities to speech sounds in schizophrenia: Heritability and relationship to genetics

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Tsuyoshi Araki

Objectives: Patients with schizophrenia are associated with abnormalities in auditory mismatch negativity (MMN) and its magnetic counterpart, magnetic mismatch field (MMF), which is compatible with glutamatergic/synaptic dysfunction hypothesis of schizophrenia. We have extended the previous findings of lower voltage of tonal MMN in schizophrenia by using MMN/MMF in response to phoneme change.
Methods: Both tonal and phonetic MMN/MMF were recorded. We examined the correlation between MMF and the gray matter volume of PT where the major generators of MMF are located. We also investigated the MMF as the intermediate phenotype using genetic information.
Results: The effect size of the reduction was larger for phonetic MMN/MMF than tonal MMN/MMF. Moreover, in patients with schizophrenia, the reduced MMF power was significantly correlated with smaller gray matter volume of PT where the major generators of MMF are located. Data from healthy monozygotic and dizygotic twins indicate that phonetic MMF shows high heritability. Variations in metabotropic glutamate receptor 3 (GRM3) and brain derived neurotrophic factor (BDNF) genotypes interactively modulate MMF strength and hemispheric specialization in healthy men.
Conclusions: These convergent data suggest that MMN/MMF may be a non-invasive probe for evaluating synaptic plasticity based on glutamatergic neurotransmission system in the auditory cortex in humans and in patients with schizophrenia. Our investigations are now moving toward applying MMN as a useful biological maker for patients at risk mental state. The preliminary date of patients at risk mental state using duration MMN and frequency MMN will be presented.

S-55-004
Mismatch negativity is associated with genetic, clinical, cognitive, and functional abnormalities of schizophrenia patients

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Tiffany Greenwood, Anthony Rissling, Marlena Pela, Barbara Haugeland, Dana Gerrits, Lisa Uemura, Joyce Sprock, David Braff, Richard Sharp, Neal Swerdlow

Objectives: Schizophrenia patients have widespread deficits ranging from abnormalities in sensory processing to impairments in cognition and daily living. Mismatch Negativity (MMN) is an EEG waveform that is a probe of the earliest automatic stages of sensory information processing and can be elicited in the absence of directed attention.
Methods: To assess the genetic architecture of MMN, a candidate gene analysis was performed on 203 schizophrenia patients and 119 controls from the UCSD Schizophrenia Program using the UCSD/Consortium on the Genetics of Schizophrenia (COGS) custom 1536 SNP chip.
Results: The initial single marker analyses revealed significant associations with 25 of 94 carefully selected schizophrenia-related genes (empirical $p<0.01$). These genes included BDNF, GRIN3A, DISC1, CTNNA2, NRG1, and ERBB4. Several of these genes also interact molecularly (e.g., NRG1 and ERBB4). Patients had MMN deficits ($p<0.01$) which were associated with impaired performance on tests of working memory ($p<0.01$), verbal recall ($p<0.01$), and negative symptoms ($p<0.01$). MMN deficits were also associated with reduced performance on a comprehensive functional skills assessment battery ($p<0.05$), and significantly ($p<0.01$) lower ratings on several measures of functional status (e.g., independence in living situation, managing finances, Scale of Functioning, Global Assessment of Functioning Scale). In contrast, MMN was not associated with performance on other cognitive measures or positive symptoms.
Conclusions: MMN deficits reflect neural dysfunction associated with the core cognitive, clinical, functional, and even genetic abnormalities of schizophrenia patients.

S-65
Functional psychopathology: Linking neurobiology with psychopathology

S-65-001
Philosophical foundations of the relation between neurobiology and psychopathology

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Objectives: Modern psychiatry has become more and more dominated by neurosciences based mainly on the ideas of empirical positivism. The main tasks of so-called biological psychiatry are to analyze and explain the nature of mental disorders and its treatment. In the last decade, however, we may observe an increasing interest in human sciences based on post-modern assumptions and discourses in psychiatry. As upcoming globalisation and simplification in diagnostics of mental disorders have resulted in a growing indifference towards clinical psychopathology in general and in a loss of fruitful diagnostic diversity in particular, psychiatry itself runs the risk to disappear in the gap between neurosciences and medical humanities. A way-out of this dilemma may be found in the re-orientation to phenomenology, clinical and theoretical psychopathology. Thus, clinical psychopathology could become the integrating platform of both, the empirical research of the positivistic neurosciences a well as the hermeneutic analyses and synthesis of post-modern human sciences. Post-modernity with its change of paradigms opens up new perspectives in diagnosis and treatment of mental disorders. As psychiatrists, it is our duty not only to analyze the conditions and nature of mental disorders but also to enter into a dialogue with the human being suffering from the disorders' nature and narratives; it is our duty not only to register the symptoms and deficiencies of the patients but also to understand the patients' sufferings and to use the patients' resources in order to develop effective treatment approaches. In a post-modern human-based psychiatry it is no longer the disorder itself but the human being in all its complexity which will be the main target of diagnostic and therapeutic procedures.

S-65-002
An introduction to functional psychopathology

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Objectives: In the course of revising the current psychiatric classification systems ICD-10 and DSM-IV, these questions are again brought up since novel neurobiological findings may need to be integrated into the revised classification systems for mental disorders. Already Kraepelin stated that if it is at all possible to bring about progress in psychopathological diagnosis, the methods of experimental psychology appear to be qualified to fill this gap at least in part. According to Van Praag, psychological dysfunctions, not symptoms, are the elementary units of psychopathology. The dissection of a psychopathological syndrome into its component parts, i.e. psychological dysfunctions, as a complement to the nosological/categorical approach, is one approach to shed new light on the non-specificity of biological variables related to psychiatric disorders and to increase the chance of finding meaningful relations between biological and behavioral variables. It may encompass the assessment of psychopathology in patients by means of experimental methods, the experimental induction of psychopathology in patients (e.g. by pharmacological challenge), the experimental induction of psychopathology in healthy probands (e.g. with psychotomimetics), and the experimental modelling of psychopathological equivalents in animals. The application of behavior-oriented objective assessment methods and experimental variation of assessment conditions in psychopathology together with the assessment of brain function provides a more valid starting point for the differentiation between related/similar syndromes, the investigation of longitudinal stability, illness specificity and effects of various treatment modalities, and the identification of meaningful correlations between biological and behavioral variables (brain-behavior-relationship). It may thus promote a functional understanding of psychopathology.

S-65-003
Modules of the brain: Linking brain function to psychopathology

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Objectives: Current neurobiological findings suggest that the brain may use both flexible extended networks and functionally specified predetermined brain regions for fulfilling its physiological functions. The term "module" had initially been used to define the latter representational mechanisms of brain functions, but may be extended to the former as well, where "links", "hubs" and "nodes" take centerstage. Also, recent findings investigating the "small world" organisation of the cerebral cortex and its disturbance in schizophrenia have recently provided a novel approach to mental disorders. We will review the current state of the art in this area of and how these findings may be applied to define functionally defined modules of the brain as the targets for pathophysiological actions of genes and environmental factors in the pathophysiology of mental disorders. This will lead to a conceptualization bridging neurobiology and psychiatry.

S-65-004
Treatment of social cognition impairments in schizophrenia regarding facial affect recognition

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Abstract: Social functioning deficits are a paramount debilitating feature of schizophrenia (SCZ) and considered amongst the most treatment refractory. These features are observed from the first episode and even premorbidly in those who later develop the illness and are considered trait related. The impaired social functioning, affects effective and empathetic communication with others, employment and interpersonal behaviors that have a significant impact in quality of life for patients, family and community. There is evidence suggesting that Social Cognition (SC) (comprising social and emotion perception, Theory of Mind (ToM) and attributional style domains), relates to functional outcomes. SC would be related but distinct from neurocognition and negative symptoms.

Regarding emotion perception and processing, information gathered through facial affect recognition (FAR) is considered crucial for social interaction and adaptive behavior involving specific brain structures and neural networks. SCZ patients are reported to have FAR deficits especially regarding negative emotions and abnormalities in the visual scanning of faces (Streit M, et al 1996; Willams ML et al 1999). Within emotion perception, remediation techniques regarding impairments in FAR by specific training programs as the Training of Affect Recognition (TAR) (Woelwer W, et al 2005; Horan WP, et al 2008), using computarized standardized exercises with white and black pictures, depicting the six basic emotions, also included audio and video clips and facial mimicry exercises, have suggested that the improvement in SC, when compared with neurocognitive remediation or controlling for this factor, would follow a separate trajectory and need to be replicated. As SC training modules tailored to the patients needs linked with other training skills could result in real world improved social behavior, development of specific assessments and remediation techniques are needed.

S-79
The neural bases of hallucinations in schizophrenia: Recent advances in research

S-79-001
Hallucination symptoms and oscillatory brain dynamics in schizophrenia

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Objectives: High frequency oscillatory activity in the brain may play an important role in the representation and selection of information by synchronizing neural activity during transient attractor states. Abnormalities in elements of the neural circuitry underlying these oscillations have been reported in schizophrenia, suggesting that the psychotic symptoms and cognitive deficits of this disorder may be related to abnormal neural dynamics.
Methods: We have examined high frequency oscillatory activity in schizophrenia in a series of studies using the scalp-recorded electroencephalogram. Time-frequency analyses were performed with the Morlet wavelet transform.
Results: Studies from our laboratory have found positive correlations between hallucination symptoms and the phase synchrony of high frequency oscillations in schizophrenia: 1) A visual perception-related oscillation was reduced in frequency from the gamma (37 Hz) to the beta range (24 Hz) in schizophrenia patients. The phase locking factor (PLF) of this oscillation was positively correlated with visual hallucinations in the patients. 2) The 40 Hz harmonic of the 20 Hz auditory steady-state response (ASSR) was reduced in power and PLF in first-episode schizophrenia and affective psychosis patients. However, the PLF of this oscillation was positively correlated with hallucination symptoms in the schizophrenia patients only. 3) Source analysis of the 40 Hz ASSR in chronic schizophrenia patients found reductions in PLF in left and right auditory cortex generators. The PLF of a left auditory cortex generator was positively correlated with auditory hallucinations in the patients.
Conclusions: These correlations between enhanced high-frequency synchronization and hallucination symptoms are consistent with evidence from other measures for cortical hyperexcitability in schizophrenia. We propose that hallucinations in schizophrenia could result, in part, from an increased propensity for a hyperexcited neural network to visit attractor states independently of external influences, such as sensory stimulation or signals from attentional control areas.

S-79-002
Corollary discharge dysfunction in Schizophrenia

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Objectives: An intention to execute a motor act is accompanied by a corollary discharge of the expected sensation resulting from the action. An internal comparison is made between the corollary discharge and the actual sensation; the closer the match, the greater the suppression of sensation (Heinks-Maldonado et al, 2005). Evidence suggests that schizophrenia is characterized by dysfunction of the corollary discharge mechanism, altering patients' experience of their own thoughts and actions and contributing to hallucinations and perceptual aberrations. Synchronization of neural activity preceding actions may reflect corollary discharge operation, which dampens sensations resulting from those actions. If true, pre-action synchrony should be related to sensory suppression. If corollary discharge deficits are characteristic of schizophrenia and related to auditory hallucinations, patients will have reduced synchrony, especially hallucinators. Sluggish corollary discharge timing may contribute to its dysfunction.
Methods: In 24 patients and 25 controls, phase coherence of single-trial electroencephalography (EEG) preceding talking was calculated across trials. N1 event-related potentials to "ah" onset during Talking and Listening were compared. In another experiment, patients (n=21) and controls (n=25) pressed a button to hear their own pre-recorded "ah", with zero or 50ms delays between pressing and hearing. Both self-generated sequences of "ahs" were played back during Listening.
Results: In healthy controls, pre-speech synchrony was related to suppression of responsiveness to the "ah" as reflected in N1 reduction during Talking relative to Listening. Pre-speech synchrony was greater in controls than patients, especially those with severe hallucinations. A 50ms delay between pressing and hearing normalized N1 suppression in patients.
Conclusions: In conclusion, EEG synchrony preceding speech reflects corollary discharge action, which dampens auditory responsiveness to self-generated speech and is deficient in patients, especially hallucinators. Corollary discharge in patients may travel too slowly to suppress sensory experience.

S-79-003
Relation beween functional and structural cerebral changes in auditory verbal hallucinations

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S-79-004
Probing the pathophysiology of auditory/verbal hallucinations by combining fMRI and rTMS

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Michelle Hampson

Objectives: The objective of this presentation is to discuss interactions between brain regions that contribute to the genesis of auditory/verbal hallucinations (AVHs) in patients with schizophrenia.
Methods: An fMRI study will be presented that assessed functional connectivity relative to a seed region defined in Wernicke's area and its right homologue. Functional connectivity was calculated from correlations derived from resting BOLD signal data. Hallucinating patients with schizophrenia (N=32), nonhallucinating patients with schizophrenia (N=24) and healthy controls (N=23) were compared. Results of a clinical trial comparing effects of 1-Hz rTMS delivered to right versus left Wernicke's region will also be discussed. 37 patients with persistent AVHs have been studied to date. These two regions were probed using active versus sham rTMS for 5 sessions each. Positioning utilized structural MRI and a BrainLab stereotactic system. Each session consisted of 16 minutes of stimulation at 90% motor threshold.

Results: Bilateral Wernicke's functional connectivity was found to shift away from cortical sites and onto thalamic and midbrain sites in patients with schizophrenia overall compared to healthy controls. AVH vulnerability was associated with spared functional connectivity linking the Wernicke's seed region to a subregion of left IFG expressed against a backdrop of reduced functional connectivity to other cortical regions. Enhanced subcortical functional connectivity to the thalamus and midbrain monoamine centers appeared to contribute to hallucination severity as evidenced by a positive correlation between these cortical/subcortical functional connectivity measures and experiential salience of AVHs. The rTMS clinical trial reveals that positive response to left Wernicke's area is a negative predictor of positive response to the right Wernicke's region and vice-versa.
Conclusions: AVHs appear arise from activation exchanged between left/right Wernicke's regions and inferior frontal regions whose access to consciousness is enhanced by subcortical systems. Left versus right Wernicke's regions may compete for access to these hallucinogenic subcortical inputs.

S-81
Auditory sensory gating in schizophrenia: Towards a better understanding of the genetical, neurophysiological, and neurochemical underpinnings

S-81-001
Clinical correlates of N100 gating deficit in schizophrenia

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Klevest Gjini

Objectives: The clinical correlates of decreased gating of the N100 mid-latency auditory evoked response (MLAER) noted in schizophrenia patients are yet to be elucidated.
Methods: We examined the clinical correlates of sensory gating of three MLAERs: P50, N100, and P200 in a large sample of well characterized patients (N=50) and age and gender matched healthy controls (N=50). All patients were stable outpatients on atypical antipsychotic medications. All subjects had a SCID interview and patients had a PANSS interview as well. All subjects had two runs of a standard paired-click paradigm (i.e, two identical 4ms clicks [S1 and S2] with 500 ms between stimuli and 8 seconds between the pairs of stimuli) and a total of 60 pairs delivered. Sensory gating was calculated for each evoked response as the ratio of S2/S1 and as the difference of S1-S2 amplitudes.
Results: Overall, the N100 ratio was significantly higher in schizophrenia patients. When covaried with the amplitude of the N100 S1 response, the N100 ratio abnormality remained significant. Neither the P50 nor the P200 gating indices survived the covariance with S1 amplitudes suggesting that the abnormality may be mainly due to a smaller response to S1 rather than decreased gating of S2. A number of clinical correlations were detected between the S2/S1 ratio of the N100 mainly negative symptoms of schizophrenia (e.g., decreased volition and motor retardation. Overall, the N100 ratio correlated positively with the negative syndrome subscale ($P<0.05$) (i.e., worse gating correlated with higher scores on the negative symptoms scale).
Conclusions: The data suggest that N100 gating is abnormal in schizophrenia patients even when stable on medications and that the abnormality is not secondary to an abnormal response to S1 stimuli. The data also suggest a correlation between negative symptoms and N100 gating deficit.

S-81-002
Role of the frontal cortex in both auditory and somatosensory habituation: An MEG study

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Objectives: Auditory and somatosensory responses to paired stimuli were investigated, using magnetoencephalography (MEG), for commonality of frontal activation possibly associated with gating. Habituation to redundant sensory input, gating, is hypothesized to protect both higher cortical centers from flooding with irrelevant information, and to protect processing of the first response by filtering redundant sensory inputs. Schizophrenia patients show gating deficits for the P50 response compared to normal subjects indicating problems with processing repetitive sensory information.
Methods: Both hemispheres independently were tested with paired stimulus paradigms for each sensory evoked response in ten normal controls. MR-FOCUSS, a current density technique, imaged simultaneously active cortical sources.
Results: Each subject showed source localization, in primary auditory or somatosensory cortex, for the respective stimuli following both the first (S1) and second (S2) impulses. In normal subjects gating ratios for the auditory M50 response, equivalent to the P50 in EEG, were 0.54±0.24 and 0.63±0.52 for right and left hemispheres. Somatosensory gating ratios were evaluated for early and late latencies as the pulse duration elicits extended response. Early gating ratios for right and left hemispheres were 0.69±0.21 and 0.69±0.41 while late ratios were 0.81±0.41 and 0.80±0.48. Regions of activation in the frontal cortex, beyond the primary auditory or somatosensory cortex, were mapped within 25ms of peak S1 latencies in 9/10 subjects during auditory stimulus and in 10/10 subjects for somatosensory stimulus. Similar frontal activations were mapped within 25ms of peak S2 latencies for 75% of auditory and for 100% of somatosensory responses. Comparison between modalities showed similar frontal region activations for 17/20 S1 responses and for 13/20 S2 responses.
Conclusions: MEG offers a technique for evaluating cross-modality gating. The results suggest similar frontal sources are simultaneously active during auditory and somatosensory habituation. The data represent evidence for a crucial frontal lobe role in sensory gating in multiple modalities.

S-81-003
The neurochemical basis of sensory gating in humans

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Objectives: Regulation of sensory gating involves several neurotransmitter systems in the brain and is disrupted in psychiatric illnesses, such as schizophrenia. Using EEG measures and a double-blind, placebo-controlled, within-subject approach, we have studied the role of serotonin in the neuropharmacological regulation of prepulse inhibition (PPI), P50 suppression, mismatch negativity (MMN) and loudness dependence of the auditory evoked potential (LDAEP), a putative non-invasive electrophysiological marker of serotonin function in the brain. There are gender differences in schizophrenia and the female sex steroid hormone, estrogen, has been proposed to be protective against the illness. Therefore, we also addressed the effect of estrogen on sensory gating mechanisms.
Results: Treatment with the serotonin-1A receptor agonist, buspirone, significantly disrupted PPI in healthy female volunteers (Gogos et al., Neuropsychopharmacology 2006). Buspirone treatment had no effect on MMN amplitude but significantly enhanced LDAEP slope, consistent with reduced serotonin function (Guille et al., submitted). Estrogen treatment prevented the effect of buspirone on PPI. Moreover, it increased LDAEP slope and prevented any further increase by buspirone treatment. Separate studies by Nathan and co-workers in healthy male volunteers showed that acute tryptophan depletion (to decrease serotonin levels) significantly disrupted PPI, but not P50 suppression or LDAEP. In those studies, acute tyrosine/phenylalanine depletion (to decrease dopamine levels) had no effect on either PPI or P50 suppression while the simultaneous depletion of both serotonin and dopamine resulted in significant reduction of both PPI and P50 suppression (Mann et al., Neuropsychopharmacology 2008).
Conclusions: These results suggest that inhibition of serotonin function in the brain produces a range of effects on sensory gating in humans. Estrogen is able to modulate at least some of these mechanisms. In schizophrenia, these results could be important for our understanding of the mechanism of disrupted sensory gating, gender differences, and the potentially protective action of estrogen.

S-81-004
Time-frequency analysis of auditory sensory gating in first episode patients and subjects at risk

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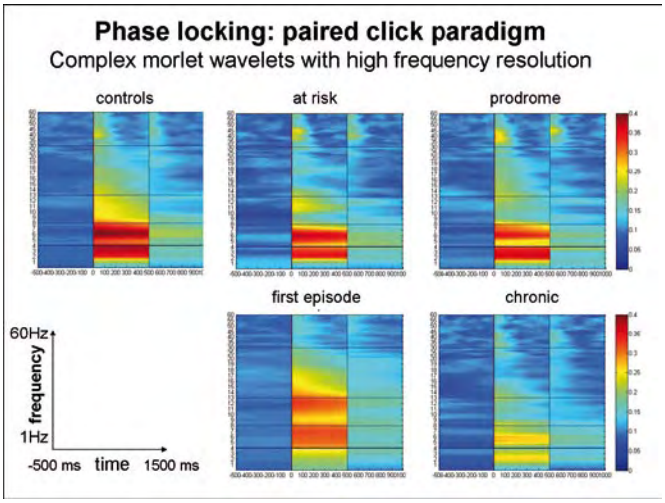
Objectives: Deficits in auditory sensory gating are well known in schizophrenia. Most research in this field is based on the analysis of mid-latency auditory evoked potentials P50 and N100. Time-frequency analyses enable a more precise investigation of stimulus-associated changes in brain oscillations.
Methods: We investigated event-related potentials (P50 and N100) and the neuronal synchronization (phase locking and oscillatory amplitude) during a paired click paradigm in 39 subjects at risk (18 without transition to psychosis within a 2 year follow up, 21 proven prodromal patients with later transition), 46 antiopsychotic-naïve first episode patients, 20 chronic schizophrenia patients free of antipsychpotics at the time of recording, and 46 healthy controls. Time-frequency analyses were based on complex Morlet wavelets separately for 5 frequency bands (gamma, beta, alpha, theta, delta) within the range from 1 to 60 Hz.
Results: Event-related potentials showed reduced N100 amplitudes elicited by the first click in proven prodromal patients, first episode and chronic schizophrenia patients, but no group differences concerning the P50 amplitudes. Phase locking (Fig 1.) in the gamma frequency range was reduced in first episode patients, but increased in the beta and alpha frequency range. In lower frequency bands phase locking was reduced in prodromal (alpha), first episode (theta), and chronic patients (theta and delta). The oscillatory amplitude in the lower frequency range (theta and delta) elicited by the first click was reduced in proven prodromal patients, first episode and chronic patients.
Conclusions: Beta phase locking reflecting interactions between distant brain regions is increased, whereas gamma phase locking reflecting sensory registration, and alpha phase locking reflecting inhibitory processes are reduced in first episode patients. In contrast to first episode patients, we found in proven prodromal patients reduced alpha phase locking indicating reduced inhibitory processes. Reduced theta phase locking and reduced theta amplitudes might reflect disturbances in working memory.



S-88
New insights into abnormal neural oscillations in schizophrenia and the structural and receptor basis of the abnormal neural circuitry

S-88-001
Gamma band and MRI structural abnormalities in first episode schizophrenia and mania

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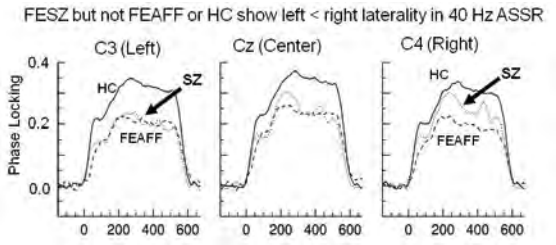
Objectives: In 1999 our group showed the auditory steady state response (ASSR) to gamma band stimulation was reduced in chronic schizophrenia, a finding since repeatedly replicated, and also reported in chronic bipolar disorder. However, it has remained unknown whether this deficit appears early in the course of the disorder or only appears later. Nor is it known whether this deficit is present in all psychoses or has features specific to schizophrenia.
Methods: Subjects were 16 first-episode patients with schizophrenia (SZ), 16 first-episode patients with affective psychosis (AFF, 14 bipolar), and 34 demographically matched healthy control subjects (HC), all right-handed. White noise clicks were at 20-Hz, 30-Hz, and 40-Hz stimulation rates and EEG responses recorded at 60 scalp sites. For ASSR analyses, the Morlet wavelet transform was applied to the single epochs in the 20–100-Hz frequency range of the EEG from -250 to 772 ms. Event-related spectral measures were computed on the wavelet-transformed epochs for each stimulus condition at each time point and wavelet frequency to yield time-frequency maps.
Results: During 40-Hz stimulation phase locking of the ASSR was reduced in SZ and AFF compared with HC, and the Group x Hemisphere interaction was significant. Compared with HC, the Group x Hemisphere interaction was significant for SZ but not AFF. (Results did not differ when only bipolars were included.) This pattern of effects reflected a larger reduction of phase locking in SZ over the left hemisphere compared with the right hemisphere (Figure). Group responses did not differ for 20 and 30 Hz stimulation.
Conclusions: The gamma band ASSR deficit is present at first hospitalization for psychosis in patients with both SZ and AFF, but differ in the presence of a left more than right deficit in SZ, congruent with strong left-lateralized structural MRI deficits in auditory regions in SZ but not in AFF.



S-88-002
Abnormal neural oscillatory activity to speech sounds in schizophrenia: An MEG study

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Objectives: Recently, it was reported that different magnetoencephalography (MEG) patterns of the evoked oscillatory activity (eOA) in 20-45Hz to speech and non-speech sounds were an evidence of a fast mechanism for the representation and identification of speech sounds in humans. In this symposium, we will present the data for neural oscillatory activity, as measured by eOA, to speech and non-speech sounds in patients with schizophrenia and bipolar disorder.

Methods: For eOA of schizophrenia, MEG data of 20 patients and 23 control subjects were analyzed. For eOA of bipolar disorder, the data of 11 patients and 24 control subjects were analyzed. MEG responses to speech and non-speech sounds were recorded and eOA power and phase-locking in 20-45Hz were measured.
Results: Schizophrenics showed significantly delayed peak latencies of the eOA power and phase-locking to speech sounds in the left hemisphere and to non-speech sounds in the right hemisphere. Schizophrenics also showed a significantly reduced eOA power to speech sounds in the left hemisphere in 0-50msec and a significantly larger eOA power to speech sounds in the left hemisphere in 100-150msec. In addition, the analyses of the lateralization index revealed the pattern of hemispheric lateralization to be the opposite in patients. For bipolar disorder, patients showed significant later peaks of the eOA phaselocking to speech sounds in both hemispheres but no significant differences to non-speech sounds.
Conclusions: These results indicated that schizophrenics showed different characteristics of eOA in comparison to normal controls, probably related to deficits in a fast mechanism for identifying speech sounds. Moreover, our data suggest that schizophrenia may be characterized by different hemispheric lateralization of eOA to speech sounds compared to bipolar disorder.

S-88-003
High-frequency oscillations during perceptual organisation in first-episode and chronic schizophrenia

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Objectives: Recent evidence suggests that patients with schizophrenia are characterized by reduced synchronous, oscillatory activity in the beta- and gamma-band range that may index a core dysfunction in the coordination of distributed neuronal responses. It is currently unclear, however, to what extent high-frequency oscillations (>60Hz) contribute to impaired neural synchronization as research has so far focussed on gamma-band oscillations between 30-60 Hz. Secondly, it is not known whether deficits in high-frequency oscillations are already present at the onset of the disorder and to what extent reductions may be related to the confounding influence of medication.
Methods: To address these issues, we employed magnetoencephalography (MEG), a method particular suited for the examination of low-amplitude, high-frequency oscillations, during perceptual organisation in a sample of chronic patients with schizophrenia (N=15), a sample of first-episode, never-medicated patients (N=14) and in a group of healthy controls (N=20). Perceptual organisation was examined with Mooney Faces. MEG signals were analysed for spectral changes in oscillatory activity in the frequency range of 30-200Hz. The sources of oscillatory activity were analysed with a beamforming approach.
Results: Compared to healthy controls, both groups of schizophrenia patients showed a highly significant decrease in gamma-band activity across a wide frequency range (30-130Hz) over parieto-occipital sensors. Chronic patients were characterized by a pronounced deficit in gamma-band activity and perceptual organisation relative to first-episode patients. Beamforming analyses revealed that the sources of gamma-band dysfunctions are located in the right temporal cortex.
Conclusions: These results suggest that schizophrenia is associated with a widespread reduction in high-frequency oscillations that indicate local network abnormalities. These dysfunctions are independent of medication status and already present at onset, suggesting a possible progressive deficit during the course of the disorder.

S-88-004
N-methyl-D-aspartic acid receptor antagonist induced frequency oscillations in mice recreates pattern of electrophysiological deficits in schizophrenia

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Objectives: Electrophysiological responses to auditory stimuli have provided a useful means of elucidating mechanisms and evaluating treatments in psychiatric disorders. Deficits in gating during paired-click tasks and lack of mismatch negativity following deviant stimuli have been well characterized in patients with schizophrenia. Recently, analyses of induced and evoked frequency oscillations have gained support as additional measures of cognitive processing in patients and animal models. The purpose of this study is to examine frequency oscillations in both schizophrenia patients and mice, across the theta (4-7.5 Hz) and gamma (31–61 Hz) bands. The effects of N-methyl-D-aspartic acid receptor (NMDAR) hypofunction and dopaminergic hyperactivity – both of which are thought to serve as pharmacological models of schizophrenia – are examined in the mouse model.
Methods: Human: Auditory evoked potentials were recorded from schizophrenia patients and healthy comparison subjects. Mouse model: Evoked potentials were recorded from mice in four treatment groups that consisted of haloperidol, risperidone, amphetamine, or ketamine. Induced and evoked power in the gamma and theta frequency bands were calculated.
Results: Schizophrenia patients exhibited decreased induced and evoked theta power and increased induced gamma power. In the mice, ketamine increased induced power in the gamma band and decreased the evoked power in the theta band. No other treatment group was able to fully reproduce this pattern in the mice. Conclusions: Ketamine-induced alterations in EEG power spectra are consistent with abnormalities in the theta and gamma frequency ranges observed in patients with schizophrenia.
Conclusions: Our findings support the hypothesis that NMDAR hypofunction contributes to the deficits in schizophrenia and that the dopaminergic pathways alone may not account for these changes.

S-04
Social brain functions in schizophrenia and mood disorders

S-04-001
Charcterization of epathy deficits in psychiatric populations

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Objectives: It has been suggested that empathy has several separate components such as identification and perspective taking, however there is no current neurobehavioral model to explain this behavior. In this study we sought to investigate the neuroanatomical bases of emotional and cognitive empathy with psychiatric populations
Methods: In a first lesion study we charachterized the neuroanatomical bases of emotional vs. cognitive empathy. We further tested this model with patients with bordeline personality disorder (BPD) and patients with psychopathy
Results: BPD patients exhibit impaired empathic capacities. While their cognitive empathy is reduced, the affective features of empathy are increased. As opposed to the Bordeline patients, psychopath did not show elevated affective empathy. On the contrary they showed impaired affective empathy. However their cognitive empathy was also impaired.
Conclusions: These findings offer new insight into the neuroantomical bases of social behavior that may underlie the profound behavioral disturbances observed in psychiatric and neurological populations such as autism, schizophrenia and frontal lobes damage.

S-04-002
Deficit in theory of mind predicts treatment outcome of depression

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Shigenobu kanba, Kazuo Yamada, Yumiko Inoue

Objectives: Recently, we reported that patients with depression have theory of mind (ToM) deficit during remission from acute episodes. ToM deficit means difficulty in social adjustment and thus may indicate a poorer prognosis.
Methods: We evaluated ToM ability of 50 patients during remission from major depressive episodes. The patients were followed for 1 year and their outcome observed.
Results: After 1 year, patients who had ToM deficit in a second order false question relapsed significantly more frequently as compared with patients who did not have a deficit (Fisher's exact test pb0.0001; relative risk (RR)=8.105; CI 2.020, 32.524). Significant differences were shown in scores of the Global Assessment of Functioning Scale (pb0.0001) between the two groups.
Conclusions: Patients with ToM deficit in second order false belief during remission may be a high risk group for recurrence and lower social function 1 year after recovering from a major depressive episode.

S-04-003
Integrated approach of theory of mind and contextual processing deficits in schizophrenia: from neurocognitive deficits to clinical assessment

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Damien Vistoli, Marie-Christine Hardy-Baylé, Christine Passerieux

Objectives: Schizophrenic handicap is underpinned by a set of neurocognitive disorders among which deficits of theory of mind and attribution of intentions to others play a specific role in the genesis of disorganized communication. Our researches have focused on two aspects of abnormal neural function related to schizophrenic disorganization: impairment of semantic processing, and of attribution of intentions to others. Both categories of paradigms are associated with behavioural deficits and with markers of abnormal neural function, respectively abnormal modulation of the N400 component during semantic priming, and reduced hemodynamic response in the prefrontal cortex during theory of mind. Both abnormalities may reflect a reduced capability to inhibit salient representations evoked by linguistic or social stimuli and to select appropriate meaning on the bases of communicative and social contexts. Within the domain of social cognition, such a hypothesis is strengthened by the investigation on the temporal characteristics of the processes participating in the attribution of mental states. It is acknowledged that a brain network involving the medial prefrontal cortex, the superior temporal cortex, and the temporal poles, among other regions, is mobilized during such mental activity, but few experimental evidences have been collected on the time courses associated to each region. In schizophrenia, preserved or exaggerated early activations in temporal regions, reflecting automatic processes, may be associated with reduced top-down control by the prefrontal cortex. We have shown in healthy subjects that the superior temporal regions and the temporal poles exhibit electrical response to visual social stimuli as soon as 250-300 milliseconds with a MEG-EEG paradigm requiring nonverbal attribution of intentions. This finding raises the question of the activity in these regions in schizophrenia. Moreover, determining at which level social processes are impaired will have important consequences for designing highly specific cognitive remediation therapies and new clinical means to measure their efficacy.

S-04-004
Social cognition and deviant behavior in schizophrenia

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Objectives: The term "theory of mind" (ToM) or "mentalising" embraces cognitive abilities that enable an individual to represent own and others' mental states. Studies into schizophrenia have revealed deficits in mentalising. Few studies have, however, addressed ToM in forensic patients with schizophrenia compared to patients who lack a criminal record.
Methods: 33 patients with schizophrenia who were treated in a forensic psychiatric hospital for various offences were examined using a cartoon ToM task. Task performance was compared with non-forensic patients and healthy controls.
Results: Both patient groups performed more poorly on ToM tasks as well as on executive functioning tasks compared to controls. Forensic and non-forensic patients did not differ in performance with regards to ToM, IQ or executive functioning. However, forensic patients scored significantly higher on the excitement and cognitive component score of the PANSS. When "excitement" was co-varied out, forensic patients outperformed non-forensic patients with regards to ToM.
Conclusions: This study supports previous findings suggesting that, relative to a non-forensic comparison group, schizophrenic patients with a criminal record may be equally impaired in their ability to infer mental states of other persons compared to healthy controls, but perhaps for different reasons associated with their psychopathological profile.

S-13
Translational neuroscience: Do we learn anything for psychiatric practice?

S-13-001
Neuroimaging in psychiatry

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Objectives: Brain imaging in concert with cognitive neuroscience and molecular biology have made progress within the last 20 years in refining our models of brain function.
Methods: Neuroimaging provides a way of investigating in vivo basic mechanisms on different levels that may underlie for example the experience of hallucinations, anxiety or craving in the human brain. Furthermore these methods are able to intersect basic and clinical efforts in elucidating underlying neuronal processes of complex groups of psychiatric disorders.
Results: By supplying data obtained on patients and first degree relatives, brain imaging has a firm hold on the clinical phenotype, and by informing on brain systems, it can link to molecular substrates and to intermediate phenotypes.

Conclusions: Thus, the diversity and complement of neuroimaging methods can place them in a crucial position for integrative translational research.

S-13-002
Sensorimotor gating and the tale of the prediction of antipsychotic effects

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Objectives: Prepulse inhibition (PPI) of the acoustic startle response has been firmly established as an operational measure of sensorimotor gating. PPI is regulated by a cortico-striato-pallido-pontine (CSPP) circuitry including frontal and mediotemporal brain regions, the ventral striatum, the ventral pallidum and pontine regions of the brainstem. Several psychiatric and neurological disorders present sensorimotor gating deficits. Especially the consistent findings of PPI deficits in schizophrenia patients have contributed to the view that schizophrenia is an attentional gating disorder. Consequently, the PPI paradigm is used as a translational model of impaired early information processes in schizophrenia because it is applicable in several laboratory animals and can be manipulated pharmacologically. Moreover, PPI has been proposed as a promising candidate endophenotype, i.e. as a biological marker that is closely related to a genetic basis. The identification of endophenotypes may have advantages for the elucidation of genetics of complex psychiatric phenotypes compared to the common genetic association studies. Finally, the amelioration of drug-induced PPI deficits in rodents has been established as an animal model for detecting antipsychotic activity. The present talk reviews the applications and limitations of the PPI-paradigm in clinical neuroscience.

S-13-003
Biomarkers of affective disorders

Lukas Pezawas
Medical University Vienna, Psychiatry and Psychotherapy, Austria

Objectives: Psychiatric diagnostics are based on behavioral and psychopathological phenotypes and hence are not intimately linked to biological endophenotypes. Today several intermediate endophenotypes have repeatedly been shown to be correlated with psychiatric disease states such as depression.
Methods: The most promising intermediate phenotypes have evolved from imaging genetic studies. Currently, imaging proteomics studies are on their way and will further increase the number of available intermediate endophenotypes.
Results: Our lecture will summarize the most promising candidates in depression research and currently applied approaches in the field.
Conclusions: Due to the increasing number of available intermediate endophenotypes of depression, it is becoming more likely that one of those candidates will evolve as true biomarker of depression vulnerability, drug response or as course specifier of this devastating disorder.

S-13-004
Neurobiology of psychotherapy

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Gregor Kasprian, Oliver Pintsov, Julia Furtner, Nina Pintzinger, Peter Anderer, Daniela Prayer, Gerda Saletu-Zyhlarz

Objectives: Recently, first brain imaging studies have established that psychotherapy can have an effect on certain brain functions in patients with psychiatric disorders. With regard to neurobiological markers, the goal of psychotherapy should be to strengthen the prefrontal activity and reduce the overactivity of the amygdala. In our study, we wanted to investigate the specific combination effect of cognitive remediation therapy and atypical antipsychotics on the specific frequently used neurobiological markers such as brain activation patterns measured by fMRI and the auditory event-related brain potential (ERP).
Methods: ERPs were recorded from 19 EEG leads in a two-tone oddball paradigm in a medication free patient with DSM-IV schizophrenia and were compared with healthy controls (n=13). Before and after four weeks of treatment, auditory-evoked ERP were investigated. For the fMRI, we used a block design focussing on cross onscreen (rest) vs. 1 back test (activation). All measurements were carried out before and after treatment using a 1.5 Tesla Philips Intera, release 11, 8 channel head coil, axial EPI sequence of 36 slices, 100 volumes and a scan time of approximately 10 min.
Results: A clinical improvement assessed with the PANSS and CGI-I was noted. The patients with schizophrenia who had been treated with cognitive remediation showed (1) a significant increase in the activation patterns in the dorsolateral prefrontal cortex and the anterior cingulum and (2) a significant increase of P300-amplitude from baseline to week four and higher P2 differentiation.
Conclusions: Our findings show for the first time that cognitive remediation leads to an increase of reduced P300 amplitude and improvements in distinguishing relevant from irrelevant auditory information. In addition, a promising effect was detected in the activation patterns in the prefrontal cortex indicating a higher cognitive functioning in patients with schizophrenia. In general, this can have an impact on functional outcome.

S-20
Deep brain stimulation in repetitive behaviors

S-20-001
Ventral capsule/ventral striatum stimulation in obsessive-compulsive disorder

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Objectives: Collaborating psychiatric neurosurgery teams in the US and Europe have studied deep brain stimulation (DBS) of the ventral anterior limb of the internal capsule and adjacent ventral striatum (VC/VS) for severe and highly treatment resistant obsessive-compulsive disorder (OCD).
Methods: This work, which began in 1998, used comparable patient selection criteria and surgical targeting. Surgical targeting and to a lesser extent stimulation parameters evolved systematically during the subsequent decade.
Results: Combined long-term results of those studies reveal clinically significant symptom reductions and functional improvement in about two-thirds of patients. DBS was well-tolerated overall and adverse effects were overwhelmingly transient. Results generally improved for patients implanted more recently, suggesting a "learning curve" both within and across centers. This is well known from the development of DBS for movement disorders.
Conclusions: The main factor accounting for these gains appears to be the refinement of the implantation site, but patient selection cannot be completely ruled out as a factor given the relatively small sample size and the open-label nature of the stimulation. Initially, an anterior-posterior location based on anterior capsulotomy lesions was used. In an attempt to improve results, more posterior sites were investigated resulting in the current target, at the junction of the anterior capsule, anterior commissure, and posterior ventral striatum. Clinical results suggest that neural networks relevant to therapeutic improvement might be modulated more effectively at a more posterior target. Taken together, these data show that the procedure can be successfully implemented by dedicated interdisciplinary teams, and support its therapeutic promise. There are also very significant issues in long-term patient management of patients receiving DBS for OCD. The benefits and burdens of DBS as it exists in 2009 will be discussed, and compared to those after state-of-the-art lesion procedures for OCD.

S-20-002
Anatomical correlates of deep brain stimulation efficacy in obsessive compulsive disorder

Bart Nuttin
UZ-KU Leuven, Dept. of Neurosciences, Belgium
Leos Gabriels

S-20-003
Deep brain stimulation of the nucleus accumbens for therapy-refractory obsessive-compulsive disorder

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Academic Medical Center, Dept. of Psychiatry, Amsterdam, Netherlands

Objectives: This study investigated the use of bilateral deep brain stimulation of the nucleus accumbens for treatment of therapy-refractory OCD.
Methods: Sixteen patients with therapy-refractory OCD according to DSM-IV criteria underwent treatment with bilateral deep brain stimulation of the nucleus accumbens.
Results: Nine out of 16 patients were responders with a mean Y-BOCS decrease of 72%.
Conclusions: The results of this study suggest that bilateral deep brain stimulation of the nucleus accumbens is an effective and safe treatment for therapy-refractory OCD

S-20-004
Effect of stimulation of limbic relays in basal ganglia on tics and compulsions

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STOC Study Group

Objectives: Basal ganglia (BG) consist of central grey nuclei which process cortical information and send back an efferent message that is used in the frontal cortex to perform selection and planification of motor and behavior programming. Three cortical functional territories, motor, associative and limbic processing motor, cognitive and emotional information, exist and transmit distinct output to separate regions of the basal ganglia. In repetitive behaviors such as Tourette's syndrome (TS) and obsessive-compulsive disorders (OCD), current pathophysiological models favor a dysfunction of the BG circuit, in particular the associative-limbic parts. In line with these hypotheses, modulation of the neuronal activity of these structures, with deep brain stimulation, could lead to improvement of such abnormal behaviors.
Methods: The effects of high frequency stimulation of basal ganglia limbic relays have been tested in 3 TS patients and 16 OCD patients. Stimulation was applied bilaterally within the thalamic intralaminar group (parafascicular/centromedian nuclei) and the antero-medial region of the internal globus pallidus (GPi) in 3 TS patients, and in the anteromedial part of the subthalamic nucleus (STN) in 16 OCD patients, in controlled double blind randomized crossover studies.
Results: In TS patients, a dramatic improvement in tics was obtained with pallidal and/or thalamic stimulation with a greater effect with the ventro-medial GPi stimulation (-78%), with no neuropsychological or psychiatric side effect. In OCD patients, STN stimulation significantly decreased obsessions and compulsions with an improvement in the global functioning. The neuropsychological, depressive and anxiety ratings were not modified. However, serious adverse events occurred in 11 patients with 8 transient stimulation-induced motor (n=2) and psychiatric (n=6) symptoms.
Conclusions: These preliminary results support the efficacy of stimulation of BG limbic relays in the treatment of severe forms of TS or OCD. The occurrence of severe adverse events, with antero-medial STN stimulation, and the small number of patients call for further confirmation.

S-41
Metabolism of psychotropic drugs in the human brain: Possible relevance for their clinical profile?

S-41-001
Brain-specific expression of cytochrome P450 enzymes and their impact on metabolism of psychoactive drugs at the site of action

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Objectives: Drug effectiveness in the treatment of disease processes depends on the amount of active drug present at the target site that in turn depends on the enzymes, which activate and/or inactivate drugs at sites of absorption, modification and transport and ultimately on those enzymes present at the therapeutic target site. Prominent among the enzymes, which activate or inactivate drugs is cytochrome P450 (P450). While many P450 forms are expressed in brain, our objective was to determine if brain-specific biotransformation of psychoactive drugs occurred and if so, characterize the human brain P450 enzymes involved in this process.
Methods: We used autopsy tissue from traffic accident victims obtained through the Human Brain Tissue Repository at NIMHANS, Bangalore. Our methods involved cloning of brain-specific P450s, assaying their levels of expression in human brain and determining their functional activity by examining their ability to metabolize xenobiotics including drugs.
Results: Human brain-specific P450 enzymes generated through alternate splicing were identified. The biotransformation mediated by the unique brain-specific P450s is different from the well-characterized hepatic pathways. Further, expression of CYP3A43, which is expressed in very low amounts in the liver, was substantially higher in brain and led to the altered metabolite(s) profile of the anti-anxiety drug, alprazolam.
Conclusions: We present evidence for the existence of novel site-specific biotransformation pathways that can potentially mediate metabolism of drugs at the site of action by mechanisms that are different from known pathways in liver. These enzymes metabolize psychoactive drugs to pharmacologically active or inactive metabolites that are capable of effecting therapeutic effects at their site of action, the brain and thus impact the pharmacodynamics of psychoactive drugs at the site of action. Identification of novel histio-specific P450 enzymes generated by alternate splicing of known genes or as yet unidentified genes may help understand metabolism at site of action and potentially predict the variable response seen in patient population.

S-41-002
Brain Cyp 4Fs in brain injury and psychotropic drug metabolism

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Objectives: Traumatic brain injury is known to cause several secondary effects, which lead to multiple organ dysfunction syndrome. An acute systemic inflammatory response seems to play an integral role in the development of such complications providing the potential for massive secondary injury. Our objective is to define the pathways involved in regulation of inflammation following injury.
Methods: We utilized the controlled cortical impact model of closed head injury with rats and observed the changes inflammatory signals and inflammation as a function of time after injury.
Results: We demonstrate that a contusion injury to the rat brain causes large migration of inflammatory cells (especially macrophages and neutrophils) in the major airways and alveolar spaces at 24h post-injury, which is associated with enhanced pulmonary leukotriene B4 (LTB4) production within the lung. However, by 2 weeks after injury, a temporal switch occurs and the resolution of inflammation is underway. We provide evidence that 5-lipoxygenase and CYP4Fs, the respective enzymes responsible for LTB4. Activation of LTB4 breakdown via induction of CYP4Fs, predominantly in the lung tissue, serves as an endogenous signal to ameliorate further secondary damage. In addition, we show that CYP4Fs are localized primarily in the airways and pulmonary endothelium.
Conclusions: Given the fact that adherence to the microvascular endothelium is an initial step in neutrophil diapedesis, the temporally regulated LTB4 clearance in the endothelium presents a novel focus for treatment of pulmonary inflammation following injury.

S-41-003
Monoamine oxidase: A challenging enzyme and its drugs

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Objectives: Monoamine oxidase (MAO)-type A and B metabolizes preferentially biogenic amines to an aldehyde, ammonia and hydrogen peroxide (H2O2). All these substances show a distinguished toxic potential if not further metabolized. Therefore a specific MAO inhibitor antagonizing these effects is of therapeutic value.
Conclusions: Oxidative stress (OS) connected to the Fenton reaction is only one example how MAO contributes to cell damage. Therefore and because of their mood facilitating beneficial action in for example "depression" inhibitors of MAO-A and –B have been developed. While the A-type inhibitors are improving symptoms of "depression", B-Type blockers are thought to be beneficial in Parkinson's disease (PD) by reducing OS and acting as neuroprotectants. Moclobemide, tranylcypromine, pargyline, selegiline and rasagiline have different actions on CYP enzymes (depending on test systems, concentrations, etc.) The most interesting recent clinical findings suggest a disease-modifying action of rasagiline in PD. If this can be confirmed a first break-through in adapting neuroprotectants has been achieved.

S-41-004
Selective metabolism of psychotropic drugs by MAO-A and MAO-B in brain

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Objectives: Cytochrome P-450 is the most important enzyme system implicated in the metabolism of psychotropic drugs in the liver, but its effectiveness in brain is limited. Monoamine oxidase isozymes A and B (MAO-A/-B) play a key role in the metabolism of biogenic amines. The antidepressant citalopram (CIT) is stereoselectively metabolised by MAO-A and MAO-B in blood, liver and brain (Rochat et al. Biochem. Pharmacol. 56 (1998) 15, Kosel et al. Molec. Psychiat. 7 (2002) 181). The objective of this investigation was to study the biotransformation of CIT in the extreme situation where one of the 2 MAO isoforms is lacking.
Methods: Brain mitochondria and microsomes of both wild-type mice (WT (WT/HeOuJ)) and from transgenic mice lacking MAO-A (knock-out MAO-A, KO-A (Tg8)), generated by infecting one-cell embryos of WT with interferon-b (IFN-b) were incubated with racemic CIT, desmethylcitalopram (DCIT) or didesmethylcitalopram (DDCIT) in the presence and absence of MAO-inhibitors. CIT propionic acid metabolite (CIT-PROP), which is formed by both MAO isoforms from CIT, DCIT and DDCIT was then stereoselectively analysed by HPLC.
Results: Production of R-CIT-PROP and S-CITP-PROP from CIT was about 5x and 2x higher, respectively, in WT- than in KO-A-mice. Due to its metabolic properties, DCIT was comprehensively studied: it has a greater affinity (Km) to MAO in WT-mice than in KO-A-mice. As expected, the MAO-A inhibitor clorgyline inhibited formation of R-CIT-PROP from DCIT in WT- but not in KO-A-mice.
Conclusions: CIT and its demethylated metabolites are not only stereoselectively deaminated in man and rat brain and liver preparations, but also in incubations performed with mouse brain preparations. In KO-A-mice, these MAO-dependant deamination pathways differ from those observed in WT-mice. This in vitro study suggests that, in vivo, CIT disposition could be different in WT- and KO-A-mice.

S-43
Immune activation and tryptophan metabolism in major psychiatric disorders

S-43-001
Tryptophan metabolism by astrocytes and microglia in neurodegenerative diseases

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Objectives: The kynurenine pathway (KP) is a major route of L-tryptophan catabolism resulting in the production of neurotoxic, neuroprotective and immune tolerance-inducing intermediates. The KP is involved in several neurodegenerative diseases. It is important to know what KP metabolites are produced by each brain cell types to be able to understand their interactions and to appropriately design and test therapies.
Methods: We characterized the KP in primary cultures of human fetal astrocytes, microglia, oligodendrocytes and neurons using RT-PCR, HPLC, mass spectrometry and immunocytochemistry
Results: We found that the different brain cells express the KP enzymes but at different levels. Astrocytes lack the enzyme kynurenine hydroxylase. Indoleamine 2,3 dioxygenase is expressed by all brain cells except oligodendrocytes. Microglial cells are the only brain cell able to produce the excitotoxin quinolinic acid.
Conclusions: Our studies represent an unique and comprehensive characterization of the KP in human brain cells. This was critical to delineate the interactions of KP metabolites between the different brain cells.

S-43-002
The outcome of postmortem studies of schizophrenia and bipolar disorder: Genes of relevance to tryptophan metabolism

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Objectives: Alterations in the kynurenine pathway of tryptophan metabolism have been demonstrated for schizophrenia and bipolar disorder by several laboratories around the world. The differences between cases and controls can be seen at the mRNA, protein and metabolite level in postmortem brain. In this study, we tested whether genes involved in kynurenine pathway regulation might interact with genes involved in the response to kynurenine products to increase risk for schizophrenia and bipolar disorder.
Methods: In DNA from cases and controls, TaqMan® PCR characterized SNPs for candidate genes (TDO2, HM74A, HM74, and the immunomodulatory melanotropin receptors, MCHR1, MCHR2, and MC5R) selected from prior gene expression studies, genetic association studies, and animal models.
Results: HM74[A,any] was associated with schizophrenia and with the combined diagnostic group of schizophrenia plus bipolar disorder, odds ratio (OR) of 1.48, p = 0.01 and 1.5, p= 0.007, respectively. TDO2[CC] trended for association with the combined diagnostic category, OR= 1.42, p= 0.05. Interactions between kynurenine pathway-related genes and genes that respond to kynurenine metabolites were then tested for augmentation of disease risk. TDO2[CC] + MC5R[G,any] + MCHR2[GC] conferred an OR maximal for schizophrenia (4.84, p= 0.005), carried by 8% of the cases. HM74[A,any] + MCHR1[T,any] + MCHR2[C,any] conferred an OR maximal for the combined diagnostic category of schizophrenia plus bipolar disorder (1.7, p= 0.003), carried by 30% of the cases.
Conclusions: The interactive risk posed by these complex genotypes may derive from a lack of adequate melanotropin sequestration of the pigments generated from tryptophan, from production of melanotropin receptor ligands or from co-regulation of the kynurenine pathway by the interacting genes. MC5R in particular may interact through its inhibition of interferon-γ expression, a key cytokine that stimulates the kynurenine pathway

S-43-003
Immune and tryptophan catabolic markers in blood and cerebrospinal fluid of patients with major depression and schizophrenia

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Objectives: The changes in blood cytokines have been reported to occur in psychiatric disorders. It was reported that cytokines such as IFN-γ reduces the synthesis of 5-HT by stimulating indoleamine 2,3 dioxygenase (IDO), an enzyme which converts tryptophan, the precursor of 5-HT to kynurenine. Kynurenine is further metabolized to kynurenic acid (KYNA), 3-hydroxykynurenine (3OHK) and quinolinic acid (QA) The 3OHK is neurotoxic apoptotic while QA is the excitotoxic N-methyl-D-aspartate (NMDA) receptor agonist. Conversely KYNA is an antagonist of all three ionotropic excitatory amino acid receptors. A series of studies were carried out to study the role of kynurenine metabolites in major psychiatric diseases.
Methods: Sstudies were carried out on (1) the plasma of drug naive and drug free depressed patients and plasma of drug naive and drug free schizophrenic patients and their healthy controls, and (2) serum and cerebrospinal fluid of patients with major depression and schizophrenia. The clinical data on psychopathology and treatment response and laboratory data on immune and kynurenine parameters were collected and analysed.
Results: Tryptophan breakdown has been found to be increased but KYNA is decreased in both depressed and schizophrenic patients compared to healthy controls. Moreover, in the patients with schizophrenia, the neurotoxic 3OHK is significantly increased. Such changes in these metabolites are reflected also in the cerebrospinal fluid of depressed and schizophrenic patients. Those metabolites in the plasma or serum and in CSF are associated with clinical symptom scores and response to treatment.
Conclusions: These findings lead to the hypothesis an imbalance in neuroprotection and neurodegeneration in terms of kynurenine metabolites and their immunological and biochemical interactions in the brain might further induce the apoptosis of the neuroprotective astrocytes and the vulnerability to stress is thereby enhanced.

S-43-004
Immunomodulating therapy in major depression and schizophrenia

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Objectives: Classical markers of inflammation are increased in depressed patients, therefore a role of inflammation in the pathophysiology of depression has been suggested. In schizophrenia, markers of inflammation have been described to be increased, too.
Methods: COX-2 inhibition seems to balance the type-1/type-2 immune response, possibly via inhibition of prostaglandin E2 inhibition and COX-2 inhibition reduces proinflammatory cytokines. COX-2 inhibition has an impact to the glutamatergic neurotransmission and influences the tryptophan/kynurenine metabolism: all three components seem to be involved in the pathophysiology of psychiatric disorders. Data from studies using selective COX-2 inhibitors, but also other anti-inflammatory agents will be presented.
Results: Celecoxib revealed a significant therapeutic effect on depressive symptoms, but also in schizophrenia. Although those preliminary data have to be interpreted cautiously and intense research has to be provided in order to evaluate further the therapeutic effects of COX-2 inhibitors in MD, those results are encouraging for further studies. Also in schizophrenia, COX-2 inhibitors show beneficial effects in certain stages of the disease.
Conclusions: While clinical effects have only been shown for marketed COX-2 inhibitors such as celecoxib or rofecoxib, in animal models of depression different types of COX-2 inhibitors have been successfully used. Preliminary results regarding the effects of other anti-inflammatory drugs underline this view.

S-49
Translational medicine in psychiatry; making sense of preclinical ad clinical research: Methodologies, opportunities, and controversies

S-49-001
Translational medicine of bipolar disorders

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S-49-002
Genetically determined dopamine signaling in schizophrenia phenotypes

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Objectives: Susceptibility to schizophrenia is largely explained by genetic factors. Dopamine dysregulation has been prominently implicated in the pathophysiology of schizophrenia and of prefrontal cortical dysfunction during working memory, a core symptom. Dopamine modulation of neuronal activity during memory tasks identifies a non-linear inverted-U shaped function. Both the dopamine transporter (DAT) and dopamine D2 receptors (encoded by DRD2) critically regulate dopamine signaling in the striatum and in prefrontal cortex during memory. Moreover, in vitro studies have demonstrated that DAT and D2 proteins reciprocally regulate each other presynaptically. Therefore, we have evaluated the interaction between DRD2 and DAT on prefronto striatal gray matter and activity during working memory.
Methods: We studied the interaction between a DRD2 polymorphism (rs1076560) causing reduced presynaptic D2 receptor expression and the DAT 3'-VNTR variant (affecting DAT expression) in a large sample of healthy subjects undergoing BOLD - fMRI during memory tasks and structural MRI.
Results: Results indicated a significant DRD2/DAT interaction in prefrontal cortex and striatum BOLD activity during both working memory and encoding of recognition memory. The differential effect on BOLD activity of the DAT variant was mostly manifest in the context of the DRD2 allele associated with lower presynaptic expression. Similar results were also evident for gray matter volume in caudate. These interactions describe a non-linear relationship between compound genotypes and brain activity or gray matter volume. Complementary data from striatal protein extracts from wild-type and D2 knock-out animals (D2R-/-) indicate that DAT and D2 proteins interact in vivo.
Conclusions: Taken together, our results demonstrate that the interaction between genetic variants in DRD2 and DAT critically modulates the non-linear relationship between dopamine and neuronal activity during memory processing.

S-49-003
Major depressive disorder is a risk factor for osteoporosis in women

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Abstract: Besides mood changes, MDD is associated with increased morbidity and mortality. In addition to poor compliance and life style factors, endocrine, immune and autonomic dysregulation may play a causative role in producing medical illnesses in patients with MDD. Osteoporosis is a debilitating condition which remains mostly asymptomatic and goes undiagnosed until a pathological fracture ensues. MDD has been associated with low BMD in several studies. Despite multiple studies linking depression and osteoporosis in hundreds of subjects, MDD still is not recognized as a risk factor for osteoporosis. Several endocrine mechanisms may account for bone loss in MDD, including hypercortisolemia and a hyperadrenergic state. Immune system alterations, such as an increase in interleukin-6 (IL-6) -one of the most potent bone resorption factors- may also contribute to osteoporosis. I present here the results of the POWER (Premenopausal, Osteoporosis Women, Alendronate, Depression) Study, a prospective study of bone turn-over in which immune, pituitary-adrenal, and sympathetic biomarkers were measured.

Subjects were 89 community-dwelling 21- to 45-year-old premenopausal women with current or recent MDD and 44 healthy control women. The prevalence of low BMD, defined as a T-score of less than -1, was greater in women with MDD vs. controls at femoral neck (17% vs. 2%, P=0.02) and total hip (15% vs. 2% P=0.03), and tended to be greater at the lumbar spine (20% vs. 9%; P=0.14). BMD, expressed as g/cm2, was lower in women with MDD at the femoral neck (0.849 + 0.121 vs. 0.866 + 0.094, P=0.05) and at the lumbar spine (1.024 + 0.117 vs. 1.043 + 0.092, P=0.05). These BMD deficits are of clinical significance, and comparable to established risk factors for osteoporosis. Women with MDD had increased mean 24h pro-inflammatory and decreased anti-inflammatory cytokines. MDD should be formally recognized as a risk factor for low BMD in premenopausal women.

S-49-004

Traslational studies and the search for new targets in psychosis treatment, methodology, success and failure

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Objectives: Among potential targets for both antipsychotics action and physiology of cognition, the Homer family of proteins has recently attracted increasing attention. Homer proteins are enriched at glutamatergic postsynaptic density and have been implicated in the modulation of signal transduction. Moreover, they have been involved in the pathophysiology of psychosis and in cognitive-behavioral disorders, both in human and animal models. However, the specific role of Homers in the mechanism of action of antipsychotics is still elusive. Here we discuss studies which tested: 1) the modulation of Homer expression by antipsychotics compared to other compounds acting directly or indirectly on dopamine receptors and transporter; 2) the involvement of different brain regions and circuitries believed to be relevant in animal models of psychosis and affected by Homer gene expression; 3) the contribution of specific dopamine receptor subtypes in Homer activation.
Methods: Molecular imaging of Homer transcripts was performed on rat brain sections with a novel analysis method after in vivo treatment with antipsychotics (haloperidol, risperidone, olanzapine, quetiapine, aripiprazole), a dopamine agonist (GBR 12909) and a NMDA receptor antagonist (ketamine), both in acute and chronic paradigms.
Results: Homer transcripts were significantly modulated by acute and chronic antipsychotic treatment and differentially induced by typical and atypical compounds. A different involvement of distinct brain regions (sub-cortical vs. cortical) believed to be crucial for psychosis and abnormal "executive-like behaviors" in animals was detected. The analysis of the effects of specific dopamine receptor subtypes on Homer modulation indicated a relatively specific contribution of each receptor in gene expression in different brain regions.
Conclusions: Taken together, these results may suggest a role for Homer-mediated signal transduction as a target for drug therapy in psychosis and cognitive dysfunctions. Moreover, these studies underline the role of dopamine-glutamate interaction in Homer modulation, its effects on striatal function and its relationship with motor and limbic function.

S-59
New strategies and tools in the field of transcranial magnetic stimulation (TMS)

S-59-001

Deep transcranial magnetic stimulation in major depression: Feasibility and safety study

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Objectives: Based on the results of the authors' physical and psychological safety study using the H-coils in healthy controls, a clinical trial was conducted to evaluate the safety and and antidepressant response induced by four weeks of high frequency (20Hz) repeated Deep-TMS over the left PFC on 65 treatment-resistant depressed patients
Methods: Three different H-coil designs were tested (H1 coil, H2, and H1L-coil). In addition, the H1L-coil was used under two different levels of intensity: 110% and 120% of the subject's motor threshold.
Results: The H-coil DTMS treatment was found to be particularly effective in the H1-coil and H1L-120%-coil treatment groups. Reduction of at least 50% in the Hamilton Depression Rating Scale (HDRS) was observed in 47% of the patients treated with H1-coil, 30% in patients treated with the H2-coil, 0% in patients treated with the H1L-110%-coil and 60% in patients treated with the H1L-120%-coil, at one-week after end of study treatment. A statistically significant difference between the treatment groups was found in the change from HDRS baseline score over time as determined by the treatment*visit interaction (F(3,58)=6.42, p=0.0008). The mean weekly reduction per treatment group was estimated from the model as -12.3 points (se=1.92) on average in the H1 coil group, -6.78 (se=1.89) in the H2 coil group and -7.6 (se=2.68) in the H1L-120% group, with the exception of H1L-110% subjects showing no benefit in this score with treatment progression. A similar pattern of improvement was evident in the patients' self-report (using the Beck Depression Inventory). Computerized cognitive tests (the CANTAB) along the study indicated selective improvement in cognitive functions.
Conclusions: To conclude, this study is the first evidence for the feasibility and safety of Deep-TMS's efficacy and safety for treating major depression.

S-59-002

New protocols of non-invasive brain stimulation: Enhancing the after-effect

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Objectives: Repetitive transcranial magnetic stimulation (rTMS) has turned into a sophisticated non-invasive brain stimulation approach since the early 1990s. For therapeutic applications rTMS is applied as intermittent treatment and does not provide permanent stimulation in contrast to deep brain stimulation (DBS). Thus, any therapeutic effects of rTMS are likely to depend on the duration of post-stimulation effects and their summation over time. Recently, novel rTMS protocols have been proposed in order to establish a more robust action of non-invasive cortex stimulation. Theta burst stimulation (TBS) is the most prominent protocol and based on cellular neurostimulation protocols for inducing long-term potentation (LTP).
Methods: Previous studies investigating novel protocols are reviewed. Two TBS trials in healthy subjects as well as pilot experience in clinical applications are presented and discussed in relation to other recent developments in this field, i.e. repeated paired-pulse paradigms, paired associative stimulation (PAS) and transcranial direct current stimulation (tDCS).
Results: Current TBS protocols have been demonstrated to be applicable at the same level of side effects as standard rTMS (Grossheinrich et al. Biol. Psychiatry 2008 Dec 12. [Epub ahead of print]). In healthy subjects, there is evidence that TBS can exert pronounced post-stimulation effects on EEG and neurobehavioral measures. The effects of such protocols, however, are more complex compared to standard rTMS and homeostatic metaplasticity has to be considered in order to direct post-stimulation effects.
Conclusions: Focussing on the enhancement of post-stimulation effects is a promising avenue in order to further develop rTMS towards a powerful therapeutic intervention. As it will be more difficult to select effective protocols for clinical trials and side effects are likely to increase with efficacy, preclinical research is strongly needed in order to clarify the differential action of such protocols.

S-59-003
Gamma synchrony, GABAB and rTMS cognitive enhancing strategies in schizophrenia

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Objectives: Recent reports have demonstrated that long interval cortical inhibition (LICI) can be indexed in the dorsolateral prefrontal cortex (DLPFC) in healthy controls. LICI is a neurophysiologic process indexed using transcranial magnetic stimulation and is closely associated with cortical GABAB receptor mediated inhibitory neurotransmission. Several previous studies have also reported that gamma band activity represents a neurophysiological process that is mediated, in part, through GABAergic inhibitory neurotransmission and may subserve several cognitive operations including working memory (WM) in the DLPFC. The intension of the current study, therefore, was to directly evaluate the relationship of these neurophysiological phenomenon in healthy subjects.
Methods: Eleven right-handed healthy subjects participated in this experiment in which gamma band activity was measured through simultaneous recording of electroencephalography (EEG) during the N-back task, a cognitive task designed to index WM. LICI was recorded through EEG from the left DLFPC, left motor cortex and through EMG of peripheral hand muscles in a separate session according to previously published methods.
Results: There was no evidence for a relationship in the DLPFC between LICI and gamma band activity elicited during the N-back task, though there was a relationship found between LICI and performance on the 3-back condition, the N-back condition of greatest difficulty.
Conclusions: These data provide evidence to suggest that in the DLPFC, there is no direct relationship between GABAB receptor mediated inhibitory neurotransmission and gamma band activity. However, our data does suggest that LICI was related to 3-back performance providing evidence implicating DLPFC GABAergic inhibitory neurotransmission in WM performance.

S-59-004
Physiological optimization of TMS pulse shape and parameters for therapeutic applications: Controllable pulse shape TMS (cTMS) and magnetic seizure therapy (MST)

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Objectives: Neural response to electrical stimulation depends upon pulse shape and stimulation parameters. Pulse shape and stimulation parameters exert powerful effects on seizure threshold and outcome with electroconvulsive therapy (ECT); therefore, optimizing them could be important for the efficiency of neuromodulation with TMS. Surprising little work has addressed the physiological optimization of the TMS pulse for subconvulsive or convulsive applications, perhaps because typical TMS devices lack control over pulse shape, width, directionality, and are capped at 50 or 100 Hz.
Methods: Using a novel monophasic controllable pulse shape TMS device (cTMS) that induces near rectangular pulses with continuous control over pulse width (PW), we tested its safety and utility in measuring neuronal membrane time constants in 10 healthy volunteers. Using a novel MST device (MagVentures) we evaluated the efficiency of seizure induction at frequencies ranging from 50-200 Hz in nonhuman primates. Using a nonhuman primate model of ECT, we evaluated the efficiency in seizure induction with unidirectional versus bidirectional pulse trains.
Results: Pulse width control with cTMS demonstrated the expected decrease in motor threshold with increasing pulse width, and allowed noninvasive estimation of the neuronal membrane time constant of the human motor cortex (186±23 μs). Frequency control with MST demonstrated an unexpected U-shaped curve, with an optimum between 25-50 Hz. Current directionality control with ECT demonstrated that unidirectional stimulation lowers seizure threshold relative to bidirectional stimulation ($p<0.0001$).
Conclusions: Control over pulse shape, frequency, and directionality exerts demonstrable effects on neural responses for both subconvulsive and convulsive applications. PW control may be desirable for measuring neuronal membrane time constants that characterize neuronal membrane thickness, myelination, and state of ion channels, and possibly for selectively targeting neuronal populations with different membrane time constants. Unidirectional stimulation enhances the efficiency of seizure induction with ECT, and should be explored with MST.

S-70
Glia cell pathology in psychiatric disorders

S-70-001
Glial changes in post mortem brains of individuals with psychiatric disorders

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Objectives: Recent research has changed the perception of glia from being no more than silent supportive cells of neurons to being dynamic partners participating in brain metabolism and communication between neurons. This discovery of new glial functions coincides with growing evidence of the involvement of glia in the neuropathology of mood disorders. Unanticipated reductions in the density and number of glial cells are reported in fronto-limbic brain regions in affective disorders (Rajkowska G) and schizophrenia (Uranova N).
Methods: The cell-density of S100B-immunopositive glia was analyzed in the anterior cingulate, dorsolateral prefrontal (DLPF), orbitofrontal, and superior temporal cortices/adjacent white matter, pyramidal layer/alveus of the hippocampus, and the mediodorsal thalamic nucleus of 18 patients with schizophrenia, 16 cases with affective disorder and 16 matched control subjects.
Results: Cortical brain regions of schizophrenia cases contained more S100B-immunopositive glia relative to controls ($P = 0.046$). Separate analysis of white matter revealed more (mainly oligodendrocytic) S100B-positive glia in paranoid schizophrenia, but indications for S100B+ glial loss in residual schizophrenia ($P = 0.021$). These effects were particularly pronounced in the DLPF brain area. Moreover, the first postmortem data on S100B+ glia in affective disorders will be presented. The evaluation of cases
Conclusions: Our study reveals distinct histological patterns of S100B immunoeactive glia in two schizophrenia subtypes and effective disorders. This may be indicative of a heterogenic pathophysiology or distinct compensatory abilities.

S-70-002
Astroglial antioxidant defense alteration in bipolar disorder

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Objectives: There is much evidence that oxidative stress accompanies the major psychiatric disorders, suggesting that imbalance of oxidants and antioxidants plays an active role in the development of these disorders. In fact, brain tissue is particularly susceptible to oxidative stress and antioxidant mechanisms of defense, particularly dependent upon astroglial metabolism, are essential for its protection from oxidative damage and related sequelae. Antioxidant defense mechanisms in astrocytes include synthesis and secretion of glutathione, the major cellular antioxidant compound, as well as ascorbic acid recycling, which is essential for neurons.
Methods: We have investigated the extracellular levels of S100B, a neurotrophic astrocyte-derived protein, which has been used as a marker of brain damage in many diseases, including psychiatric disorders. S100B has been measured by Enzyme Linked Immuno Sorbent Assay, in human serum, astroglial culture of rats, and acute brain slices of rats.
Results: Apparently, oxidative stress alters S100B secretion, as well as the neurotrophic activity of this protein. We found a significant increment of serum S100B in bipolar patients, particularly during episodes of mania and depression.

Conclusions: Our group has identified some oxidative alterations in psychiatric patients and in vitro preparations that could potentially be associated, and together with increasing evidence in the literature, we aim to evaluate psychiatric disorders, searching for new molecular targets for therapeutics and neuroprotection in a more wide sense. Support: CNPq and INCT-National Institute of Science and Technology for Excitotoxicity and Neuroprotection.

S-70-003
Inflammatory markers in children and adolescents with psychotic disorders, the role of glia cells

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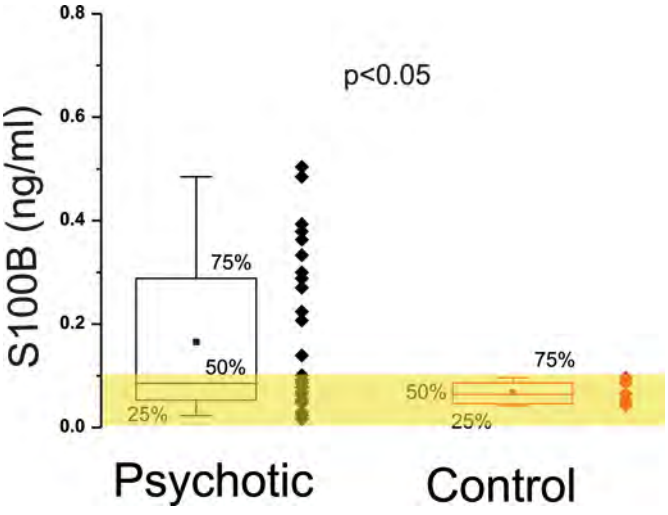
Objectives: 1) To study the relationship between psychosis and inflammation in a group of children and adolescents; 2) To test the hypothesis of a relationship between psychosis and blood-brain barrier (BBB) dysfunction
Methods: A prospective study where the relationship between S100Beta, inflammatory mediators, and acute psychosis in children and adolescents were examined. Patients included had a diagnosis of acute psychosis. Blood samples were taken upon admission to the unit. All patients underwent serum analysis of S100Beta, IL-1beta, IL-2, IL-4, IL-6, IL-8, IL-10, IFN gamma, TNFalpha, CBC, and CRP. We analyzed serum samples from 30 psychotic children and compared the data to 30 healthy adolescents. In the healthy control group, a preliminary interview ruled out psychosis, any neurodegenerative disorder, fever, current infection, and current use of antibiotics
Results: S100Beta levels were significantly elevated $p < 0.05$ compared to normal controls. Most psychotic children had serum S100Beta levels above the recognized normal range. Serum samples were process for a panel of cytokines and inflammatory mediators, which are believed to play a significant role in inflammation. IL-1beta, TNF-alpha, IL-5, IL-10, and IL-6 were found to be significantly higher among psychotic children.
Conclusions: There is a link between psychosis, inflammation, and the role of the glia cell demonstrated by elevation in S100b, TNF-a, IL-6, and IL1-b in the serum of psychotic children. These inflammatory mediators are often directly involved in BBB damage. Our results strongly support the "inflammatory theory" of schizophrenia formulated over a 100 years ago.



S-70-004
Glial activation in psychiatric disorders

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Objectives: Until recently, astrocytes were regarded as mere supporters of neurons regulating the environmental milieu. New research, however, has demonstrated that astrocytes together with microglial cells are the major immunocompetent cells of the brain and play an important role in the regulation of neuronal proliferation and differentiation. Since neuronal remodelling appears to be a relevant pathogenic factor in various psychiatric disorders the role of astrocytes needs to be evaluated. S100B, a calcium binding astrocyte-specific cytokine, presents a marker of astrocytic activation.
Results: Several independent studies showed increased S100B levels in medicated acutely psychotic patients with schizophrenia and drug naïve schizophrenics. A positive correlation between negative symptoms and S100B was described. In a longitudinal approach over 24 weeks a continuously increased S100B concentration was associated with continuity of negative symptoms and deceleration of therapeutic response. Cognitive deficits are observed primarily in patients with persistently elevated concentrations of S100B. Increased S100B concentrations are associated with increased myo-inositol, another astrocytic marker measured by MR-Spectroscopy. In acute major depression S100B has been found to be significantly increased directing towards astrocyte activation. Obviously, this phenomenon is limited to the more biologically determined types of depression such as the melancholic subtype. In these patients a moderately elevated S100B concentration seems to be beneficial since patients with higher S100B showed better response and remission rates. Antidepressant treatment appears to normalize S100B concentrations. On a functional level it could be shown that depressed patients with increased S100B experience a better normalization of initially pathological evoked potential (ERP) patterns than patients with unchanged S100B.
Conclusions: These findings suggest that the activation of astrocytes is an important pathogenic factor for the development of schizophrenia and depression. Astrocytic activation is associated with course of disease, treatment response, and functional outcome. This exemplarily illustrates the importance of immunological mechanisms in the etiopathogenesis of major psychiatric disorders.

S-76
Neuroanatomical aspects of prepulse inhibition in schizophrenia: Animal models and human psychoses

S-76-001
Reduction of prepulse inhibition (PPI) after neonatal excitotoxic lesion of the ventral thalamus in pubertal and adult rats

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Objectives: Growing evidence has indicated the role of the thalamus in schizophrenia. The aim of this study was to investigate the effect of neonatal excitotoxic lesions in ventral thalamus on sensorimotor gating in Sprague-Dawley rats.
Methods: At postnatal day (PD 7) male pubs were bilaterally infused into ventral thalamus using ibotenic acid (IBA) or artificial cerebrospinal fluid (controls). Measurements of prepulse inhibition (PPI) of the acoustic startle response were performed in puberty and adulthood.
Results: IBA animals showed lower PPI ($p<0.001$) levels in comparison to controls. The extent of ventral thalamic lesions correlated negatively with PPI levels ($p<0.001$), and in comparison to corollary lesions caused by cannulation only the extent of ventral thalamic lesions exert a predominantly PPI lowering effect (construct validity). PPI deficits in IBA animals were observed at PD 43 and increased significantly after puberty without reaching control levels. Hyperlocomotor activity occurred at PD 43 in IBA rats which declined during development, but still remained in adulthood. Therefore, sensorimotor and locomotor results may contribute to face validity of this animal model. Acute and subchronic clozapine (CLZ: 5 or 10 mg/kg i.p.) treatment did not significantly increase low PPI in IBA rats. In contrast, locomotor behaviour remained reduced during treatment. This provided a positive control for the drug's effectiveness.

Conclusions: Using a neurodevelopmental model, these results support our view that the ventral thalamus plays a role in regulating sensorimotor gating and may be involved in PPI deficits observed in schizophrenia. However, the missing effectiveness of CLZ on ventral thalamus-related PPI deficits needs to be further investigated.

S-76-002
Perinatal hypoxia as probable animal model of schizophrenia

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Objectives: Hypoxia has been discussed as a possible factor of obstetric complications in the pathophysiology of schizophrenia. The present study investigated the effects of mild chronic neonatal hypoxia in an animal model.
Methods: (1) After chronic neonatal hypoxia (11%O2, 89%N2) between postnatal days (PD) 4-8, rats were (2) tested on PD 36, 86, 120 and 150 using three different behavioural tests: prepulse inhibition (PPI), social interaction and recognition, and motor activity in an open field. (3) Before the PD 150 test, 50% of the animals had been chronically treated with the antipsychotic drug clozapine (45 mg/kg/day). (4) At PD 155, brain regions have been used for expression profiling of synaptic genes on cDNA microarrays ("glutamate chip") with qRT-PCR confirmation.
Results: Rats exposed to hypoxia exhibited deficits in locomotor activity on PD 86, 120, and 150, as well as a PPI deficits on PD 120 and 150, but not before. Chronic treatment with clozapine reversed hypoxia-induced PPI deficits, but not the decreased locomotor activity. Several presynaptic genes such as SNAP-25, syntaxin 1A, neurexin, neuropeptid Y and complexin I were downregulated and subunits of the NMDA receptor were upregulated by hypoxia. These differential gene regulations could be partially compensated for by clozapine treatment.
Conclusions: The time course of hypoxia-induced PPI deficits and their reversal by clozapine supports the validity of our animal model and the hypothesis that hypoxia as an obstetric complication is an important factor in the pathophysiology of schizophrenia. Differential gene expression in cortical and subcortical brain regions as well as correlations to deficits of PPI support the view of an involvement of synapse-associated gene products and glutamatergic and GABAergic neurotransmission in the pathophysiology of behavioural deficits occurring as delayed responses to neonatal hypoxia in adulthood.

S-76-003
Pharmacological studies of prepulse inhibition models of schizophrenia

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Objectives: Prepulse inhibition (PPI) of acoustic startle is now widely used in experimental studies of animal models of schizophrenia because of its strong validity and straightforward methodology. Pharmacologically-induced disruption of PPI in rats and mice represents a model of its disruption in psychiatric illnesses, such as schizophrenia. Several typical and atypical antipsychotic drugs are able to reverse PPI disruption in animal models as well in clinical studies.
Results: A large number of neurotransmitter systems and brain regions have been implicated in the regulation of PPI. However, the complex pharmacology of this sensory gating mechanism is still only partially elucidated and emerging evidence suggests important species differences. It is clear that dopaminergic stimulation, either by direct agonists, such as apomorphine, or indirect agents, such as amphetamine, disrupts PPI in almost all studies. However, the dopamine receptors responsible for this effect appear to differ between species. Administration of NMDA receptor antagonists, such a phencyclidine or MK-801, also potently dirsupt PPI. However, the mechanism by which NMDA receptor blockade disrupts PPI is complex, for example there are contradictory accounts on the involvement of dopaminergic stimulation in the effects of phencyclidine on PPI. The wide variety of serotonin receptors makes defining a role of this neurotransmitter in PPI regulation difficult. Several studies have shown a major involvement of 5-HT2A and 5-HT1A receptors and, again, species differences are evident. For example, 5-HT1A receptor stimulation disrupts PPI in rats and, possibly, in humans, whereas it enhances PPI in mice.
Conclusions: Further studies on the pharmacology of PPI regulation and the mechanism behind species differences could be important for our understanding of the causes of its disruption, for example in schizophrenia or in genetically-modified mouse models of this illness, and for the action of antipsychotic drugs to reverse these effects.

S-76-004
Brain imaging (fMRI) studies of startle gating deficits in schizophrenia patients treated with typical or atypical antipsychotics

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Objectives: Prepulse inhibition (PPI) of the startle response is reliably impaired in schizophrenia. Animal models of disrupted PPI have proved valuable for the evaluation of antipsychotic substances. The cortico-striato-pallido-thalamic circuitry is primarily responsible for modulation of PPI in animals. Our previous and ongoing studies have attempted to examine the neural basis of impaired PPI, and of the effects of antipsychotic treatments on PPI, in schizophrenia patients.
Methods: We examined tactile PPI (using airpuff stimuli as both the prepulse and the pulse) and its brain correlates, using functional magnetic resonance imaging (fMRI), in schizophrenia patients treated with typical or atypical antipsychotics.
Results: Our findings show reduced PPI in patients compared with healthy controls. Within the patient group, those on typical antipsychotics show significantly impaired PPI but those on atypical antipsychotics show a milder (non-significant) deficit. At the neural level, our data demonstrate increased activity in the striatum, thalamus, insula, hippocampal, temporal, inferior frontal and inferior parietal regions occurred in association with PPI in controls. Patients treated with atypical, but not with typical, antipsychotics, show significant activation in PPI-relevant regions.
Conclusions: Our findings provide evidence that atypical antipsychotics positively influence PPI and partially restore associated brain functions in schizophrenia.

S-80
Social cognition, social hormones and psychophathology

S-80-001
Neural and genetic mechanisms of human social behavior

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Objectives: Well-being and survival in primates, including humans, depends critically on social interactions, and disturbed social behavior is a key component of diseases such as autism, schizophrenia, and anxiety disorders. However, little is known about specific neurobiological factors shaping the human social brain. Since many aspects of social function are highly heritable, we have adopted a genetic approach to identify molecular and systems-level mechanisms of social cognition in humans.
Methods: Studies in Williams Syndrome, a genetic condition with pronounced hypersociability, identified abnormal prefrontal regulation of amygdala as a neural substrate of social fear regulation under genetic control. Studies of candidate gene polymorphisms (5-HTTLPR, MAOA vNTR) impacting on personality, aggressive behaviour, and emotional regulation modulate on similar circuitry. In animals, oxytocin and vasopressin are key mediators of complex emotional and social behaviors, reduce anxiety and impact on fear conditioning and extinction. Recently, oxytocin administration in humans was shown to increase trust, suggesting involvement of the amygdala, a central component of the neurocircuitry of fear and social cognition that has been linked to trust and highly expresses oxytocin receptors in many mammals.

Results: We report on functional neuroimaging studies in healthy human subjects. In males receiving oxytocin or placebo, oxytocin potently reduced activation of the amygdala and reduced coupling of the amygdala to brainstem regions implicated in autonomic and behavioral manifestations of fear. We also report on imaging genetic studies characterizing the effects of genetic variation in the vasopressin receptor (AVPR1A) and the oxytocin receptor gene (OXTR), implicated in risk for autism, on brain structure and function related to emotional regulation and social behavior.
Conclusions: Taken together, the results suggest neural mechanisms for social cognition in the human brain that begin to define mechanisms for both pro- and antisocial behavior as well as molecular approaches to modulate and treat these behaviors.

S-80-002
Neuroanatomical bases of envy and gloating (schadenfreude)

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Objectives: Fortune of other's- these emotions involve two-person situations in which one's loss or gain depends on the other's gain. Given the importance of envy and schadenfreude in social interactions in humans as well as primates and monkeys, we suggest that these emotions may be mediated by specialized neural networks. The neural bases of envy and schadenfreude were therefore examined
Methods: We conducted three experiments involving lesion study (involving patients with prefrontal damage), neuroimaging (fMRI) and neuroendocrinological (administration of oxytocin) study.
Results: In the first experiment we show that patients with ventromendial lesions are impaired in recognizing envy and schadenfreude, indicating that the mentalizing network is involved in these emotions. The imaging study further support the role of the mentalizing and the reward systems in envy and schadenfreude. Fruthermore, administration of oxytocin increased envy and schadenfreude.
Conclusions: We proposed that the neural network which mediates fortune-of-others emotions such as envy and schadenfreude involves both the ‚mentalizing network' and the reward/punishment systems.

S-80-003
The neuroendocrinology of social cognition

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Objectives: In non-human mammals, the neuropeptide oxytocin (OT) is a key mediator of complex social behaviors, including attachment and social recognition. In particular, OT reduces behavioral and neuroendocrine responses to social stress and seems both to enable animals to overcome their natural avoidance of proximity and to inhibit defensive behavior, thereby facilitating approach behavior. Initial studies in humans from our laboratory suggest behavioral, neural, and endocrine effects of OT, similar to those found in animal studies.
Methods: Three double-blind, placebo-controlled studies in humans on the effects of intranasal oxytocin on (i) cognitive processing of social stimuli compared to nonsocial stimuli, (ii) conflict behavior and pair bonding in couples, and (iii) emotion recognition and brain activity in Asperger Syndrome will be presented.
Results: A single dose of intranasal OT administration (i) specifically improves memory for social stimuli (faces), but not for nonsocial stimuli, (ii) increases positive verbal and nonverbal communication in couples, and (iii) enhances emotion recognition specifically from the eye region in Asperger Syndrome. Moreover, OT increases the acitivity of brain regions that are known to be involved in social cognition (anterior insula, cuneus/precuneus, rostral anterior cingulate cortex, and temporal parietal junction).
Conclusions: Our results might contribute to a deeper understanding of the neurobiology of the 'social brain' and to the development of novel therapeutic approaches in disorders that are characterized by social deficits such as autism spectrum disorders or social phobia. A model of the interactions of social anxiety and stress, social approach behavior, and the oxytocinergic system will be presented (Heinrichs & Domes 2008), which integrates the novel approach of a psychobiological therapy in psychopathological states. Supported by the Swiss National Science Foundation (NSF P001-114788) and the Research Priority Program "Foundations of Human Social Behavior" of the University of Zurich. M. Heinrichs, G. Domes, Prog Brain Res 170, 337-350 (2008)

S-80-004
Genetics of social cognition

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Objectives: The hormones oxytocin (OT) and arginine vasopressin (AVP) have been the luminaries behind a growing set of studies exploring the neurobiology of trust, bonding and other affiliative behaviors. Initially demonstrated in rodents such as the vole, these two nonapeptides with a shared evolutionary history have been shown to influence pup-rearing, social recognition and memory. Increasing evidence suggests that genetic polymorphisms across the OT-AVP pathway are involved in shaping social behavior for humans as well. We demonstrate this across a broad set of social cognitive phenotypes including: prepulse inhibition (PPI) of the acoustic startle response, social stress in a laboratory based paradigm, self report measures of empathy, and pro-social giving in two economic tasks.
Methods: Participants, primarily university students and their families, were recruited via advertisements on campus for a genetic study investigating social behavior. DNA was extracted from mouthwash samples and participants were genotyped for the arginine vasopressin receptor 1a (AVPR1a) gene; a sample of 198 students that participated in the behavioral economic games were also genotyped for the oxytocin receptor (OXTR).
Results: Significant associations were found among AVPR1a promoter region microsatellite repeats and PPI, social stress response, self report empathy measures and giving amounts in the economic tasks. In addition, significant associations were found between OXTR single nucleotide polymorphisms and giving amounts in the economic tasks.
Conclusions: These experiments provide a robust scale of association across a developing hierarchy of social measures beginning with the relatively more autonomic (PPI) up to higher level cognitive aspects such as economic behavior and empathy. Notably, a consistent pattern emerges-with longer alleles in the promoter region of the arginine vasopressin receptor 1a (AVPR1a) associating with more pro-social phenotypes. We expect that future studies will continue this advance and deepen our understanding of these fascinating neurohormones.

S-85
Neural circuitry and mood disorders: Relationship to course of illness and treatment outcome

S-85-001
Neural circuitry in depression: Concepts and rationale

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S-85-002
Hippocampal volumes predict remission rates early in the course of depression

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Objectives: The objective is to examine whether hippocampal volume is associated with clinical response or remission to treatment in patients with major depressive disorder (MDD).
Methods: We examined patients with nonpsychotic, unipolar MDD who had minimal lifetime history of exposure to psychotropic medication (less then one week of lifetime medication on average, no patient with more than 3 weeks lifetime exposure) or pscyhotherapy. Baseline MRI scans were obtained and patients were followed for clinical response and remission over 8 weeks.
Results: Patients who remitted had larger pretreatment hippocampal body/tail volumes bilaterally compared with those who were not in remission at 8 weeks. This difference was not apparent in either the right or left hippocampal head.
Conclusions: These findings extend previous reports suggesting that regional brain volumes might be associated with rate and extent of clinical response to antidepressant medication. This patient sample was unusual because subjects had minimal lifetime exposure to medication, thereby minimizing the possibility that past responsiveness to treatment is a contributing factor to the link between HC volumes and clinical outcome.

S-85-003
Has depression-related decline of brain morphology an impact on illness course?

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Objectives: Experimental studies found that stress results in neuroplastic changes and suggest that these processes may also occur during depressive episodes. Therefore, in the longitudinal course of the disease both structural as well as functional changes will be expected. The studies were carried out to examine whether structural and functional brain changes occur during the course of major depression and whether these alterations normalize during treatment.
Methods: We investigated patients with major depression and healthy controls during the illness course over 3 years using high resolution structural MRI (1.5T) and over 4 weeks during a treatment trial using functional und structural MRI (3T).
Results: Our investigations in patients with major depression support the findings from experimental studies that neuroplastic stress-related processes occur in hippocampus, amygdala, DMPFC, DLPFC and ACC during depressive episodes. In turn, those patients with more structural abnormalities had a more severe illness course. Moreover, stress and genetics interact and have effects on structural integrity of the brain. Structural alterations also influence the function of brain networks implemented in regulation of emotions as shown with combined structural MRI and functional MRI investigations. Antidepressant treatment can normalize these functional abnormalities in ACC, DMPFC and DLPFC, whereby antidepressants with different mechanisms of action have different effects on the functional brain networks.
Conclusions: In conclusion, depressive episodes can result in structural abnormalities particular in patients with a more severe disease course and, in turn, these structural abnormalities predict a bad clinical outcome as well as functional alterations in the network of emotion regulation. Antidepressant therapy results in normalization of altered functional brain circuits. Whether antidepressant therapy also affects the brain structures remains unknown and needs further investigations.

S-85-004
Towards the development of neurobiological predictors of treatment response: Studies in neuroimaging

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S-01
Genetic strategies in the search for genes in schizophrenia

S-01-001
DISC 1 interacting molecule and schizophrenia

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Objectives: DISC1 is a promising candidate susceptibility gene for schizophrenia. To identify other novel susceptibility gene for schizophrenia, we investigated the genetic association between one of DISC1-interacting molecules, 14-3-3Δgene (YWHAE) and schizophrenia in a Japanese population.
Methods: In the genetic association analyses, two independent set of samples were examined: for the first-set screening scan, 384 patients with schizophrenia and 352 healthy controls, and for the second-set confirmation analysis 1045 patients with schizophrenia and 1376 controls. For LD-based association analysis using the first-set samples, we consulted the HapMap and dbSNP database to pick-up "tagging SNPs" from databases. To examine the influence of the expression level of YWHAE by the significant promoter SNP, we developed in vivo and in vitro expression assays: Dual-Luciferase assay, real-time RT PCR and Western blotting analysis. MRI was used to investigate the relation between the significant SNP and volumetric measurements in a sample of 33 schizophrenia patients and 29 healthy subjects. Ywhae+/- and wild-type mice were compared in experiments including behavioral tests (8-arm radial maze test, Elevated plus-maze test, T maze test, Light/dark transition test, and Startle response/prepulse inhibition tests) and neuropathological examinations.
Results: A promoter SNP for YWHAE of which minor allele frequencies were higher in controls than those of schizophrenia. The promoter SNP enhanced transcription of the luciferase gene in reporter gene assay. Both mRNA transcription and protein expression of 14-3-3Δwere increased in the lymphocytes of subjects harboring heterozygous and homozygous minor allele compared to homozygous major allele subjects. The schizophrenic subjects carrying the major allele had a smaller left hippocampus than those without it. Ywhae+/- mice displayed defects in working memory, enhancement of anxiety-like behavior and deficits in neuronal network.
Conclusions: These results suggest that the YWHAE is a novel susceptibility gene for schizophrenia.

S-01-002
Genetic findings in schizophrenia and related intermediate phenotypes: New genes and pathways

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Objectives: There is evidence for a strong genetic component in the etiology of schizophrenia, as demonstrated by family, twin and adoption studies. The risk of developing the disease increases exponentially with the genetic relatedness to an individual suffering from the disorder. Furthermore, schizophrenic patients, and their unaffected relatives display alterations in brain function (intermediate phenotypes).
Methods: We use complementary strategies to approach the pathobiology and genetics of schizophrenia. We aim to identify schizophrenia genes in a case-control and family-based study. Over 1000 patients, 200 first degree relatives and 2500 community-based healthy volunteers entered the study. Furthermore, the use of schizophrenia-related intermediate phenotypes represents a complementary approach which has been used in this study. These comprise, among others, neuropsychological (e.g. working memory, attention/vigilance, verbal/visual learning and memory, speed of processing, and problem solving) intermediate phenotypes. High-throughput targeted and genome-wide genotyping was performed.
Results: We identified several novel putative schizophrenia-associated genes which also associated with intermediate schizophrenia phenotypes adding to the notion that intermediate phenotypes may be useful to learn about the functional significance of these genes.
Conclusions: Ultimately, combining multiple approaches (including positional and functional candidate gene studies, genome-wide association studies, intermediate phenotypes) may lead to further understanding of the genetic component of schizophrenia and thus to a more in depth understanding of the pathophysiology of this disorder.

S-01-003
CAPON gene in schizophrenic Latin America population

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Objectives: The aim of this study is to evaluate association of polymorphisms in the NOS1AP gene region to schizophrenia, in patients from a South American (Colombia) population isolate, and to assess if these variants are associated with specific clinical dimensions of the disorder.
Methods: We genotyped 24 densely spaced SNPs in the NOS1AP gene region in a schizophrenia trio sample (102 patients). The transmission disequilibrium test (TDT) was applied to single marker and haplotype data. Association to clinical dimensions (identified by factor analysis) was evaluated using a quantitative transmission disequilibrium test (QTDT).
Results: We found significant association between eight SNPs in the NOS1AP gene region to schizophrenia (minimum p-value = 0.004). The QTDT analysis of clinical dimensions revealed an association to a dimension consisting mainly of negative symptoms (minimum p-value 0.001).
Conclusions: Our findings are consistent with a role for NOS1AP in susceptibility to schizophrenia, especially for the "negative syndrome" of the disorder.

S-01-004
Cognition guided genetics of schizophrenia

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Objectives: Based on findings on cognition in schizophrenia patients and healthy probands, this presentation will show how the genetics of cognition can contribute to the etiology and treatment of schizophrenia. A prime example is the glutamate system and the glutamate receptor GRM3. Another example are the investigations on the cognitive effects of nicotine, given that the frequency of cigarette smoking is much higher in schizophrenia patients than in the general population.

S-07
Gene-environment interactions in mental health: New paradigms in basic and clinical research

S-07-001
How to model the environment in human GxE studies of psychosis

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Objectives: Concern is building about high rates of schizophrenia in large cities, and among immigrants, cannabis users and traumatised individuals, some of which likely reflects the causal influence of environmental exposures. This, in combination with very slow progress in the area of molecular genetics, has generated interest in more complicated models of schizophrenia aetiology that explicitly posit gene-environment interactions (EU-GEI Group, 2008).
Methods: Although findings of epidemiological GxE studies are suggestive of widespread gene-environment interactions in the aetiology of schizophrenia, numerous challenges remain. For example, attempts to identify gene-environment interactions (GxE) cannot be equated with molecular genetic studies with a few putative environmental variables "thrown in": GxE is a multidisciplinary exercise involving epidemiology, psychology, psychiatry, neuroscience, neuroimaging, pharmacology, biostatistics and genetics.

Results: Epidemiological GxE studies using indirect measures of genetic risk in genetically sensitive designs have the advantage that they are able to model the net, albeit non-specific, genetic load. In studies using direct molecular measures of genetic variation, a hypothesis-driven approach postulating synergistic effects between genes and environment impacting on a final common pathway, such as "sensitization" of mesolimbic dopamine neurotransmission, while simplistic, may provide initial focus and protection against the numerous false positive and false negative results that these investigations engender.
Experimental ecogenetic approaches with randomized assignment may help to overcome some of the limitations of observational studies, and allow for the additional elucidation of underlying mechanisms using a combination of functional enviromics and functional genomics.
Conclusions: Translation of results to clinical practice will be facilitated by additional experimental research and risk assessment bioinformatics approaches. This may result in (i) the identification of modifiable biological and cognitive mechanisms underlying gene-environment interactions and (ii) the construction of Risk Assessment Charts and Momentary Assessment Technology tools.

S-07-002
Human G x E interactions in depression using experimental ecogenetic approaches

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Objectives: The complexity of behavioural disorders such as depression requires studies to take into account both genetic factors, G x E interactions as well as dynamic person-context interactions in daily life. Given these complexities, the use of momentary assessment technology such as the Experience Sampling Method can aid in unraveling the underlying mechanisms of depression. Furthermore, research should be focused not only on causes of vulnerability but also on areas of resilience.
Methods: Several hypotheses regarding mechanisms of vulnerability and resilience have been tested in a population twin sample(n=621) using GE interaction and momentary assessment of daily life experiences.
Results: The negative affective (NA) response to minor daily life stressors (stress-sensitivity), was shown to represent an endophenotype of depression. Support was found for the hypothesis that between-subject variation in daily life stress-sensitivity develops partly through the process of sensitisation: developmental stress exposures were associated with increased daily life stress-sensitivity. Genes for depression acted by facilitating the sensitisation process to major stress exposures previous in life, rendering these subjects more stress-sensitive after exposure than those without genetic risk. Regarding mechanisms of resilience: positive emotions buffered against daily life stress-sensitivity and the positive affective (PA) response to pleasant daily life situations (reward experience) appeared to be partly under genetic control. Moreover, reward experience protected people with vulnerability to depression (due to previous stress exposure or genetic vulnerability) from developing future depressive symptoms. In fact, this ability of reward experience predicted, independently from severity of depression and neuroticism, whether remitted depressed subjects would relapse to depression at follow-up.
Conclusions: Daily life stress-sensitivity contributes to vulnerability for depression, while positive affect and daily life reward experience protect in case of vulnerability. New treatments should aim at reshaping person-context interactions in a way that subjects build their own source of resilience.

S-07-003
Gene-environment interactions throughout development: Adaptability and resilience in monkey model

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Objectives: This paper examines the consequences of different patterns early social attachment on behavioral and biological development in non-human primates.
Methods: Prospective longitudinal studies of rhesus monkeys documented the effects of differential early social attachments on multiple measures of behavioral and biological functioning throughout development
Results: Monkeys who developed insecure early attachment relationships with their caregivers exhibited significant deficits in the development of affiliative, play, and aggressive behavior relative to monkeys with secure attachment relationships. Insecurely attached infants also exhibited excessive HPA axis reactivity to stress and chronic deficits in serotonin metabolism, as well as reduced levels of serotonin transporter binding and cerebral blood flow. These differences were especially pronounced among monkeys carrying the "short" allele of the serotonin transporter gene, reflecting specific gene X environment interactions arguably resulting from "maternal buffering" by mothers developing secure attachment relationships with their offspring. Moreover, because the attachment style of a monkey mother is typically "copied" by her daughters when they become mothers themselves, similar "buffering" will likely to occur for the next generation of infants carrying that specific polymorphism
Conclusions: Differential early social attachment experiences among rhesus monkeys can have significant consequences for behavioral and biological development and often are transmitted to the next generation.

S-07-004
Gene-environment interactions in psychiatry: DISC1 mouse model

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Objectives: The pathogenesis of mental illnesses of involves interactions between vulnerable genes and environmental factors, including prenatal viral infections that induce immune activation in utero. We evaluated how prenatal immune activation interacts with mutant human Disrupted-In-Schizophrenia-1 (DISC1) in producing neurobehavioral abnormalities in transgenic mice.
Methods: Mutant DISC1 or control mice were stimulated at ED9 with saline or an immune activator, polyriboinosinic-polyribocytidilic acid (poly IC). We measured production of neuroinflammatory factors in pregnant dams and fetal brains and the brain and behavior alterations in the adult offspring.
Results: Injections of poly IC dramatically increased production of pro- and anti-inflammatory soluble factors in serum of pregnant dams and fetal brain samples. Curiously, mutant DISC1 modulated basal and poly IC-induced secretion of cytokines in fetal brains. In adult mutant DISC1 mice, prenatal immune activation led to previously unseen neurobehavioral abnormalities such as elevated startle reactivity and anxiety, decreased exploratory activities, depression-like response and deficient spatial recognition memory. In contrast to DISC1 mice, control poly IC-treated mice had the increased volume of the brain and lateral ventricles. Compared to untreated mutant mice, poly-IC treated mutant animals had the significantly decreased linear spine density on neurons of the dentate gyrus of the hippocampus.
Conclusions: The present findings suggest the synergistic effects of mutant DISC1 and prenatal immune activation on brain and behavior development in mice. Our animal model serves as a valuable system for elucidating the specific molecular pathways of gene-environment interplay in the pathogenesis of mental diseases.

S-18
Neurosciences of suicidal behaviour: New targets for prevention?

S-18-001
What genes tell us – ethical perspectives

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S-18-002
Will emotional and cognitive endophenotypes provide new therapeutic targets?

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Objectives: Although psychiatric disorders are the main risk factors of suicidal behaviour (SB), improvement in their treatments didn't translate in real decrease in completed and attempted suicides. The evidence base to guide treatment is thin. Nevertheless, there is hope that better understanding of the pathophysiology may translate into more sophisticated treatments. Moreover, as all the psychiatric patients won't commit a suicidal act, prevention strategies need the identification of high-risk groups of patients. Therefore, the vulnerability to SB appears to be underlied by genetic factors coding for traits rendering the individual less able to cope with stressing situations, and more likely to be engaged in the suicidal process.
Methods: During the recent years, neuroscientific studies begun to identify potential endophenotypes.
Results: We shown that decision making, an executive function related to the functioning of the orbitofrontal cortex, was involved in the vulnerability to SB. Decision-making impairment appears to be independent of comorbid psychiatric disorders, associated with emotional dysregulation (i.e. affective lability trait and skin conductance responses), and modulated by serotonergic and CRHR1 genotypes associated with SB. In recent fMRI studies, SB was associated with a decreased response of the left lateral orbitofrontal cortex during risky choices, a higher activation being correlated to a better decision-making. Interestingly, an increased response of the same region was associated with the response to angry faces. The risk valuation deficit and excessive response to specific emotional stimuli may represent key processes in the vulnerability to SB.
Conclusions: Ideas about how to translate endophenotypes into treatment will be introduced. It seems to be time to investigate targeted psychotherapeutic (using cognitive remediation and emotional relearning), pharmacological and neurophysiological (e.g. repetitive Trans Magnetic Stimulation) treatments.

S-18-003
Predictive value of genetic findings: New analytical methods

Enrique Baca Garcia
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Maria Oquendo, Antonio Artes

Objectives: Complex behaviors are the results of multiple biological, genetic and clinical factors. These factors are combined in different ways to produce the same observable behaviors. That means that different combinations of different factors may produce the same output. Moreover, the effect of each single factor is very small. In our opinion, to test individual hypotheses is no longer the adequate approach. In this symposium We introduce the use of data mining techniques in genetic research.
Methods: Data mining can be defined in a technical way such as "algorithmic and database-oriented methods that search for previously unsuspected structure and patterns in data" or "the science of searching large bodies of data seeking interesting patterns and structures. Data mining based on statistical inference can be approached in two major ways, predictive models (also called discriminative models) and explanatory or generative models. Both predictive and explanatory models use patient attributes to provide information concerning a not yet observed event,. Yet, predictive and explanatory models are developed and evaluated differently and have different purposes.
Results: As example we use data mining techniques to find combinations of SNPs associated with suicide behavior in males. We searched for the most important SNPs to discriminate between suicide attempters and non attempters by genotyping 800 SNP in a training sample of 222 psychiatric patients. We used data mining techniques to build a classifier using this training sample. The algorithm included 3 SNP. The accuracy was 69% with an OR 5.02 (2.74-9.21). The algorithm was tested in a new sample (55 subjects) with results similar to those obtained in the training sample The classifier is a black box and therefore we cannot know which is the relation among these SNPs that causes an increase of the suicide attempt risk.
Conclusions: Data mining provide a new frame to improve the analysis of large genetic databases.

S-18-004
Suicide risk in prisoners: Genes environment interactions

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Vladimir Carli, Francesco Basilico, Miriam Iosue, Caterina Cesaro

Objectives: Suicide is the leading cause of death in prisons. Number of studies has indicated disturbances in serotonin neurotransmission in persons displaying suicide behaviour and depression. We hypothesized that 5-HT2A -1438G/A polymorphism would modulate the influence of childhood trauma on suicide and depression among prisoners in a gene-environment-dependent manner.
Methods: Study participants were 427 male prisoners detained in jails of the District of Abruzzo-Molise in Italy. All were assessed through psychiatric interview, Hamilton Rating Scale for Depression (HRSD-21 items) and Childhood Trauma Questionnaire (CTQ). The component structure of the 21 HRSD items was determined using principal component analysis with varimax rotation and three components were extracted. We proposed a new gxe model with all components dichotomised at the median and used as dependent variables when creating logistic regression.
Results: Significant interactions were found with the suicide/insomnia component only. The major findings were: 1) emotional abuse during childhood interacts with 5-HT2A AA genotype to increase the risk for later-life suicide and insomnia, 2) 5-HT2A AA genotype and childhood traumas (emotional abuse and physical neglect) independently of each other increased the risk for later-life suicide and insomnia, 3) 5-HT2A AG and GG genotypes might be protective against suicide and insomnia, even when in interaction with childhood traumas.
Conclusions: Our results add evidence to the fact that suicide and insomnia are both complex traits shaped by interactions between genetic and environmental factors. These factors might interact dynamically throughout prenatal and postnatal periods, thus shaping the brain development and leaving long-term consequences on adult behaviour.

S-30
Translational research in the neurogenetics of NPY

S-30-001
Distribution of NPY and its receptors: Significance for anxiety/depression and neurogenesis

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Inga D Neumann, David Slattery, Gregers Wegener

Objectives: Dysregulation of the monoaminergic systems may be sufficient but is likely not necessary for etiology or pathophysiology of major depressive disorder (MDD). MDD, as well as anxiety disorders (AD) remain phenotypical diagnoses. The fact that clinically effective antidepressant drugs, including SSRIs which are also used as anxiolytics, all affect serotonin and noradrenaline (and dopamine) in itself is not evidence of underlying pathology; a useful analogy is that of beta receptor agonists alleviating bronchial asthma but not playing a role in its etiology.
Methods: Substantial evidence indicates that neuropeptides and the glutamatergic system play important roles in mood disorders. This presentation will focus on neuropeptide Y (NPY), a peptide widely distributed in brain.

Results: We found that both NPY mRNA and protein are decreased in hippocampus of FSL rats, a genetic model of depression, compared to control FRL and Sprague-Dawley rats. Moreover, environmental stress, such as early maternal deprivation, also decreases NPY expression in the hippocampus. In a novel model, more faithfully mimicing the real life situation, "depressed" FSL animals were subjected to maternal separation and behavioral and brain neurochemistry sequelae investigated in adult life. Lithium, SSRI and electroconvulsive stimuli, as well as running in running wheels all affect behavior and increase NPY expression in hippocampus of FSL strain. These findings are in line with our previous studies which have demonstrated decreased NPY in CSF of depressed patients as well as increases in NPY following successful treatment with citalopram and ECT. Lastly, NPY in itself alleviates "depressive " and anxiety-like behaviors in rats via agonist action at the NPY-Y1 and antagonism at the NPY-Y2 and NPY-Y5 receptors.
Conclusions: In conclusion, both animal and human data indicate that NPY plays a role in mood disorders. These findings provide further support for the idea that NPY analogues (that can cross the blood-brain barrier) should be developed as antidepressive and anxiolytic drugs.

S-30-002
Effects of viral vector-induced overexpression of neuropeptide Y and Y2 receptors in seizure models

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Objectives: Gene therapy with adeno-associated viral (AAV) vectors causing overexpression of neuropeptide Y (NPY) in the hippocampus has been shown to cause seizure-suppressant effects. This approach might be used in future treatment of neuropsychiatric disorders, including temporal lobe epilepsy. NPY Y2 receptors mediate antiepileptic effects of NPY in the hippocampus and overexpression of Y2 receptors could be a more specific alternative to overexpressing NPY alone.
Methods: Using an AAV vector construct, overexpression of functional Y2 receptors was induced in the adult rat hippocampus, and the effects were studied in two temporal lobe epilepsy models: rapid electrical kindling and kainate-induced seizures. In addition, it was tested whether combined AAV-induced overexpression of Y2 and NPY could induce a better antiepileptic therapeutic response than with the single gene approach.
Results: Overexpression of functional Y2 receptors caused seizure-suppressant effects in both models. Inhibitory effects were also found after NPY-AAV treatment, consistent with previous studies. However, the combined overexpression of Y2 and NPY enhanced the seizure-suppressant effect as compared to that of single transgenes with regard to several seizure parameters.
Conclusions: These results show that Y2 receptor-based gene therapy could be a novel treatment strategy for seizures and that combining Y2 and NPY overexpression might improve the therapeutic response.

S-30-003
NPY and its receptor genes in personality disorder

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Objectives: The NPY system has been implicated in the control of a wide range of behaviors as well as psychiatric diseases including anxiety disorders and attention-deficit/hyperactivity disorder (ADHD). The latter is a childhood behavioral neurodevelopmental disorder with high persistence into adulthood. Twin and family studies demonstrated heritability of up to 80%, yet the underlying molecular mechanisms remain unclear and likely are highly complex. We have thus utilized hypothesis-driven and hypothesis-free approaches to further explore the genetics of ADHD.
Methods: First, we conducted a genome-wide screen for copy number variations (CNV) in a cohort of 99 children and adolescents with ADHD using high-resolution array Comparative Genomic Hybridization (aCGH). Second, we specifically examined the genomic region containing the genes for NPY itself as well as its receptors Y1, Y2 and Y5 for an association with ADHD and personality disorders using primer extension PCR methods.
Results: The gene encoding neuropeptide Y (NPY) on chromosome 7p15.2-15 was included in a 3 Mb duplication. Investigation of additional pedigree members and phenotypic assessment suggested association of this 7p15 duplication with ADHD (empirical FBAT p = 0.041), increased BMI (p = 0.034) and binge eating (p = 0.031), but not peripheral NPY plasma concentrations. On a population based level, genetic variation in NPY as well as its receptor Y2 however did not seem to confer risk towards ADHD. Complex relations however were evident for personality disorders and personality traits.
Conclusions: Taken together, converging evidence from rodent and human studies make a compelling case that the NPY system is implicated in a variety of psychiatric disorders. Accordingly, NPY and its receptors are not only positional, but also functional candidate genes for ADHD and related behaviors. Their impact appears to be complex in nature; however, the data gathered thus far suggest that the NPY system has a role in balancing proactive and retreating behaviors.

S-30-004
Molecular genetic evidence for a 4q31-34 panic disorder risk locus

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Objectives: There is strong evidence for a genetic contribution to the pathogenesis of panic disorder, with a recent linkage study pointing towards a risk locus on chromosome 4q31-q34. Genes coding for neuropeptide Y (NPY) Y1, Y2 and Y5 receptors are located in the suggested risk region (4q31-q32) and the neuropeptide Y system has repeatedly been reported to be involved in the pathophysiology of anxiety. Therefore, NPY receptor genes constitute most promising functional as well as positional candidate genes for association studies in panic disorder.
Methods: In the present study, tagging variants in the NPY (rs16157, rs16147, rs16139, rs9785023, rs16474), NPY Y1 (rs12507653, rs12510104, rs7687423, rs4691075), Y2 (rs11099992, rs12507396, rs1047214, rs11728843) and Y5 (rs4234955, rs11724320, rs11946004) genes were investigated for association with panic disorder in a sample of 230 German patients with panic disorder (f=135, m=95) and 230 age- and sex-matched healthy controls.
Results: A synonymous (Gly-426-Gly) NPY Y5 coding variant (rs11946004) as well as haplotypes including rs11946004 and an intronic NPY Y5 variant (rs11724320) were significantly associated with panic disorder (p=0.027), with the effect originating from the subgroup of female patients (p=0.030), particularly with concurrent agoraphobia (p=0.002-0.019). No association was observed for any variants located in the genes coding for NPY, NPY Y1 or NPY Y2.
Conclusions: The present results suggest an influence of NPY Y5 receptor variants on the etiology of panic disorder in a potentially gender-specific manner and further strengthen the evidence for a risk locus on chromosome 4q31-q34 in anxiety disorders.

S-47
Biological markers and clinical features in depression: A difficult puzzle

S-47-001
The relevant relationship between genetic and clinical presentation

Raquel Terese Zamora-Cabral
Uruguay

Objectives: The aim of this presentation is to review the importance of the genetic research to guide the clinical psychiatric in the diagnosis and treatment of the patients.
Methods: Literature research.
Results: Until the 1950s the gene was a hypothetical construction in the science of genetics. In 1953 J. Watson and F.Crick proposed that deoxyribonuclei acid (DNA) is the basis of the gene and constructed a molecular structure that could account for its biological properties. Since that momentous discovery, the molecular mechanisms of heredity have been extensively investigated. The influence of genes on behavior is complex and is always intertwined with the physiology and environmental possibilities of the organism. Genetic studies have confirmed the importance of genes in the etiology of many mental disorders. Schizophrenia and mood disorders are the most studied but we found research in personality disorders, anxiety disorders, among others. The mode of transmission is complex, including multiple genes interacting to one another. Some papers are oriented in the relevant relationship between the genetic and clinical presentation, this point will be continued for the next co-speakers. Search for genetic susceptibility might be improved by the identification of intermediate phenotypes related to more fundamental aspects of brain development and function. Day to day the science is advancing and giving relevant information that will help the clinic practice. It is fundamental to know the findings and to use the knowledge in diagnosis and treatment of our patients. Today, an exhaustive familiar history including different kinds of treatment, drugs usage, hospitalization, suicides must be done. In the future it is possible we can include biological markers.
Conclusions: The genetic researches help the psychiatric in the clinic practice.

S-47-002
Neuropsycological endophenotypes in bipolar disorder

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Colombia

Objectives: Patients with Bipolar Disorder (BD) have been reported to present disturbances in the performance of cognitive functions such as memory, attention and executive function, even during euthymic periods. Also, a strong association with some chromosome zones has been demonstrated to be etiologically determinant in the presentation of the disorder, as has been described for chromosomes 12, 18, and 21.
Methods: In this symposium we will revise the findings related to neurocognitive disfunction of patients with BD, which can be considered endophenotypes of BD, both in those patients which are on medication and in those who are not.
Results: We will also review which chromosome regions are associated to these neurocognitive disfunctions, found as a result of a study a special population of a genetically isolated Colombian region with high prevalence of bipolar disorder.
Conclusions: The possible association of these neurocognitive and genetic findings will also be analyzed in relation to neuroimage studies in the same population. We will show the importance of these findings and how they can be considered possible biological markers which help to better understand the disorder and to make an earlier diagnosis.

S-47-003
International studies on SERT and subtypes of depression – an update

Andrea Lopez Mato
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Objectives: To determine if allelic variations of SERT gene (or HTTLPR) are related to stress triggered depression and prone to the presentation of any particular subtype of depression or may influence the therapeutical response to several antidepressants families
Methods: The summary of over 50 specific published papers on SERT gene expression and different clinical types of depression are presented. Focus is made on Caspi´s pioneer work, published in Science in 2003, which showed the influence of life stress on depression moderation by a polymorphism in the 5-HTT gene (SERT). It clearly states that SERT heterogenic variance x/l or homogenic x/x prone to stress triggered depression SERT alleles and relation to melancholic, atypical, unipolar, bipolar, psychotic, female or male depression and the clinical presentation of suicidality or seasonality will be presented. Patients response to different therapheutical approaches concerning specially SSRI will be discussed, clearly describing response, recovery, relapse and remission
Results: SERT is highly related to depressive symptomatology after stressful life events. The association between SERT gene promoter and depressive responses to tryptophan depletion in healthy women with and without family history of depression has robust evidence. Moreover it seems to be a clear relation between the presence of SERT gene polymorphism and violent suicidal behavior, melancholic depression and seasonality Short aleles of SERT may lead to poor response to SSRI medication. This results may be confounding because very few studies correlate other allelic variations (COMT, MAO, tryptophan hidroxilase, DAT, among others) adjunctively to SERT
Conclusions: The determination of SERT allelic variances in individuals under stress may show a predisposition to the presentation of subsequent depression. However there is no hint towards the subtype of depression. Therapeutical choice of antidepressant may be helped by this and other transporters, enzimes, peptidergic and neuroaminergic metabolites and receptor functionality studies

S-47-004
Correlation between the Serotonin transporter gene in depressive patients and suicide victims

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Objectives: As recent studies suggest that different allelic distribution of the serotonin transporter gene might be involve in depression, suicidal behavior and suicide we investigated the (5-HTTLPR) serotonin transporter gene polymorphisms distribution and personal background in 45 suicide subjects.
Methods: 45 caucasian subjects who commited suicide in Argentina were investigated. Personal background were obteined by interviews to a relative or close member or by legal reports. Only in 24 suicides it has been possible to genotyped the serotonin transporter gene from postmortem tissue. The results were compared to a control group comprised by 30 blood donors.
Results: 90% of the suicide had a diagnosis of depression or were described as being depressive. 63% were male. The average age was 61 years old in women and 49 in men. The most used method among women was precipitation and hanging followed by shooting with firearm in men. In almost all cases the fact was commited by night at home. 38% of the population was under psychiatric treatment at the moment of suicide. 18 % was under alcohol effects. In all cases stressfull life events were found related to suicide except in a young adult man.There were no significant differences in 5-HTTLPR and intron 2-VNTR genotype- and allele- frequency distributions between suicide victims and control group.
Conclusions: Our finding didnt provide evidence that a functional polymorphism in the regulatory region of serotonin transporter gene may be associated with complete suicide. As the sample size was small it would be necessary to replicated these studies in a large population from Argentina.

S-61
The genetics of unipolar depression and bipolar affective disorder

S-61-001
The uses and abuses of genome wide linkage and association studies

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Objectives: To review the benefits and potential problems of genome wide linkage and association studies.
Methods: Consideration of the theoretical basis of phenomena of linkage and association and practical implications for studies aiming to detect association.
Results: Linkage occurs over comparatively large distances but can only detect large effects. Association in outbreeding populations is only observed over tiny genomic distances but is capable of detecting very small effects. Hence genome wide association studies (GWAS) have only become feasible fairly recently.
Conclusions: While GWAS have revolutionized the study of common, complex familial diseases there are many potential pitfalls in therir interpretation.

S-61-002
Genome-wide association studies of bipolar disorder

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Objectives: The enormous public health importance of mood disorders, when considered alongside their substantial heritabilities, has stimulated much work, predominantly in bipolar disorder, aimed at identifying susceptibility genes using both positional and functional molecular genetic approaches
Methods: The advent of powerful molecular genetic tools such as genome-wide association studies of single nucleotide polymorphisms and measurement of copy number variation has made a major impact on understanding of common non-psychiatric diseases and is starting to produce replicable findings in psychiatric phenotypes, including mood disorders.
Results: Very large samples (thousands or tens of thousands of samples) are needed and, hence, collaborations are crucial. In bipolar disorder, genes implicated at genome-wide levels of statistical significance include CACNA1C and ANK3. The product of both genes is involved in ion channel function, suggesting a key mechanism of importance in the pathogenesis of bipolar disorder.
Conclusions: In addition to informing understanding of pathogenesis, recent findings provide opportunities to explore the relationship between bipolar disorder and other major psychiatric illnesses, such as schizophrenia. The data suggest an overlap in pathogenesis that will shape future nosological thinking. The pace of development of the field of mood disorder genetic research is rapid and will be summarized in this presentation.

S-61-003
Genetics of bipolar affective disorder

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S-61-004
A genome wide association study of unipolar depression

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Objectives: Although the substantial genetic contribution to depression predisposition is well-established, specific genes have failed to be consistently identified through 'traditional' single-gene association studies. Genome-wide association studies (GWAS) have become viable through recent advancements in genotyping platforms and reduction in chip-genotyping costs. GWAS allows the greater statistical power of association over linkage to be retained in the identification of genes with low effect sizes. Furthermore the possibility of swift identification of novel targets may be realized as demonstrated by the Wellcome Trust Case Control Consortium (WTCCC) which used the Affymetrix 500K GeneChips®. Recurrent unipolar depression is a complex disease that was not included in the WTCCC project, however it is one that would benefit from the same strategy.
Methods: Case samples from four genetic studies in depression were combined; Depression Case-Control (DeCC) study, Depression Network (DeNT) study, Genome Based Therapeutic Drugs for Depression (GENDEP) study, and a GSK-Munich sample. Control individuals from two studies were combined; Bipolar Association Case-Control (BACC) study and the DeCC study. In total the sample presented includes approximately 4,200 cases and 1,500 controls. Each case individual has suffered a minimum of 2 episodes of DSM-IV/ICD-10 depression, of at least moderate severity, assessed by SCAN interview. Control individuals were screened by questionnaire and/or telephone interview for absence of psychiatric disorder. Samples were genotyped by CNG (Paris) using the Illumina Human 610-quad DNA analysis bead chip, including over 620,00 SNPs and CNVs.
Results: SNPs that show evidence for association in this study will be presented, alongside a clear description of the quality control applied. This represents the largest and most thorough clinical case-control GWAS to date investigating recurrent unipolar depression.
Conclusions: With important and far-reaching implications for pharmaco-genetic studies, more directed and economical research may be applied to further elucidate the underlying aetiology, and ultimately treatment, of unipolar depression.

S-75
Recent advances in the neurobiology of suicide

S-75-001
Separating effects of genes and stress on the neurobiology of suicidal behavior

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Leo Sher

Objectives: Past neurobiological models of suicidal behavior have tended to emphasize clinical or biological aspects and have rarely considered etiology or a developmental perspective.
Methods: Recently enough data regarding candidate genes and the impact of adverse early experience have permitted description of a plausible and heuristically useful hypothetical causal and developmental model. This talk will integrate known effects of susceptibility genes and childhood adversity in explaining the psychopathology and biological phenotype of the diathesis for suicidal behavior including data from postmortem studies of suicide, molecular genetics and in vivo brain imaging.
Results: Within the landscape of neurobiological changes some abnormalities are linked to genetics, some to early life stress and some to recent stress effects, and finally some combining as interaction effects.
Conclusions: Examples include more serotonin neurons due to early deprivation, more TPH expression due to homeostatic response to a genetic deficit in serotonin release, low CSF 5-HIAA due to genetic and childhood adversity interaction, ventral PFC deficient serotonin input due to genetics and impaired doral lateral PFC control due to depression and genetics.

S-75-002
Early life adversity, biological modifications and impulsive-aggressive suicide

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Objectives: Among factors associated with early adversity, childhood abuse and neglect are one of the strongest predictors of major depression and suicidality. Childhood sexual abuse, in particular, is associated with earlier age of onset of depression, chronic course and more severe depressive outcome. Moreover, history of childhood sexual abuse increases the odds of suicidal behavior up to 12 times. This presentation will present data on ongoing studies investigating epigenetic factors associated with suicide
Methods: Methylation mapping and histone modification in suicide completers and controls, controlling for history of childhood abuse
Results: While no excess methylation is associated with suicide, several genes of interest indicate a pattern of increased promoter methylation.
Conclusions: Epigenetics changes observed in suicide completers are consisten with data from animal studies, which have recently given us important insight into some of the epigenetic processes that modify behavior and result from early social environmental experiences. These results will be discussed in terms of a general conceptual framework for the understanding of suicide risk.

S-75-003
Orbitofrontal cortex, decision-making and suicidal behaviour

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Objectives: Understanding the cognitive processes leading to suicidal acts and their neuroanatomical basis is of major importance in a preventive perspective. Post-mortem studies have previously shown alterations of serotonergic receptor / transporter binding in the ventral parts of the prefrontal cortex suggesting an impaired modulation of the functioning of these regions.
Methods: A series of neuropsychological studies including the Iowa Gambling Task (IGT); an fMRI study using emotional faces and a modified version of the IGT.
Results: At the cognitive level, decision-making alteration is found in euthymic suicide attempters independently of Axis-I disorders and may therefore represent a vulnerability trait of vulnerability to suicidal acts. A preliminary functional imaging study has confirmed the involvement of the ventral prefrontal cortex in decision-making deficit in euthymic suicide attempters in comparison to non-suicidal patients, notably a decreased activity of the left orbitofrontal cortex. Interestingly, the right orbitofrontal cortex shows an increased activity in response to angry faces that may represent an increased sensitivity to reject and disapproval.
Conclusions: The orbitofrontal cortex appears to play a key role in the vulnerability to suicidal acts and may underlie deficits in decision-making and social perception in suicide attempters.

S-75-004
Genetics of aggressive and impulsive behavior

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Abstract: Suicidal behavior is a major health problem worldwide. Risk of suicide-related behavior is supposed to be determined by a complex interplay of sociocultural factors, traumatic life experiences, psychiatric history, personality traits, and genetic vulnerability. This view is supported by adoption and family studies indicating that suicidal acts have a genetic contribution that is independent of the heritability of Axis I and II psychopathology. The heritability for serious suicide attempts was estimated to be 55%. Neurobiological studies have shown that serotonergic dysfunction is implicated in suicidal behaviors. Additionally aggression-related traits are mediated by the serotonergic system. Since both, aggression related traits and serotonergic activity are partially heritable and correlate inversely, variations in genes of the serotonergic system might then, to some extent, account for variations in aggression-related behavior. For that reasons we have initiated a large scale case control genetic association study which comprises of 250 suicide attempters and 2100 healthy volunteers and investigated the role of a comprehensive set of serotonergic candidate genes in this behavior. Additionally we conducted a large-scale gene expression analysis using cDNA-microarrays to identify new candidate-genes for suicide. We found several genes to be differentially expressed in the orbitofrontal cortex of suicide completers. Cross-validation experiments using quantitative RT-PCR validated 9 genes so far. These genes have been genotyped in our patients and controls and associations with suicidal behavior and intermediate phenotypes will be presented.

S-05
Near-infrared spectroscopy (NIRS) in psychiatry: Current status and future prospect

S-05-001
Bilateral frontal activation during a phonological working memory task in schizophrenic patients

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Junghee Lee

Objectives: Impaired working memory (WM) is a core feature of schizophrenia (SZ). The neural correlates of WM map onto the functional subdivisions of the prefrontal cortex (PFC). In a previous near infrared spectroscopy (NIRS) study we showed that spatial memory representation in SZ patients was maintained in WM supported by more bilateral prefrontal activity than in controls who showed a clear lateralized activation in the right frontal cortex. In the present study, we sought to extend the findings of the spatial WM study to verbal domain. It was hypothesized that phonological WM maintenance would recruit more diffuse bilateral frontal areas in SZ but left-lateralized in control subjects.
Methods: We examined the neural correlates of phonological WM in SZ with NIRS using an event-related design so that we could compare correct vs. error trials. Each trial began with the presentation of three nonsense stimulus words on the computer screen followed by a delay of 8s. After the delay, a nonsense word was presented on the screen and subjects were required to decide whether this word was one of the three target words presented before the delay. Then they rated their confidence before starting a new trial. A Hitachi ETL NIRS system was used to measure the oxy, deoxy and total hemoglobin concentrations in the frontal cortex during the WM task.
Results: SZ patients showed increased bilateral frontal activity on correct trials of the phonological WM task compared with controls. Thus both spatial and phonological WM tasks recruit more bilateral and diffuse frontal regions in SZ.
Conclusions: WM is supported by the PFC in SZ patients on correct trials but the patients may be using different strategies to maintain mental representations in WM. Reduced hemispheric asymmetry of spatial and verbal functions in SZ is consistent with the evidence for overall reduced laterality in SZ.

S-05-002
Near-infrared spectroscopy in mood disorders

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Objectives: Near-infrared spectroscopy (NIRS) has been increasingly employed in psychiatry as functional neuroimaging studies of sleepiness [1], fatigue [2], personality [3], aging [4], brain activation time course [5], transcranial magnetic stimulation effects [6, 7], and psychiatric disorders such as schizophrenia [8, 9], mood disorders [8, 10], panic disorder [11], and eating disorder [12].
Methods: Characteristics of frontal lobe function were investigated using multichannel NIRS machines in schizophrenia, unipolar depression, bipolar depression, and eating disorder. Changes of oxygenated-hemoglobin concentration ([oxy-Hb]) were monitored every 0.1s during a verbal fluency task using Hitachi ETG-100 and ETG-4000 with the probes placed on the subjects' frontal and temporal regions.
Results: Four psychiatric groups demonstrated different patterns of [oxy-Hb] changes from those in the control group. The schizophrenic group was characterized by reduced [oxy-Hb] increase during the task period followed by [oxy-Hb] re-increase during the post-task period, the unipolar depression group by smaller [oxy-Hb] increase, the bipolar depression group by comparable but delayed [oxy-Hb] increase, and the eating disorder group by smaller [oxy-Hb] increase in the right-than-left hemisphere.
Conclusions: The observed patterns of [oxy-Hb] changes suggest the characteristics of reactivity of frontal lobe function: inefficient, reduced, preserved but delayed, and lateralized activation in schizophrenia, unipolar depression, bipolar depression, and eating disorder, respectively. NIRS can be employed as a clinical laboratory test for diagnosis and treatment of psychiatric disorders in the near future. [1] Neurosci Res 60:319, 2008; [2] Brain Res, in press; [3] Neuropsychobiology 52:45, 2005; [4] NeuroImage 22:1715, 2004; [5] Neurosci Res 58:297, 2007; [6] Neurosci Lett 414:99, 2007; [7] Neurosci Res 63:47, 2009; [8] Biol Psychiatry 55:501, 2004; [9] Schizophr Res 99:250, 2008; [10] NeuroImage 29:172, 2006; [11] Neurosci Res 59:107, 2007; [12] Eating Weight Disord 12:183, 2007.

S-05-003
NIRS in Attention-Deficit / Hyperactivity Disorder (ADHD)

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Objectives: Like many psychiatric diseases attention-deficit / hyperactivity disorder (ADHD) is associated with alterations in brain function. This has been shown with multiple brain imaging approaches, in particular with functional Magnetic Resonance Imaging (fMRI). FMRI is undoubtly the imaging method with the best spatial resolution providing a neuroanatomical image of the brain within the same measurement. However, it's setting and ecological validity is not optimal for patients with psychiatric illnesses. In particular the lying position, the fixation of the head, the extremely narrow surrounding and the loud EPI sequences are stressing for psychiatric patients and do definitely affect the results of fMRI studies.
Methods: Near-Infrared Spectroscopy (NIRS) is suitable to elegantly measure concentration changes of oxygenated and deoxygenated hemoglobin in a more natural setting than fMRI with high ecological validity.
Results: Studies with different perceptional, cognitive and emotional tasks proving test-retest reliability of NIRS in healthy subjects will be presented. First results in ADHD demonstrate dysfunctions of dorsolateral prefrontal and orbitofrontal brain areas, which are partly influenced by genetic variants affecting the dopaminergic neurotransmission.
Conclusions: NIRS is a very suitable method to conduct brain imaging and also imaging genetic studies in ADHD.

S-05-004
Clinical NIRS application to psychiatric diagnosis and evaluation

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Objectives: Functional abnormalities in frontal and temporal lobes are assumed to underlie clinical symptoms and functional impairments in psychiatric disorders. The next step in psychiatric neuroimaging is to apply putative surrogate bio-markers to assessments in clinical settings. Near-infrared spectroscopy (NIRS) is one of the promising candidate biomarkers that can non-invasively detect cortical brain function under natural settings. To explore clinical usefulness in psychiatric diagnosis and evaluation, we investigated fronto-temporal hemodynamic response in normal controls and patients with psychiatric disorders using NIRS, and also examined the association with polymorphism of susceptibility genes in psychiatric disorders.
Methods: Fronto-temporal hemodynamic response in patients with psychiatric disorders, measured by multi-channel NIRS (ETG-4000), was compared to that of normal controls during a 60-sec verbal fluency task and the association with clinical evaluations or genetic variants was also investigated. All the subjects gave informed consent prior to the participation according the ethics committee of The University of Tokyo Hospital.
Results: Both patients with schizophrenia and major depression commonly showed a smaller-than-normal activation during the task, whereas the initial 5-sec slope was significantly different between the two psychiatric groups. The reduced hemodynamic response during the task was significantly associated with severer functional impairment (measured by global assessment of functioning score) in the two psychiatric groups. In addition, the variation in catechol-O-methyltranseferase (COMT val-158met) functional polymorphisms was associated with the prefrontal hemodynamic response in patients with schizophrenia.

Conclusions: The hypofrontality in patients with major depression and schizophrenia was consistent with previous neuroimaging studies, while NIRS could differentiate the two psychiatric disorders. In patient with schizophrenia, prefrontal hemodynamic response was influenced by functional impairment and COMT genetic variation. These results suggest that NIRS might have a potential to use as an aid for diagnosis and evaluation in psychiatry.

S-16
Advances in the neuroimaging of ADHD

S-16-001
Neuroimaging findings implicating fronto-cerebellar circuit abnormalities in the pathophysiology of ADHD

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Objectives: Neuroimaging studies suggest that the neurobiology of ADHD involves structural and functional abnormalities in numerous regions of the brain. However, a recent meta-analysis found that the greatest volumetric reductions for ADHD children relative to controls were in cerebellar and frontal regions. Also, although there have been only a few structural MRI studies that have examined ADHD adults, the results from these studies suggest that the frontal and cerebellar volumetric reductions persist into adulthood. Interestingly, evidence from functional imaging studies often show reduced neural activity for ADHD relative to control participants in frontal regions, but cerebellar regions have been much less studied.
Methods: We used functional magnetic resonance imaging with working memory and finger-tapping paradigms to examine neural activation in frontal and cerebellar regions of ADHD and control adults. We used Statistical Parametric Mapping to compare the BOLD response between ADHD and control adults while performing these tasks.
Results: Behavioral differences indicated that, relative to controls, ADHD adults showed increased within subject variability during performance of the tapping task. ADHD adults also showed reduced activation in cerebellar and contralateral frontal regions during performance of both of these tasks.
Conclusions: We show altered neural activity in nodes of a frontal-cerebellar circuit while performing motor and non-motor tasks. Various lines of research have clearly demonstrated that there are reciprocal neural connections between frontal and cerebellar regions providing an anatomical substrate for understanding how these regions can work together and for understanding how the cerebellum can be involved in both motor and non-motor processes. It is suggested that future neuroimaging studies focus on functional networks such as these in order to best understand the implications of structural and functional abnormalities in ADHD.

S-16-002
Frontal lobe cortical-limbic deficiencies in adults with ADHD comorbid with bipolar disorder: A cortical thickness MRI analysis

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Objectives: Attention deficit-hyperactivity disorder (ADHD) and bipolar disorder (BPD) frequently co-occur and represent a particularly morbid clinical form of both disorders. Neuroimaging research addressing this comorbidity, however, is scarce. Our aim was to assess the morphometric MRI underpinnings of the comorbidity of ADHD with BPD in the cerebral cortex, using cortical thickness analysis.
Methods: Morphometric MRI findings were compared between 31 adults with ADHD and BPD with those of 23 healthy control subjects.
Results: Compared to group matched control subjects, individuals with comorbid ADHD plus bipolar disorder showed cortical thinning in a cortico-limbic frontal lobe network including both the lateral prefrontal and paracingulate cortex as well as the medial frontal cortex, orbitofrontal cortex and the frontal pole.
Conclusions: Results support the hypothesis that the comorbid state of ADHD plus BPD presents selective alterations of distinct brain structures subserving mood and cognitive regulation. Attention to comorbidity is necessary to help clarify the heterogeneous neuroanatomy of both BPD and ADHD.

S-16-003
Pharmacoimaging studies of stimulant formulations in ADHD using positron emission tomography

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Objectives: DAT is a key regulator of dopamine in the brain. Abnormal DAT binding may contribute to the pathophysiology of ADHD. Both the therapeutic effects and the abuse potential of psychostimulants are associated with occupancy of DAT. Many clinicians are concerned that treating ADHD adults with psychostimulants creates a risk for abuse or dependence. The abuse potential of methylphenidate, for example, is related to the drug's capacity to produce a rapid onset of blockade of DAT. Some long-acting formulations of methylphenidate produce a more gradual rise in plasma methylphenidate concentration, compared with immediate-release methylphenidate. Does this reduce the risk of "likeability" and abuse?
Methods: One controlled study, for example, measured DAT binding using a highly selective ligand (C-11 altropane) and PET in 47 well-characterized, treatment-naïve, nonsmoking, non-comorbid adults with and without ADHD.1 Another study randomly assigned 12 healthy adults to receive single doses of immediate-release or osmotic-release methylphenidate to produce equivalent Cmax values.2 Plasma drug levels, responses to detection/likeability questionnaire items, and DAT occupancies using PET and altropane were obtained at regular intervals.
Results: The first study showed significantly increased DAT binding in the right caudate in ADHD subjects compared with matched control non-ADHD subjects. The other study showed that osmotic-release methylphenidate was associated with longer time to maximum plasma concentration, longer time to maximum CNS DAT occupancy, and no detection/likeability, compared with immediate-release methylphenidate
Conclusions: Abnormalities in DAT binding may contribute the pathophysiology of ADHD. Formulations of methylphenidate with a more gradual rise in plasma methylphenidate concentration may reduce the risk of "likeability" and abuse.

S-16-004
Genetic imaging as a method for identifying pathophysiological heterogeneity in psychiatric disorders: Evidence from ADHD

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Objectives: Although many candidate genes have been identified for psychiatric disorders, associations tend to be weak, probably at least partially because of heterogeneity within diagnostic groups. Imaging genetics studies may be a powerful way to identify varying biological profiles within diagnoses. We sought to investigate if an ADHD-associated polymorphism (DAT1 3' UTR) predicted variance in brain activation in adults with ADHD during an executive function task. We hypothesized that even within a sample of subjects with ADHD, the risk allele (10R) would be associated with hypoactivation in an executive function network, and specifically in the dorsal Anterior Cingulate Cortex (dACC).
Methods: We collected fMRI scans on 42 adults with ADHD while they performed the Multi Source Interference Task (MSIT), shown to robustly activate attentional-executive networks rich in dopamine. Brain activity was compared between individuals homozygous for the 10R allele and 9R-carriers.

Results: ADHD individuals homozygous for the 10R allele were comparable to 9R carriers on all demographic and clinical variables measured, as well as on behavioral performance during the MSIT task. In terms of brain activity, however, the 10R/10R group hypoactivated dACC, prefrontal cortex and cerebellar vermis as compared to the 9R-carriers. Results in each of these areas were comparable for groups either heterogeneous or homogenous for the 9R allele, indicating two copies of the 10R allele are necessary for hypoactivity.
Conclusions: In a sample of individuals with ADHD, a high-risk DAT1 genotype was associated with hypoactivity in an attentional-executive network. Therefore, this genotype may add variation to brain alterations found within ADHD samples and may help us to understand how genetic variation adds to neuronal variation within the diagnosis. The results suggest that the genetic imaging method may be used to identify biological heterogeneity within a childhood-onset diagnosis, even in adulthood, leading to a better understanding of varying etiological trends within a disorder.

S-27
Positron emission tomography (PET) and functional magnetic resonance imaging (fMRI) of human brain monoamine neurotransmission

S-27-001
Influence of Fenfluramine challenge of Serotonin-2A receptor binding

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Objectives: Although alterations of serotonin (5-HT) system functioning have been proposed for a wide variety of neuropsychiatric disorders, a method quantitatively assessing 5-HT release capacity in the living human brain is still lacking. Therefore, we tested a novel method to assess 5-HT release capacity in the human brain using dexfenfluramine challenge and [18F]altanserin positron emission tomography (PET).
Methods: Eight healthy male subjects received placebo and single oral doses of 40mg (n=4) or 60mg (n=4) of the potent 5-HT releaser dexfenfluramine separated by an interval of seven days. Two hours later, 250 MBq of the 5-HT2A receptor selective PET-radiotracer [18F]altanserin were administered intravenously as a 30 sec bolus. Dynamic PET data were subsequently acquired over 90 min. Moreover, in arterial blood samples drawn for measurement of total activity, dexfenfluramine levels as well as cortisol and prolactin plasma concentration-time profiles were quantitatively determined.
Results: Pretreatment with dexfenfluramine decreased the total distribution volume of [18F]altanserin in all investigated brain regions in a dose-dependent manner. Cortisol and prolactin plasma concentrations were dose-dependently increased following administration of dexfenfluramine.
Conclusions: These pilot data strongly suggest that the combination of 5-HT release using dexfenfluramine and subsequent assessment of 5-HT2A receptor availability with [18F]altanserin PET is suitable to assess 5-HT release capacity in the healthy, as well as the psychopathologically or neurotoxically altered human brain.

S-27-002
Effects of SSRIs on brain serotonin function revealed by PET and phfMRI

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Objectives: Recent results from three neuroimaging studies focused on frequently prescribed Selective-Serotonin-Reuptake-Inhibitors will be presented
Methods: PET with the radioligands [11C]DASB and [carbonyl-11C]WAY-100635. Pharmacological fMRI.
Results: The results of 2 PET and 1 fMRI studies will be presented: (1) Serotonin transporter occupancy changes comparing single dose and steady-state in patients with major depression using PET and the radioligand [11C]DASB, and the associated with treatment outcome (2) Changes in binding of the serotonin-1A receptor, the main inhibitory serotonergic receptor subtype, following SSRI treatment in patients suffering from anxiety disorders as revealed by PET and the radioligand [Carbonyl-11C] WAY. (3) Modulation of brain activation (especially in the amygdala) by SSRI treatment measured by pharmacological functional magnetic resonance imaging (fMRI).
Conclusions: Using multimodal neuroimaging with PET and fMRI in pharmacological research, changes in transporter occupancy, receptor binding and modulation of brain activation can be related to treatment outcome.

S-27-003
Brain monoamino-oxidase-A imaging using [11C]harmine and positron emission tomography

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Objectives: In the brain, monoamine oxidase type A (MAO-A) is responsible for the degradation of serotonin and noradrenalin, and thus plays a central role in the regulation of these neurotransmitter levels. Given the central role of serotonin in depression, and given the antidepressant properties of selective MAO-A inhibitors, there has been a strong incentive to explore MAO-A levels and how it is affected by antidepressant therapy directly in patients. However, there have been relatively few radioligands suitable for studies of MAO-A by positron emission tomography (PET). [11C]-harmine is a specific and reversible inhibitor of MAO-A that has shown a high potential for imaging MAO-A. We recently evaluated the prospect of using PET and [11C]harmine for quantification of MAO-A binding sites in the human brain.
Methods: Regional brain uptake curves of [11C]harmine were quantified using kinetic modeling analyses, both at placebo condition and after treatment with moclobemide in healthy subjects and in unmedicated depressed patients vs control volunteers.
Results: [11C]harmine shows high brain uptake and reversible kinetics in all regions with specific binding in humans. Our data showed that PET measures of [11C]harmine specific distribution volume (DVs) provide reliable estimates of MAO-A density as attested by the close relationship between [11C]harmine DVs and regional MAO-A densities reported postmortem. The MAO-A inhibitor moclobemide used at clinically recommended doses can block 80% of [11C]harmine specific binding in humans, suggesting that antidepressant efficacy may occur at high levels of MAO-A inhibition. PET determination of [11C]harmine binding showed widespread increases in MAO-A density in unmedicated depressed patients, suggesting that elevated MAO-A density is responsible for monoamine loss during major depressive episodes.
Conclusions: [11C]Harmine thus provides a unique tool to unravel MAO-A function in pathophysiological conditions and underlying mechanisms to antidepressant action in human using in vivo imaging.

S-27-004
Influence of season and light on human serotonin transporter binding and function

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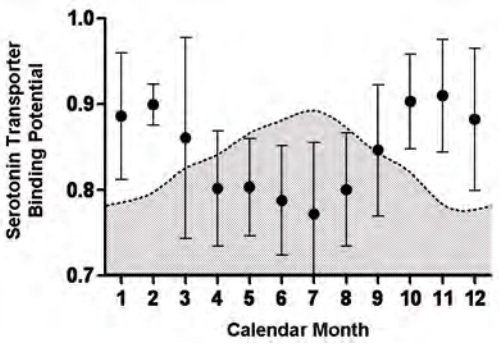
Objectives: Mood and several serotonin related behaviours show clear seasonal fluctuations in people living in temperate and polar regions. The serotonin transporter regulates intensity and spread f the serotonin signal. This study assessed seasonal variations in brain serotonin transporter binding in healthy human subjects.
Methods: Drug-naïve healthy subjects were investigated using positron emission tomography (PET) and the selective serotonin transporter ligand [11C]3-amino-4-(2-dimethylaminomethyl-phenylsulfanyl)-benzonitrile ([11C]DASB). 5-HTT binding potential (BP) values in seven regions of interest (ROIs) were evaluated in 88 consecutive [11C]DASB PET scans.

Results: Serotonin transporter BP values, an index of serotonin transporter density, were significantly higher in all ROIs in subjects scanned in fall and winter as compared to those scanned in spring and summer (p=.01 to .001). Moreover, serotonin transporter BP values correlated negatively with the average duration of daily sunshine at scanning time (p=.05 to .0002).
Conclusions: This finding proposes a new and simple physiological mechanism that has the potential to explain seasonal changes in mood and serotonin related behaviours in healthy and clinical populations.



S-38
Brain imaging in drug development: Traditional nosological versus endophenotype-directed approaches

S-38-001
MRI-based endophenotyping as outset for drug targeting

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Philipp A. Csomor

Objectives: Deficits in early information processing have been suggested to underlay the positive and cognitive symptoms in schizophrenia. Prepulse inhibition (PPI) of the startle response and suppression of the P50 event-related potential (P50 suppression) are two neurophysiological gating measures that have repeatedly been shown to be deficient in schizophrenia patients. Moreover, we have recently found that the antipsychotic clozapine but not haloperidol increase PPI in healthy human volunteers exhibiting low baseline PPI levels.
Methods: Study 1: In order to investigate the impact of several antipsychotics (aripiprazole, risperidone, amisulpride) and lorazepam (negative control) on gating in healthy volunteers (n=60) with either low or high baseline gating levels have been tested. Study 2: To further explore the functional neuroanatomy of PPI, a PPI-H2O PET co-registration study was conducted in never medicated first-episode schizophrenia patients.
Results: Study 1: The preliminary data analysis revealed that aripiprazole but not risperidone or amisupride increased PPI in healthy subjects with low PPI levels and that the anxiolytic lorazepam even reduced PPI. Furthermore, all antipsychotics, but not lorazepam enhanced P50 gating in subjects exhibiting low levels of P50 suppression. Study 2: A SPM analysis showed first that an extended network including the orbitofrontal cortex, the hippocampus, the basal ganglia, and the thalamus are involved in the regulation of PPI. Secondly, unmedicated first-episode schizophrenia patients as compared to normal subjects differ in their response to prepulse-pulse stimulation in their activation of the hippocampus and thalamus.
Conclusions: The present data suggest that normal subjects with low baseline gating levels provide a useful translational model to explore the impact of novel antipsychotics in humans. Furthermore, the data of our PPI-PET co-registration study suggest that the hippocampus and thalamus represent two neuroanatomical targets to determine the impact of antipsychotics on sensory gating and possibly also psychotic symptom formation in schizophrenia.

S-38-002
From nosological to endophenotype-directed drug targeting: The role of PET

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Objectives: Brain imaging represents an important tool in early drug development. Target validation and proof of concept/proof of principle are major applications especially of positron emission tomography, but magnetic resonance techniques are becoming increasingly important in the drug development process. However, while drug development is still based on traditional nosological diagnostic entities, it is becoming clear that syndromal, endophenotype-directed approaches might be more appropriately reflect the biological basis of psychiatric disorders.
Methods: PET studies of some of the most important neurotransmitters and their role in neuropsychiatric diseases will be reviewed. This includes studies on D2-like dopamine receptors, but also D1 dopamine, 5-HT1A and 5-HT2 serotonin, muscarinic acetylcholine, and NMDA glutamate receptors, in disorders such as schizophrenia, depression, and substance abuse.
Results: It is well documented that specific psychopathological aspects of psychiatric disorders can be related to certain neurobiological characteristics which can be studied with PET. This includes abnormalities in dopaminergic neurotransmission in the putamen of patients with depression, reduced dopamine in ventral striatum of patients with substance abuse, and exaggerated dopamine transmission in striatum of patients with psychosis.
Conclusions: Here it is suggested that future psychotropic drug development should focus more on the underlying pathogenetic mechanisms (endophenotypes) of psychiatric disorders rather than diagnostic entities. Various aspects of the heterogeneous neurobiology of those disorders should be addressed, while searching for molecules with specific sites of action. Perhaps in the future patients will be treated with an array of drugs ("rational polypharmacy") that reflect their specific psychopathology ("target symptom" approach, Freyhan 1955).

S-38-003
The role of PET in early risk discharge in CNS drug development

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S-38-004
Enabling personalized medicine through novel imaging techniques in drug development

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S-58
Are there really progressive brain abnormalities in association with schizophrenia? Current longitudinal magnetic resonance imaging studies from at risk-states and first-episode psychosis to chronic illness

S-58-001
Progressive brain changes across the transition to psychosis: Where to from here?

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Objectives: Although the underlying neurobiology of emerging psychotic disorders is not well understood, there is a growing conviction that there are progressive brain changes in patients at clinical high risk for the illness. These changes are likely to begin well before the frank onset of the disorder and may continue for a number of years. In this talk, I will summarize the extant neuroimaging studies of people at clinical high risk for psychosis, both cross-sectional and longitudinal. By and large, there are few denitive markers that distinguish those who go on to develop the illness from those who do not. The two most consistently abnormal brain regions in schizophrenia research, the hippocampi and the lateral ventricles, do not show volumes signicantly different to those of healthy controls prior to psychosis onset. However, frontal lobe measures (eg, cortical thickness in the anterior cingulate) do show promise, as do functional imaging measures sensitive to prefrontal cortex dysfunction. Further, longitudinal magnetic resonance imaging ndings in individuals at clinical high risk show that there are excessive neuroanatomical changes in those who convert to psychosis. These aberrant changes are observed most prominently in medial temporal and prefrontal cortical regions. While the pathological processes underlying such changes remain unclear, speculatively they may reect anomalies in genetic and/or other endogenous mechanisms responsible for brain maturation, the adverse effects of intense or prolonged stress, or other environmental factors. Active changes during transition to illness may present the potential to intervene and ameliorate these changes with potential benet clinically.

S-58-002
Brain changes 6 years after the first episode of a psychosis

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Objectives: It remains unclear whether brain changes observed in patients with psychosis remain stable or progress over the illness course. Unfortunately existing studies have used relatively small samples and have investigated patients at various stages of their illness, with few at illness onset. We investigated changes in brain volume 6 years after the first episode of psychosis.
Methods: We evaluated brain volumes (grey and white matter) at the first psychotic episode and 6 years later, using an SPGR sequence acquired with a 1.5T scanner. Brain volumes were measured with a voxel-based automated method (Statistical Parametric Mapping, SPM5). We evaluated 49 patients (17 females; mean age 27 SD 9; 26 schizophrenia) and compared them with 46 healthy controls (21 females; mean age 31 SD 9). Mean length of follow up was 6.5 (SD 1.4) years. We also evaluated neurological function at the time of presentation with the Neurological Evaluation Scale (Buchanan and Heinrichs, 1988).
Results: At first presentation, patients had significantly lower grey and white matter volume (p=0.001). However, over time they showed similar reductions of grey and white matter. Patients with more neurological signs at baseline had lower grey matter volume than those with less signs (p=0.06), and lost less grey matter over time (p=0.02).
Conclusions: Brain changes occur at a similar rate in patients and controls. However, different progression may reflect the interaction of abnormal neurodevelopmental processes with environmental insults such as use of antipsychotic drugs.

S-58-003
Brain changes in schizophrenia across the age range

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S-58-004
Longitudinal MRI investigation of brazilians with first-onset psychosis over 4 years

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Objectives: To investigate whether first-episode psychosis (FEP) patients would exhibit different brain volume changes compared to controls over time, and whether illness course and treatment exposure would be related to such changes.
Methods: 122 FEP and 94 asymptomatic controls from the same catchment area were drawn from an epidemiological-based study in Sao Paulo, Brazil. Participants were submitted to serial structural magnetic resonance imaging scans (baseline, 15 months follow-up, and 4-5 years follow-up). Voxel-based morphometry and region of interest techniques were employed to assess gray matter and lateral ventricle volumes, respectively. Between-group comparisons of volume changes over time were conducted with Analysis of Covariance, group-by-time interaction, significant findings reported at $p<0.05$.
Results: At baseline, FEP patients exhibited gray matter reduction in fronto-temporal regions and lateral ventricular enlargement compared to controls. After a mean follow-up period of 15 months, there was no difference in the rate of change of gray matter volume or ventricle-brain ratio between FEP subjects (n=80) and controls (n=52). The subgroup of patients with schizophrenia/schizophreniform disorder (n=39) showed a greater degree of gray matter preservation in the left superior temporal cortex and in the right hippocampus relative to controls. Antipsychotic exposure was associated with greater ventricle-brain ratio increase, while a remitting course was related to reversal of baseline regional gray matter volume deficits in the temporal lobe. 4-5 years MRI follow-up of this sample is being conducted and results will be discussed.
Conclusions: Structural brain abnormalities already present at psychosis onset are non-progressive during a short term follow-up, and some of the abnormalities may even exhibit a reversible pattern, especially in patients with a remitting course of schizophrenia. A longer follow-up investigation might elucidate whether progressive changes in FEP patients will be present at later stages of illness.

S-66
More insight into auditory verbal hallucinations

S-66-001
Auditory hallucinations and perceptual mechanisms

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Michael Hunter, Simon Eickhoff, Iain Wilkinson

Objectives: The propensity to hallucinate represents a natural characteristic of the human brain. Rarely, except in severe neuropsychiatric conditions such as schizophrenia, do hallucinations naturally predominate. The neural substrate for auditory verbal hallucinations, investigated using structural and functional neuroimaging techniques, includes multiple cortical regions. So far, evidence falls short of a definitive model that explains why auditory hallucinations are perceived in the absence of an external auditory stimulus. Hence the objective is to develop a perceptual model for the genesis of auditory hallucinations that can be tested and improved.

Methods: I will review relevant studies and describe some of our own that use functional magnetic resonance imaging. These studies examine 'spontaneous' activity of auditory cortex as well as between-condition contrasts using Statistical Parametric Mapping in those individuals with and without a tendency to hallucinate.
Results: A series of neuroimaging studies help us build up a workable neural model that helps explain the pathogenesis of auditory hallucinations. Within this model is a description of component perceptual processes that lead to an individual's perception of auditory hallucinations as real auditory events in the absence of external auditory signals.
Conclusions: Auditory hallucinations are perceived as real mental events that engage specific 'perceptual modules'.

S-66-002
Cerebral activity before and during auditory verbal hallucinations

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Kelly Diederen

Objectives: Introduction: Previous fMRI studies demonstrated activation in a network of language-related regions during auditory verbal hallucinations (AVH). It is, however, unclear where AVH originate in the brain. Identifying brain regions showing significant signal changes preceding AVH might reveal their origin.
Methods: Methods: Fifteen psychotic patients indicated the presence of AVH during 3T fMRI scanning by squeezing a small balloon. To control for motor related activation fifteen control subjects squeezed this balloon at matched time intervals. A tailored ‚selective averaging' analysis method was used to enable analysis of brain activation 6-0 seconds prior to the AVH without any a priori assumptions concerning the heamodynamic response profile.
Results: Results: Prominent deactivation preceding AVH was observed in the left parahippocampal gyrus. In addition, significant deactivation was found in the left superior temporal, right inferior frontal and left middle frontal gyri as well as in the right insula and left cerebellum. No significant signal changes were revealed prior to the balloon-squeezing in the control subjects.
Conclusions: Conclusions: AVH in psychotic patients are consistently preceded by prominent deactivation of the parahippocampal gyrus. This could imply that auditory verbal hallucinations are triggered by memory retrieval.

S-66-003
Self-monitoring and inner speech models of AVH; Is there any evidence?

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Objectives: A range of psychological theories have been proposed to account for the experience of auditory hallucinations in patients with psychosis. One of the most influential cognitive models proposes that auditory verbal hallucinations (AVH) result from an impairment in the ability to monitor one's own inner speech leading to the misidentification of verbal thoughts or memories as alien voices.
Methods: Evidence from studies of patients with schizophrenia, individuals in the prodromal phase of the illness and non-clinical subjects will de presented and discussed.
Results: Overall the available data suggest that cognitive impairments other than self-monitoring, such as difficulties with appraising degraded stimuli, may contributed to the observed misidentification bias. The specificity of such a bias to AVH is also questionable as most studies report that patients with delusions tend to make external misidentification errors when listening to their own distorted speech.
Conclusions: Taken together these findings provide little evidence for a self monitoring deficit being a causal mechanism for AVH.

S-66-004
Right temporoparietal junction and spatial

Marion Plaze
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Objectives: Auditory verbal hallucinations are a cardinal symptom of schizophrenia. Bleuler and Kreapelin distinguished two main classes of hallucinations: hallucinations heard outside the head (external hallucinations) and hallucinations heard inside the head (internal hallucinations). This distinction was confirmed by recent phenomenological studies which identified three independent dimensions in auditory hallucinations: language complexity, self-other attribution and spatial location. Brain imaging studies in schizophrenia patients with auditory hallucinations have already investigated the language complexity and self-other attribution, but the neural substrate of hallucination spatial location remains unknown.
Methods: Magnetic Resonance Images of 45 right-handed patients with schizophrenia and persistent auditory hallucinations and 20 healthy right-handed subjects were acquired. Two homogeneous subgroups of patients were defined based on the hallucination spatial location: patient with only external hallucinations (N=12) and patients with only internal hallucinations (N=15). Between-group differences were then assessed using two complementary brain morphometry approaches: voxel-based morphometry and sulcus-based morphometry.
Results: Reduced white matter volume was found with VBM in the right temporo-parietal junction (rTPJ) of patients with outer space hallucinations compared to patients with inner space hallucinations. Further analysis revealed a sulcus displacement between the two patient subgroups around the junction of the superior temporal sulcus and its anterior branch (i.e. the angular sulcus). In comparison to healthy subjects, opposite white matter volumes and opposite sulcus displacements in rTPJ were found in patients with internal and patients with external hallucinations.
Conclusions: The current results indicate that spatial location of auditory hallucinations is associated with the rTPJ anatomy, a key region of the auditory pathway. The detected tilt in the sulcal junction suggests impairments during early brain maturation, when the STS and its anterior branch appear and merge, in line with the common hypothesis that schizophrenia has a developmental component.

S-67
Neuroimaging the impulsivity in psychiatry

S-67-001
Ventral striatum and impulsivity: fMRI in pathological gambling, OCD, and autism

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Objectives: To examine the relationship between ventral ACC activity on fMRI response inhibition tasks and measures of impulsivity and compulsivity in Impulsive (Pathological Gamblers) and Compulsive (Obsessive-Compulsive Disorder, Autism) Disorders.
Methods: Patients with Pathological Gambling, OCD and Autism underwent fMRI noGo-Go tasks to determine dorsal and ventral striatum activity by BOLD signal. Subjects also underwent neurocognitive and personality and temperament testing to determine measures of compulsivity and impulsivity.
Results: Subjects with both Impulsive and Compulsive Disorders had deficits in dorsal ACC activity during response inhibition tasks vs healthy controls. There was, however, a double dissociation of ventral ACC bold signal. In subjects with Impulsive disorders (PG), greater ventral ACC activity was stronly associated with greater impulsivity and less compulsivity. In subjects with Compulsive disorders (autism, OCD), greater ventral ACC activity was associated with greater compulsivity and less impulsivity.
Conclusions: Both compulsive and impulsive disorders are associated with response inhibition deficits in dorsal ACC activity. However, in Impulsive disorders, greater ventral ACC activity is associated with greater impulsivity, whereas in Compulsive disorders, greater ventral ACC activity is associated with greater compulsivity.

S-67-002
Functional neural correlates of inhibitory control in mania and schizophrenia

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Régine Jeanningros, Jean-Michel Azorin, Pascale Mazzola-Pomietto

Objectives: Impulsivity is an important clinical feature of schizophrenia and of bipolar disorder, in particular during mania. In these two disorders, it is commonly conceptualized as resulting from deficits of inhibitory control. Examining the neural substrate that underlies these deficits is important not only for our understanding of the functional neuroanatomy of impulsivity but also of the relatedness between these two disorders. This will be the aim of the present talk.
Methods: We will report the findings of two studies, in which we compared separately a group of bipolar disorder patients in a manic state and a group of acute schizophrenic patients to a group of healthy subjects. In each study, the brain network subserving specifically motor response inhibition was investigated under identical experimental conditions, by using event-related fMRI in conjunction with a warned equiprobable Go/NoGo task.
Results: In both schizophrenic and manic patients, we evidenced a deficit of brain activation during response inhibition that was restricted to the ventrolateral prefrontal cortex (VLPFC), in the presence of comparable task performance accuracy. However, the lateralization of this deficit seems to distinguish manic from schizophrenic patients. It was confined to the right hemisphere in individuals with schizophrenia, whereas it was bilateral in those with mania.
Conclusions: Our data indicate that a lack of engagement of the right but not of the left VLPFC during response inhibition is a common characteristic of schizophrenia and mania. Given that the right and left VLPFC are thought to play crucial but different roles in the suppression of irrelevant responses, our findings might help to understand and differentiate the neural mechanisms underlying impulsivity in these two disorders.

S-67-003
Genetic and disease related impact on the neural correlates of response inhibition in bipolar disorder

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S-67-004
Functional correlates of cognitive control in children with attention-deficit hyperactivity disorder and their unaffected siblings

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Objectives: Attention Deficit Hyperactivity Disorder (ADHD) is a developmental disorder defined by a variety of complex symptoms and traits. Studies of the neurobiology of ADHD that have started from diagnostic categories have not yet succeeded in fully explaining the mechanisms underlying symptoms. Research methods that target phenotypes intermediate between neurobiology and diagnosis may offer new avenues of investigation. Neuroimaging is one such method. Impairments in cognitive control may explain some of the symptoms in ADHD. Neuroimaging studies have shown associated changes in brain function, such as diminished activity in fronto-striatal and fronto-cerebellar circuits during paradigms that elicit response and expectancy conflicts.
Methods: To investigate whether these deficits were specific to the disorder or rather have a heritable component, we ran several neuroimaging studies of subjects with ADHD (combined subtype), their unaffected siblings and typically developing control subjects.
Results: Both fronto-striatal and fronto-cereballar circuits were vulnerable to heritable effects. Findings were replicated and appear to be robust.
Conclusions: These findings suggest that neural circuits underlying cognitive control are sensitive to heritable effects and deficits are not always directly related to the disorder. As such, they may form a possible endophenotype for studies of gene effects in ADHD.

S-71
Catatonia: An update

S-71-001
Introduction

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S-71-002
Child and adolescent catatonia is associated with an increase in mortallity and morbidity: Evidence from a prospective follow-up study

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Objectives: To assess the long-term outcome of catatonia in youths and the relevance of chronic catatonic schizophrenia (CCS) in this age group.
Methods: A cohort was prospectively recruited from 1993 to 2004 and followed up at least one year after discharge. The sample included 35 inpatients with catatonia, aged 12 to 18 years. Outcome measures included standardized mortality ratio (SMR), clinical evaluation with the Diagnostic Interview for Genetic Studies, the Bush-Francis Catatonia Rating Scale, and the Social Adjustment Scale (SAS).
Results: Mean duration between index episode and follow-up evaluation was 3.9 years (range 1-10). At follow-up, 4 patients were lost. Among the remaining 31 subjects (mean age 19.5 years, range 15-26), diagnosis was unchanged in 28 patients, with schizophrenia being the most frequent (65%). Mortality (all causes SMR=6266; 95%IC: 1181-18547) and morbidity were severe with 3 deaths (2 suicides), 6 patients presenting a causal organic condition and 14 subjects needing continuous psychiatric care. A poorer prognosis was associated with schizophrenia (p=.04), European origin (p=.006) and males (p=.009). All the males (N=8) who had chronic catatonic schizophrenia at index episode still had chronic catatonic signs at follow-up, supporting the hypothesized relationship of adolescent catatonia to this diagnosis.
Conclusions: Catatonia is among the most severe psychiatric condition in young people, with a 60-fold increased of premature death, and a high proportion of organic diseases. There is a need for research in the field of chronic catatonic schizophrenia in adolescents as it appears to be a rare, severe, understudied but clinically relevant subgroup.

S-71-003
Catatonic syndrome in liaison psychiatry: An overview

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Objectives: Catatonic syndrome is no more considered as a subtype of schizophrenia. Catatonia is more frequently associated with mood disorders (mania, melancholia, and psychotic depression) as well as general medical conditions (neurological disorders, drug induced and toxic induced conditions, metabolic conditions).
Methods: After an overview of current diagnosis and management of catatonia, we present the results of a prospective clinical study of catatonia due to general medical conditions realized in our Consultation-Liaison Psychiatry Department to highlight several points:
Results: - Psychiatric and somatic conditions frequently occur together. A purely medical etiology of catatonia is never definitive. Rather, these psychiatric disorders, observed in a medical context, seem to be more accompanying, triggering or aggravating factors than causative factors. – The importance of the choice of the emergency treatment and especially the usefulness of the Zolpidem test, the superiority of Lorazepam and the danger of neuroleptics. – The importance to recognize the "catatonic part" of all types of agitation or bizarre behavior. Such behaviors should alert the medical and surgical staff, so that the first-line treatment is based on benzodiazepines rather than neuroleptics (which can be a potentially fatal triggering or aggravating factor in catatonia)

S-71-004
Pathophysiology and the orbitofrontal cortex in Catatonia

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Objectives: Catatonia is a psychomotor syndrome characterized by concurrent emotional, motor, and behavioural anomalies. Pathophysiological mechanisms of psychomotor disturbances may be related to abnormal emotional-motor processing in prefrontal cortical networks. We therefore investigated prefrontal cortical activation and connectivity patterns during emotional-motor stimulation using fMRI.
Methods: We investigated 10 postacute akinetic catatonic patients and compared them with 10 non-catatonic psychiatric (same diagnosis without catatonia, same medication, same age and sex) and 10 healthy controls. Pictures for emotional stimulation were taken from the International Affective picture System (IAPS).
Results: Catatonic patients showed significant abnormalities in orbitofrontal cortex and its connectivity to premotor/motor cortex when compared to psychiatric ad healthy controls. Catatonic affective and behavioural symptoms correlated significantly with orbitofrontal cortical dysfunction.
Conclusions: We conclude that catatonic symptoms might be closely related to altered emotional-motor processing in orbitofrontal-premotor cortical networks.

S-78
Paralimbic determinations and developmental psychiatry

S-78-001
Cortex gyrification in schizophrenia and bipolar patients

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Objectives: The most striking, yet poorly understood gross morphological features of the human cerebral cortex are the diverse and complex arrangements of its foldings: the sulci and gyri. Cortical folds mature from antenatal period to late adolescence. It has been suggested that abnormal maturation could be a risk factor for schizophrenia and some affective disorders. Evaluations of the folding patterns could then provide cues of the neurodevelopmental aspects related to these psychiatric conditions.
Methods: A new approach was applied to magnetic resonance images to automatically extract, label and measure the sulcus anatomy in the whole cortex (http://brainvisa.info). Gyrification was assessed using both global and local 3D gyrification indices, defined respectively as the ratio between the total sulcal area, or the area of each labelled sulcus, and the outer cortex area.
Results: A number of studies have associated language and brain development, and changes of brain language-related regions with development of schizophrenia. In a sample of chronic schizophrenia patients with treatment-resistant auditory hallucination, local gyrification differed in Broca and Wernicke regions. Alterations of cortical folding in schizophrenia were also found in adolescent patients: relative to healthy individuals, adolescent patients had lower local gyrification in the frontal lobe and collateral sulcus in the left hemisphere. The localization of these deviations might be related to the age-at-onset since adolescence is a key maturation period for these regions. In bipolar patients, gyrification was found to differ between age-at-onset subgroups of patients: intermediate-onset patients (between 25 and 45 years) had a significantly reduced local gyrification in the right dorsolateral prefrontal cortex in comparison to both early-onset patients (before 25 years) and healthy subjects.
Conclusions: Current developments in antenatal imaging and recent studies of gyrification heritability should provide new insight into the genetic and early developmental factors involved in these cortical deviations.

S-78-002
Pharmaceutical challenges and at-risk subjects

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S-78-003
Addiction imaging implication for prevention

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S-78-004
Cognitive reserve Alzheimer's disease and temporal

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S-84
New imaging evidence for illness progression throughout the course of schizophrenia

S-84-001
Morphometric evidence of illness progression in schizophrenia

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Objectives: Brain imaging studies have consistently demonstrated brain abnormalities in patients with schizophrenia. These changes are largely confined to decreases in gray matter volumes and enlargement of the lateral and third ventricles. To date schizophrenia has been considered to result from abnormalities in neurodevelopment, with brain changes to be static. However, schizophrenia has long been thought to be a progressive or a degenerative, not a developmental, disorder. Indeed, Kraepelin considered the progressive clinical deterioration to be the hallmark of the disorder, naming it dementia praecox to reflect this particular aspect. Lately, others have re-emphasized the importance of the decline in functioning in schizophrenia as a clue to its pathogenesis, suggesting that the brain abnormalities in schizophrenia could be expected to reflect this clinical progression. Indeed, we and others have reported brain abnormalities to increase over time in schizophrenia. Interestingly, not all patients show changes in brain volumes over time: we demonstrated that the changes are particularly pronounced in those patients with a poor prognosis in the first years of illness. Moreover progressive changes are most pronounced in the frontal and temporal areas as postulated by Kraepelin over a hundred years ago. Interestingly, white matter did not change over time. Finally, the progression in these frontal brain changes appeared to be attenuated by treatment with atypical, but not by typical antipsychotics. Thus, not only are brain changes progressive in schizophrenia, they are clinically relevant since they are related to outcome and my be reversed by some of the atypical antipsychotics. With the evidence pointing to a link between progressive disease and patient outcomes, questions such as whether these changes can be reversed with early pharmacological intervention and whether there is a point at which the brain changes become irreversible, become pertinent.

NEUROIMAGING - Symposia

S-84-002
Diffusion tensor imaging tractography in schizophrenia

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Objectives: While a great deal of progress has been made over in identifying gray matter abnormalities in schizophrenia, only recently has the same level of scrutiny been applied to white matter. Moreover, recent longitudinal magnetic resonance imaging studies demonstrate progressive changes in gray matter in temporal and frontal cortices, following illness onset. In contrast, far less is known about the evolution and progression of white matter abnormalities, or about the integrity of white matter connections, particularly those that connect frontal and temporal lobes, tracts long thought to be abnormal in schizophrenia. With the development of diffusion tensor imaging (DTI), such abnormalities can be explored. Here, fronto-temporal connections are investigated, including uncinate fasciculus (UF), fornix, and cingulum bundle (CB), in chronic schizophrenia, in schizotypal personality disorder (SPD) and in first episode patients with schizophrenia or bipolar disorder.
Methods: DTI was acquired from a 1.5T magnet. Study one focused on chronic patients and controls, using region of interest measures of UF, fornix, and CB. Studies two and three focused on SPD, and first episode patients with schizophrenia or bipolar disorder. Fractional anisotropy was the dependent measure for all studies.
Results: UF, fornix, and CB abnormalities were observed in chronic patients compared with controls. For SPD and first episode patients, compared with controls, UF but not CB or fornix abnormalities were observed. In addition, left UF abnormalities were observed in first episode bipolar disorder.
Conclusions: Findings suggest that CB, UF, and fornix abnormalities are observed in chronic schizophrenia, but only UF abnormalities are observed in SPD and first-episode patients. UF abnormalities, however, are not specific to schizophrenia or SPD as they are also observed, on the left, in first episode bipolar patients. Further studies are needed to follow the course of such changes over time and to further characterize white matter abnormalities in schizophrenia and bipolar disorder.

S-84-003
Structural brain changes during transition-to-illness phase in individuals at risk for schizophrenia

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Objectives: Structural neuroimaging in established schizophrenia consistently identifies ventricular enlargement, and reduced volume of frontal and temporal lobes regions. Recent studies have identified that these changes evolve over time, particularly during the early stages following illness onset. Our work in Melbourne has identified individuals at ultra-high risk of developing psychosis (criteria developed by Yung & McGorry) and examined brain changes before and during transition to illness. The aim was to identify which brain regions are changing as illness develops.
Methods: Subjects were scanned on a 1.5 Tesla GE Scanner. 135 individuals at ultra-high risk (UHR) for psychosis (39 converters to psychosis) were scanned at baseline. Longitudinal scans were available on 35 UHR (12 converters), 16 FE schizophrenia and 14 controls (CTLS). In a series of studies we examined cross-sectional and longitudinal grey matter changes in prefrontal and temporal cortices (hippocampus, amygdala, superior temporal gyrus (STG) and insular (INS)), anterior cingulate grey matter thickness (ACC), as well as corpus callosum width (CC), and ventricular volume (VV).
Results: Cross-sectionally, abnormalities were seen in converters to psychosis in prefrontal regions, STG, ACC, INS and CC, while medial temporal structures and VV were normal. Compared with non-converters, those converting to psychosis showed longitudinal changes in the following regions: superior and orbital frontal regions, medial temporal, ACC, STG, INS, while VV increased post-psychosis onset.
Conclusions: The longitudinal MRI findings in individuals at ultra-high risk for developing psychosis show that there are excessive neuroanatomical changes in those who convert to psychosis. These aberrant changes are observed most prominently in temporal and prefrontal cortical regions. Further changes may occur post-illness onset. Whilst the pathological processes underlying such changes remain unclear, they may reflect anomalies in genetic and/or other endogenous mechanisms responsible for brain maturation, and/or the adverse effects of stress and other environmental factors.

S-84-004
A longitudinal study of white matter morphometry and organization in chronic schizophrenia

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Objectives: Previous studies have reported continued focal gray matter loss after the clinical onset of schizophrenia. Longitudinal assessments in chronic illness, of white matter in particular, have been less conclusive.
Methods: We used diffusion-tensor and structural magnetic resonance imaging at baseline and at follow-up four years later to evaluate progressive gray and white matter changes in 49 chronic schizophrenia patients and 16 healthy subjects. Patients were subdivided into good-outcome (n=23) and poor-outcome (n=26) groups.
Results: At baseline, schizophrenia patients had 1) lower anisotropy in the frontoparietal white matter and the corpus callosum, 2) larger posterior frontal white matter volumes and smaller callosal volumes, and 3) smaller frontal, temporal, and parietal gray matter volumes. On follow-up, healthy subjects showed a more pronounced 1) decline in anisotropy, 2) expansion of regional white matter volumes, and 3) reduction in regional gray matter volumes than schizophrenia patients. Volume of the corpus callosum, however, continued to decline in schizophrenia patients faster than in healthy subjects. Good-outcome patients showed a more pronounced decline in white matter and callosal anisotropy and a less pronounced increase in white matter volumes than poor-outcome patients. Poor-outcome patients, however, displayed a greater gray matter loss throughout the brain and greater decline in callosal volume than good-outcome patients.
Conclusions: In the chronic phase of the illness, longitudinal changes in both gray and white matter are in the direction of an effacement of between-group differences among schizophrenia patients and healthy subjects. Similarly, preexisting white matter differences between good-outcome and poor-outcome patients diminish over time. These patterns are consistent with earlier onset of aging-associated changes in schizophrenia. In contrast, gray matter volumes in poor-outcome patients continue to decline more rapidly than in patients with good outcome. Illness progression is also evident in the continued loss of callosal volumes, especially pronounced in those with poor outcome.

S-06
The endocannabinoid system in psychiatric disorders: From basic neuroscience to clinical practice

S-06-001
Breakdown of cell assembly synchronization by CB1 receptor activation

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Hungary

Objectives: Cannabinoids impair hippocampus-dependent memory in both humans and animals but the network mechanisms responsible for this effect are unknown.
Methods: Large-scale recording of multiple single neuronal activity and local field potentials in behaving rats.
Results: We demonstrate that activation of CB1 receptors at recreational doses decrease the power of theta, gamma and ripple oscillations in the hippocampus of rats. Seeking for a neuronal mechanisms of these macrocopic events, we show that CP55940 severely disrupts the temporal coordination of cell assemblies in short time windows (<100 ms) yet only marginally affects population firing rates of pyramidal cells and interneurons. Population coordination of place fields is also negatively affected. Critically, the decrease in temporal synchrony correlates well with the cannabinoid-induced memory deficit. CP55940 causes similar impairment of network synchrony in the neocortex as well. However, the decreased synchrony of neocortical neurons is occasionally interrupted by supersynchronous thalamocortical high-voltage spindles (a rodent analog of human μ and alpha rhythms), suggesting that thalamocortical terminals may lack CB1 receptors.
Conclusions: We hypothesize that cannabinoids can enhance vertical (i.e., thalamocortical) synchronization by dampening lateral (i.e., corticocortical) streams of activity.

S-06-002
Endocannabinoids in anxiety and depression

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Objectives: The major psychoactive constituent of cannabis, Δ9-tetrahydrocannabinol, affects emotional states in humans and laboratory animals by activating brain CB1-type cannabinoid receptors.
Methods: Two primary endogenous ligands of these receptors are anandamide, the amide of arachidonic acid with ethanolamine, and 2-arachidonoylglycerol (2-AG), the ester of arachidonic acid with glycerol. Anandamide and 2-AG are released in select regions of the brain and are deactivated through a two-step process consisting of transport into cells followed by intracellular hydrolysis. Selective pharmacological inhibition of anandamide deactivation – by inhibiting either anandamide transport into cells or its intracellular hydrolysis catalyzed by fatty-acid amide hydrolase (FAAH) – produces analgesic, anxiolytic-like and antidepressant-like effects in rats.
Results: These actions are not associated with behavioral responses typical of direct-acting cannabinoid agonists and are accompanied by profound changes in serotonergic adrenergic transmission. On the other hand, selective blockade of intracellular 2-AG hydrolysis – catalyzed by monoacylglycerol lipase – enhances stress-induced analgesia.
Conclusions: These findings suggest that anandamide and 2-AG contribute to the regulation of pain and emotion, and that the deactivation of these endocannabinoid lipids might be the target for novel analgesic, anxiolytic and antidepressant drugs.

S-06-003
eCB, processing reward-related stimuli and substance use disorders

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Objectives: Endocannabinoids are known to play a role in processing hedonic states and reward related stimuli, but the specific mechanisms are not clear. The aim of this presentation is to describe new findings indicating a specific role for peripheral anandamide in modulating alcohol and drug cue-related craving.
Methods: Healthy social drinkers and abstinent, treatment engaged alcohol and cocaine dependent individuals participated in an experiment where they were presented with stress, alcohol/drug cue and neutral relaxing cues, utilizing individually calibrated script-driven imagery procedures, one imagery session per day in 3 separate sessions on consecutive days. Order of imagery condition was randomized and counterbalanced across subjects. Plasma anandamide and 2AG, subjective craving and heart rate was assessed at repeated timepoints. In addition, a separate functional magnetic resonance imaging (fMRI) session was also conducted to assess insula activity during cue-induced craving.
Results: Findings indicate that anandamide levels increased with alcohol/drug cue exposure but not with stress or neutral cue exposure in healthy social drinkers and these levels were positively correlated with both alcohol cue-induced craving and increases in heart rate. Furthermore, increased levels of anandamide during cue-induced craving were also correlated with increased activity in the insula during alcohol/drug cue exposure. Addicted patients showed significantly lower basal anandamide levels and no cue-induced increases in plasma anandamide. No significant correlations between high levels of cue-induced craving and anandamide were found in addicted patients.
Conclusions: These findings indicate that peripheral anandamide signaling contributes to modulating desire for hedonic stimuli, such as alcohol, in healthy individuals and such signaling is disrupted in addiction. Implications of these findings for development of substance use disorders and relapse susceptibility in addicted individuals will be discussed.

S-06-004
Translational studies on eCBs in schizophrenia: Bench to bedside

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Objectives: The human endocannabinoid system interacts with various neurotransmitter systems and the endocannabinoid anandamide was found significantly elevated in CSF and inversely correlated to psychopathology (Giuffrida et al. 2004) providing a link to the neurobiology of schizophrenia. While delta-9-tetrahydrocannabinol, the psychoactive compound of Cannabis sativa, shows psychotomimetic properties, the major herbal cannabinoid compound cannabidiol was suggested recently a re-uptake inhibitor of anandamide. In addition potential antipsychotic properties have been hypothesized.
Methods: We performed an explorative, 4-week, double-blind, controlled clinical trial on the effects of purified cannabidiol in acute schizophrenia compared to the antipsychotic amisulpride. The antipsychotic properties of both drugs were the primary target of the study. Furthermore, side-effects and anxiolytic capabilities of both treatments were investigated.
Results: 42 patients fulfilling DSM-IV criteria of acute paranoid schizophrenia or schizophreniform psychosis participated in the study. Both treatments were associated with a significant decrease of psychotic symptoms after 2 and 4 weeks as assessed by BPRS and PANSS. However, there was no statistical difference between both treatment groups. In contrast, cannabidiol induced significantly less side effects (EPS, increase in prolactin, weight gain) when compared to amisulpride.
Conclusions: Cannabidiol proved substantial antipsychotic properties in acute schizophrenia. This is in line with our suggestion of an adaptive role of the endocannabinoid system in paranoid schizophrenia, and raises further evidence that this adaptive mechanism may represent a valuable target for antipsychotic treatment strategies.

S-08
Non-classical mechanisms of action of antidepressants

S-08-001
Role of lipid rafts for antidepressant induced G-protein signalling

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Objectives: Several lines of investigations from several laboratories suggest a post-synaptic effect of chronic antidepressants and a possible post-synaptic target for these drugs. Data from rats, cultured neural and glial cells and tissue from brain of depressed subjects all suggest the localization of the G protein, Gs alpha, in lipid rafts is modified by chronic treatment with a number of antidepressant compounds. Removal of Gs alpha from lipid rafts facilitates the activation of adenylyl cyclase.
Methods: Methods and **results:** Cultured C6 glioma cells were (depending on experiment) transfected with a Gs alpha-GFP fusion protein (or not transfected) and treated for up to 5 days with varying doses of antidepressants from the following classes: SSRI, SNRI, MAOI and tricyclic for 1-5 days. The raft association of Gsalpha was determined by detergent extraction and cell fractionation and the mobility of Gs alpha on the plasma membrane was determined with Fluorescence Photobleaching and Recovery (FRAP) using either confocal (lateral mobility) or Total Internal Reflectance Fluorescence (TIRF) microscopy ("horizontal" mobility). Chronic treatment with any of these compounds decreases the association of Gsalpha with lipid rafts and decreases "membrane-anchoring" as determined by FRAP. Gs alpha-mediated activation of adenylyl cyclase is augmented by chronic antidepressant treatment, but not by closely-related compounds lacking antidepressant efficacy.
Conclusions: Cellular, animal and postmortem studies suggest that depression includes a dampening of Gs-adenylyl cyclase coupling due to a higher proportion of Gs-alpha localized to lipid rafts vs. that seen in controls. Similarly, rat and cultured cell studies show augmented Gs-adenylyl cyclase coupling and a diminished proportion of Gs alpha in the lipid raft fraction. Biochemical or genetic disruption of lipid rafts increases Gs-activated adenylyl cyclase and it is suggested that chronic antidepressant treatment has a similar effect on caveolae/lipid rafts.

S-08-002
Modulation of ligand-gated ion channels by antidepressants

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Objectives: Antidepressants and antipsychotics have been shown to modulate ligand gated ion channels such as the serotonin type 3 receptor in a non-competitive manner. Our studies aim to invetigate the role of lipid rafts for the accumulation of antidepressants and antipsychotics within the cell mebrane and for their ability to modulate ligand gated ion channels.
Methods: We use cell lines stably and transiently transfected with ligand gated ion channels as well as neuronal cell lines expressing endogenous neurotransmitter receptors for electrophysiological recordings. Lipid rafts are prepared by sucrose density gradient cenntrifugation. The localization of neurotransmitter receptor subunits is determinded by Western blotting.
Results: Our studies show that both antidepressants and antipsychotics colocalize with serotonin tye 3 receptors in lipid rafts. This accumulation in lipid rafts appears to be an important determinant for their ability to modulate such ligand gated ion channels. Ongoing studies investigate the role of lipid rafts for the modulation of other ligand gated ion channels by psychopharmacologcial agents.
Conclusions: The accumulation of psychopharmacological agents in lipid rafts appears to be an important determinant for their ability to modulate ligand gated ion channels. This may represent an novel pharmacological principle for the molecular mechanisms of action of antidepressants and antipsychotics.

S-08-003
Role of P-glycoprotein for HPA axis activity and antidepressant treatment

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Objectives: Clinical studies have demonstrated an impairment of glucocorticoid receptor (GR)-mediated negative feedback on the hypothalamus–pituitary–adrenal (HPA) axis in patients with major depression (GR resistance), and its resolution by antidepressant treatment. Accordingly, reduced GR function has also been demonstrated in vitro, in peripheral tissues of depressed patients, as shown by reduced sensitivity to the effects of glucocorticoids on immune and metabolic functions.
Methods: This talk reviews the in vitro studies that have examined the effect of antidepressants on GR expression, number and function in human and animal cell lines, and the possible molecular mechanisms underlying these effects.
Results: We and others have shown that antidepressants in vitro are able to modulate GR mRNA expression, GR protein level and GR function. Antidepressants are shown to both increase and decrease GR function in vitro, based on different experimental conditions. Specifically, increased GR function is likely to be mediated by an increased intracellular concentration of glucocorticoids, while decreased GR function seems to be the consequence of GR downregulation.
Conclusions: We suggest that the study of the effects of antidepressants on glucocorticoid function might help clarify the therapeutic action of these drugs.

S-08-004
5-HT6 receptor stimulation regulates excitatory and inhibitory neurotransmission and induces neuronal plasticity: Potential mechanisms for antidepressant drug action and neuroprotection

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Objectives: Significant advances in our understanding of the 5-HT6 receptor have been made through the development of the 5-HT6 agonists, WAY-208466 and WAY-181187 (SAX-187), which now indicate that this molecular target may be involved in mood regulation and neuronal plasticity.
Methods: Methods and **results:** WAY-208466 and WAY-181187 (SAX-187) are high affinity selective full agonists as determined by radioligand binding and intrinsic activity determinations. Neurochemical evaluations using in vivo microdialysis reveal that 5-HT6 receptor stimulation can increase extracellular levels of GABA in prefrontal cortex, hippocampus and striatum. 5-HT6 receptor agonists had no effect on basal levels of glutamate in vivo but can decrease stimulated levels of glutamate as evaluated in a hippocampal slice preparation. The data support the previous evidence that 5-HT6 receptors are co-localized on GABAergic neurons and suggest that these receptors may tonically regulate glutamatergic neurotransmission through the modulation of GABAergic input. In behavioral evaluations these agents appear to be active in models of anxiety and depression indicating potential anxiolytic/antidepressant properties. Interestingly, 5-HT6 receptor agonists have neuroprotective properties both in vitro and in vivo. In addition to inducing neurite outgrowth and survival, 5-HT6 receptor agonists induce an increase in BDNF protein levels in cortical and hippocampal neurons in a time-dependent manner. In vivo studies performed using preclinical stroke models reveal that 5-HT6 agonists provide significant neuroprotective efficacy.
Conclusions: Notably over the last decade it has become apparent that there are neurodegenerative aspects of depression where it has been observed that there is volume reductions in both cortical and hippocampal tissue that may be attenuated following antidepressant drug treatment (Sheline et al, 2003). It is interesting to speculate that 5-HT6 receptor stimulation may play a role in the mechanism of action associated with SSRIs or SNRIs in depression and anxiety, and as such may be a potential strategic target.

S-29
Antipsychotic treatment of aggression in the intellectually disabled – a growing controversy

S-29-001
Antipsychotic withdrawal induced activation of aggression in the intellectually disabled

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Objectives: This study was designed to determine the percentage of intellectually disabled aggressive individuals treated with antipsychotic medications who can be successfully withdrawn from the latter medications, and to determine if withdrawal associated relapses predict future relapses.
Methods: The quarterly neurobehavioral records of 151 aggressive, intellectually disabled institutionalized individuals maintained on antipsychotic medications and undergoing attempts to decrease or stop these agents between 1990 and 2005 were analyzed. The goal was to determine if relapse occured on one or more occasions following antipsychotic withdrawal.
Results: Sixty percent of individuals with self or other directed aggression, receiving antipsychotic agents, can be withdrawn from such agents, with 2/3 rds being antipsychotic drug free a decade later. Of the remaining 40% experiencing an initial relapse of aggression upon either lowering or termination of the antipsychotic medications, 90% were still receiving these agents a decade later. Furthermore, of those who experienced an initial relapse and endured a subsequent withdrawal, more than 90% experienced subsequent relapses when withdrawal was again attempted, with l-4 additional relapses occuring over a decade.
Conclusions: A relatively high percentage of intellectually disabled individuals with self or other directed aggression can be successfully withdrawn from antipsychotic agents. However, if short term relapse occurs when antipsychotic agents are lowered or stopped, it is very likely that subsequent withdrawal associated relapses will occur if such withdrawals are attempted. Since relapses can be quite dangerous, it is suggested that great caution be utilized if a previous antipsychotic withdrawal linked increase in aggression has occured, especially if the relapse has occured multiple times or is obviously dangerous.

S-29-002
Evidence for the effectiveness of antipsychotic medications to manage problem behaviors in adults with intellectual disability

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Objectives: Identify and review relevant research into the effectiveness of antipsychotic medication in adults and children with intellectual disabilities (ID) in the management of problem behaviours.
Methods: We conducted a systematic review of placebo controlled RCTs.
Results: Three RCTs included adults with ID. Two used a parallel design and one used a cross over design. In two studies risperidone showed better effectiveness than placebo but in one study placebo was better. Six RCTs included children with ID with or without autism. All studies showed that risperidone was significantly more effective than placebo in managing behaviour problems in children with ID. However, most studies highlighted adverse effects in the form of primarily somnolence and weight gain. Three of the RCTs were further extended over a period of up to 48 months using open label designs. These studies showed that the positive effect of risperidone that started within the first two weeks of starting the treatment had lasted over a long period of time and the adverse effects were not so troublesome in the long run. The overall drop out rate was very low.
Conclusions: The current evidence for better effectiveness of risperidone over placebo among adults with ID is rather equivocal. There is better evidence of risperidone's superiority over placebo among children with ID. However, because of possible adverse effects these medications have to be used with great caution. Regular monitoring of not only the target behaviours and adverse effects but also the quality of life of the person with ID must be in place if medication is prescribed. The lowest possible dose of medication should be used for the shortest period of time necessary. Non-medication based interventions should always be considered and an attempt to withdraw medication should be made at regular intervals.

S-29-003
Antipsychotic agents in the treatment of autism

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Objectives: A synthesis of the burgeoning literature informing the use of antipsychotics in the treatment of autism will be presented. Data from recent studies of atypical antipsychotics will be reviewed to better delineate which symptoms are most responsive to treatment.
Methods: The U.S. National Institute of Mental Health-funded Research Units on Pediatric Psychopharmacology (RUPP) Autism Network published the largest randomized controlled trial of an antipsychotic in autism. Children and adolescents (n=101) with autism and significant irritability or aggression were randomized to risperidone or placebo during the course of an 8-week, double-blind trial. Several other atypical antipsychotics have also been studied, but to a more limited extent.
Results: Haloperidol has been shown to improve disruptive behavior in autism, but its frequent potential to cause extrapyramidal symptoms and tardive dyskinesia is problematic. In the RUPP study, risperidone was significantly more efficacious than placebo (response rate of 69% vs. 12%; $p < 0.001$) for the primary outcome of irritability, aggression, and self-injury. Risperidone also led to significant improvement in hyperactivity and repetitive phenomena, but exhibited less effects on social and communication impairment. The most clinically significant side-effect associated with risperidone treatment was weight gain. Following 6 months of treatment, responders to risperidone entered a placebo-controlled discontinuation trial. Relapse occurred more frequently with placebo compared to risperidone. Other atypical antipsychotics have been studied in small controlled or open-label trials. For example, preliminary studies of aripiprazole are suggestive of efficacy and a relatively lower risk of weight gain.
Conclusions: Risperidone is efficacious in improving several symptoms associated with autism. Additional research is needed on the efficacy of other atypical antipsychotics, the tolerability of the class as a whole, and to determine the specific types of symptoms that are most likely to respond to treatment.

S-29-004
The argument against antipsychotic agents in the intellectually disabled

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Sherva Elizabeth Cooray

Objectives: To discuss the reason why antipsychotic drugs should not be prescribed regularly for those with challneing behaviour in intellectual disability
Methods: Narrative review of randomised controlled trials of antipsychotic drugs for challenging behaviour in adults with intellectual disability
Results: In all published studies in which antipsychotic drugs have been shown to be effective in aggressive challenging behaviour in adults with intellectual disability there have been methodological deficiencies, and when taken together with the results of other studies the consensus is that these drugs are not effective in routine use.
Conclusions: Antipsychotic drug treatment in intellectual disability should be reserved for specific diagnostic indications, not a condition which has no diagnostic status and in which these agents have little value.

S-45
Are biological measures useful in predicting antipsychotic treatment response in schizophrenia?

S-45-001
Prediction of antipsychotic response with diffusion tensor imaging

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Objectives: There are no antipsychotic treatment studies of schizophrenia patients with an a priori hypothesis of a specific cerebral structural alteration that predict treatment outcome. Diffusion Tensor Imaging (DTI) informs about the integrity and organization of the white matter tracts. DTI studies of adult chronic schizophrenia patients and first break patients reported disseminated low anisotropy in white matter in the absence of volumetric differences. We hypothesized that individual differences in white matter microstructural alterations may influence response to specific antipsychotics in schizophrenia patients.
Methods: Twenty-two neuroleptic-naïve, first psychotic break adolescent patients were enrolled in a double blind, random parallel design treatment with olanzapine and haloperidol. Patients received anatomical MRI and DTI's before starting medication. For each treatment group, there were 6 responders and 5 non-responders. We measured anisotropy in the anterior cingulate, Brodmann areas (BA) 25, 24 and 32 and the internal capsule.
Results: In the cingulate, haloperidol responders had higher anisotropy than haloperidol non-responders and in contrast, olanzapine responders had lower anisotropy, specifically in BA25. Olanzapine responders had higher anisotropy in the anterior limb of the internal capsule, within an area that carries the thalamo-cortical connections. Furthermore, they had lower anisotropy in the area that has corona radiate projections as compared with non-responders. When compared with haloperidol responders, olanzapine responders had higher anisotropy in the anterior limb of the internal capsule, where thalamo-cortical connections are prominent.
Conclusions: DTI provides important information about predicting individual response to a specific antipsychotic. By integrating pharmacologic differences in mechanism of action and individual brain structural profiles of patients undergoing treatment, antipsychotic response failures will be minimized and evidence-based practice developed.

S-45-002
Pharmacogenetic prediction of antipsychotic response

Maria Arranz
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Objectives: Pharmacogenetic prediction of antipsychotic response Dr. Maria J. Arranz Dept. Psychological Medicine, Institute of Psychiatry – King's College London, UK
There is good evidence that response to antipsychotic treatment is a multifactorial trait with a strong genetic component. However, decades of pharmacogenetic research have only identified a limited number of genes related to antipsychotic response. Clear associations have been found between functional polymorphisms in metabolic enzymes (i.e. CYP2D6, CYP2C19, CYP1A2, CYP3A4) and drug-induced side effects and dose requirements. However, their influence is attenuated in the case of antipsychotics with several metabolic pathways (i.e. second generation antipsychotics). Treatment response is also affected by genetic variants in drug-targeted neurotransmitter receptors, as associations between polymorphism in dopaminergic (D2 and D3) and serotonergic (5-HT2A and 5-HT2C) receptors have shown. The role played by variants in other drug targeted receptors (i.e. glutamatergic, histaminic and muscarinic) is still unclear and require further investigation. Other genes related to synaptic plasticity, transport and metabolism (i.e. BDNF, COMT, NRG1, SNAP25) have been reported to contribute to treatment variability, although their contribution to the antipsychotic mechanism of action is still unknown. Most reported associations have moderate genetic effects (with average odds ratios of 1.5-2) and therefore are of limited clinical value. Algorithms combining information in several genes can increase the clinical value of these findings, and several pharmacogenetic tests have been developed using this strategy.
However, currently available pharmacogenetic tests are very rarely used as prescription aid in psychiatry. A better knowledge of clinical, environmental and genetic factors determining treatment response and improved predictive values are required if pharmacogenetic testing is to become routinely performed in everyday's clinical practice.

S-45-003
Predicting best treatment response in schizophrenia with striatal function

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Objectives: A complex trial-and-error process is used in psychiatry to try to match an antipsychotic medication to each patient with schizophrenia. Human and animal functional neuroimaging studies indicate that the striatum is sensitive to the effects of neuroleptics. We examined individual differences in treatment response in first-break patients and hypothesized that caudate function provides important information about predicting individual response to a specific antipsychotic.
Methods: We acquired FDG-PET and anatomical MRI in 22 never-previously medicated psychotic adolescents (ages 13-20). Patients received FDG-PET prior to 8-9 weeks of a randomized double-blind trial of either olanzapine or haloperidol. Symptom assessments were made at baseline and following the medication trial using the BPRS. During the FDG-uptake period, patients performed a verbal memory task based on the California Verbal Learning Test. PET scans were coregistered with structural MRI for accurate anatomical identification of regions-of-interest (caudate, putamen, globus pallidus) traced on the MRI.
Results: We found that low relative glucose metabolic rates in the caudate predicted haloperidol response on the BPRS total score (dorsal right caudate at baseline vs. change in BPRS total: r=-0.64, positive symptoms r=-0.76) while high metabolic rates predicted olanzapine response (r=0.41, Fisher z=2.23, p<0.05). For the left and right caudate and putamen, the multiple R was 0.95, F=14.0, df=4,5). For the ventral striatum, the caudate and putamen were not significant for haloperidol but positive symptoms were predicted from globus pallidus activity (r=-0.69). In the ventral striatum, left and right putamen predicted improvement in negative symptoms (0.78, and 0.79, respectively).
Conclusions: Our findings indicate caudate activity provides a useful way to predict individual response to a specific antipsychotic—haloperidol vs. olanzapine. The observed prediction rates, although based on a small sample suggests that clinical utility is a possibility. Larger-scale studies are needed for replication.

S-45-004
Loudness dependence of auditory evoked potentials as predictor of therapeutical response to psychotropic medication

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Objectives: Predictors of treatment response to serotonergic versus non-serotonergic psychotropics are of considerable clinical relevance as it could help to reduce the the occurrence of patients receiving weeks or even months of unsuccessful treatment. For example, several studies show that the response to selective serotonin reuptake inhibitors (SSRI) can be successfully predicted by using the loudness dependence of auditory evoked potentials (LDAEP), which denotes the change in their amplitudes in response to different stimulus intensities, and is to date one of the best validated indicator of the central serotonergic system.
Methods: The aim of studies is to investigate whether or not LDAEP also allows the differential prediction of treatment response to serotonergic versus noradrenergic antidepressants or typical (DA influence only) versus atypical (plus 5-HT) neuroleptics.
Results: As a first prospective randomized study revealed, responders to the citalopram treatment (50% improvement on HDRS) were characterized by a strong LDAEP at baseline, and responders to reboxetine were characterized by a weak LDAEP. Non-responders to citalopram or reboxetine showed the inverse LDAEP characteristics, respectively.

Conclusions: This is one of the first findings that demonstrates differential prediction of different classes of antidepressants. Patients at the beginning of an antidepressive treatment, who show an initially strong LDAEP, have a greater probability to response to a serotonin-agonistic antidepressant; while patients with a weak LDAEP will probably more benefit from a non-serotonergic antidepressant. If these results can be replicated in a larger sample as well as similar findings can be observed concerning neuroleptic treatment in patiente with schizophrenia, this simple EEG method could be more broadly used in clinical practice to support clinicians to replace the trial and error method by a more targeted and individualized antidepressant treatment.

S-56
Recent developments in affective disorders during pregnancy and lactation

S-56-001
Recent developments in antenatal depression

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Objectives: We will review the most recent evidence in the biology of antenatal depression and speculate on potential consequences for the newborn stress response.

S-56-002
New data on the reproductive safety of antidepressant drugs

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Objectives: The prevalence of depression during pregnancy is about 10-20%. Several of the affected women are treated with an antidepressant drug, primarily with an SSRI but also other kinds of ADs. No antidepressant drug is approved for use during pregnancy but reproductive safety data for ADs is reassuring with no general increased serious teratogenic risk. However, differences between substances are observed and an increased risk for ventricular-septum defects is seen for clomipramine and possibly for paroxetin. Further, an association between maternal use of SSRI and persistent pulmonary hypertension in the neonate (PPHN) has been shown, and later confirmed in another study. Moreover, combination therapy with an AD and a benzodiazepine (BZ) is not uncommon. Recently a report indicated that infants with a prenatal exposure to this combination had a higher incidence of congenital heart disease compared to no exposure. These data has to be confirmed. Finally, the long term developmentally consequences for the prenatal AD exposed child are of concern as is the consequences for children to untreated depressed mothers.

S-56-003
New insights into bipolar disorder in childbearing women

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Objectives: The public health importance of episodes of postpartum mood disorder is starkly illustrated by recent Confidential Enquiries that find suicide to be a leading cause of maternal death in the UK. It has long been recognized that childbirth is a time of considerable risk for bipolar women with severe postpartum episodes (postpartum / puerperal psychosis) following between 25% and 50% of deliveries. This represents a many hundred-fold increase on the population rate of around 1 in 1000 and demonstrates the importance of considering issues regarding pregnancy and childbirth in bipolar women.
Methods: In this talk I will review the literature on the link between bipolar disorder and childbirth, discuss recent work from our group on genetic factors and consider the clinical implications of these findings.
Results: A number of studies from our group have confirmed Bipolar women are at very high risk of episodes of severe postpartum affective disorder and have demonstrated genetic factors influence vulnerability to the puerperal trigger. Based on these findings we are conducting molecular genetic studies employing both candidate gene and linkage approaches which have implicated regions of Chromosomes 16 and 8 as harboring genetic variants that may predispose to bipolar affective puerperal psychosis.
Conclusions: It is hoped that this line of research will uncover the nature of the puerperal trigger, allow a more individualized estimation of risk for bipolar women and improve our understanding of the aetiology of mood disorders in both the puerperium and at other times.

S-56-004
The safety of mood stabilizing medication in pregnancy and lactation

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Objectives: To analyze the potential relationship between in utero exposure to classic mood stabilisers (lithium, lamotrigine, valproate, and carbamazepine) and the increased risks for birth defects, neonatal adverse reactions, and neurodevelopmental delay. Available information on infant safety during breastfeeding exposure to this class of drugs will be also discussed.
Methods: A systematic computerized search was carried out on Medline/PubMed/TOXNET/EMBASE covering the period between 1980 and January 2009.
Results: PREGNANCY Whereas recent information seems to suggest that lithium does not seem to be a significant teratogen, valproate is associated with increased rates of congenital malformations. Moreover, in exposed children, valproate may induce both minor and major cognitive dysfunctions. Carbamazepine may, in general, increase the rate of major malformations and, specifically, that of spina bifida. The drug has also been suspected of increasing the risk for orofacial cleft. The risk for orofacial cleft has been also hypothesized for lamotrigine. BREASTFEEDING No specific mood stabilizers show specific advantage in safety for the breastfed infant.
Conclusions: On the basis of evidence-based information during pregnancy, lithium should be preferred for both bipolar 1 and 2 patients. Obviously, strict gynaecologic surveillance must be provided. During breastfeeding, no specific mood stabilizers show any specific advantage in safety for the breastfed infant.

S-69
Promises and pitfalls of genetic research in drug treatment of depression and schizophrenia

S-69-001
Results from a whole genome association study in depression: Will putative etiologic genes predict antidepressant response?

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Objectives: To identify genetic risk factors for major depressive disorder, and to test whether candidate genes for response to antidepressants increase risk for depression.
Methods: We have conducted two major depressive disorder case-control genome-wide association studies (GWAS) and their meta-analysis. The two cohorts comprised a total of 1,359 cases and 1,782 controls, all of declared Caucasian origin. The case control analysis was conducted on approximately half million genotypings. A panel of candidate genes for response to antidepressants was identified through literature search. The results for SNPs in this panel of candidate genes were interrogated on our GWAS meta-analysis results.

Results: Our individual GWAS and the meta-analysis of the two studies failed to produce any association p value that reached genome-wide significance. Among the candidate genes for response to antidepressants it was of certain interest to observe some degree of association for SNPs within 5HT2A. Our best 5HT2A SNP (rs17289304) showed an association p = 0.002 in the GWAS meta-analysis results. The 5HT2A SNP (rs17289304) reported to be associated with response with antidepressants was not genotyped in our data set and is not in LD with our SNP.
Conclusions: The results from our study suggest that SNPs with substantial risk (odds ratio around 2) are unlikely to exist for MDD, at least in our data sets and among the relatively common SNPs genotyped or tagged in our study. The lack of genome-wide significant associations of our case-control GWAS did not allow to fully understand whether candidate genes for response to antidepressants are also involved in increasing risk for depression.

S-69-002
Impact of MAOA-, COMT- and serotonergic system gene variants in antidepressant drug treatment

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Objectives: In major depression, an increasing number of pharmacogenetic studies have examined association of antidepressant treatment response with variation in candidate genes, especially those involved in the serotonergic, noradrenergic and dopaminergic system. Given only few consistently reproducible findings, we attempted to further refine the investigated clinical phenotype in pharmacogenetic studies in Major Depression with particular attention to the melancholic and anxious subtypes of depression as well as potential gender-specific effects.
Methods: In a sample of 256 Caucasian patients with Major Depression (f=145, m=111), variants in genes coding for the serotonin transporter (5-HTT), serotonin receptor 1A (5-HT1A), monoamine oxidase A (MAO-A) and catechol-O-methyltransferase (COMT) were investigated for their impact on antidepressant treatment response as measured by the intraindividual HAMD score change over the course of six weeks.
Results: Particularly in the female subgroups of patients, the MAO-A VNTR and the COMT val158met polymorphism were found to influence antidepressant treatment response. The 5-HT1A -1019 C/G polymorphism was associated with treatment response in patients suffering from melancholic, but not from atypical depression, while the less active S allele of the 5-HTTLPR was observed to significantly impair treatment response particularly in anxious depression.
Conclusions: The present results suggest a significant impact of 5-HTT, 5-HT1A, MAO-A and COMT gene variants on antidepressant treatment response with differential effects regarding gender as well as the clinical subtypes melancholic/atypical and anxious depression. These findings point towards a network model of factors contributing to antidepressant treatment success with direct and indirect effects of genetic factors.

S-69-003
Pharmacogenetics of antidepressants in mood disorders, what can be improved? A proposal for methodological guidelines

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Objectives: Pharmacogenetic studies in mood disorders are rapidly proliferating after the initial reports linking gene variants to treatment outcomes. However, as common in the psychiatric genetic field, a considerable range of methodologies and results is present.
Methods: Following available evidence, a set of strategies both from the clinical side and from the genetic one are suggested with the aim of performing more informative studies.
Results: From the clinical point of view, we suggest to specify the sampling source, standardize diagnostic systems and treatments, monitor compliance through plasma levels, use a sufficient length of observation (3-6 months), use of a range of response criteria and include possible environmental confounding variables (life events, social support, temperament).
From the genetic side, the most important aspects are a complete coverage of the investigated gene using SNPs and all other known source of variations, and to consider the possible different or opposite activity of some gene variants in the brain (examples will be presented).

S-69-004
Pharmacogenetics of antipsychotics using an animal model

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Objectives: One major problem of the therapy with neuroleptics is the lack of efficacy in many of the patients and the occurrence of extrapyramidal side effects that can both limit the therapy and the compliance. Thus, the availability of a predictive tool for the response to psychopharmacologic agents in the therapy of psychiatric disorders is desirable.
Methods: To search for genes associated with e.g. response to neuroleptics or extrapyramidal symptoms (EPS) a hypothesis free approach was used including animal models, neuronal cell cultures, and differential gene expression analyses. Immunohistochemical analyses were performed in rats that received an agent mimicking aspects of psychosis (MK-801), or haloperidol, or a combination of these agents, or saline.
Results: Genes differentially expressed between the different groups had been genotyped in our clinical sample on pharmacogenetics including one hundred four patients with acute psychosis (schizophrenia, schizoaffective, brief psychotic, and substance-induced psychotic disorder) treated with haloperidol for up to 28 days. Diagnosis was established by applying the SCID I and II interview. Patients were assessed at baseline and on days 3, 7, 14, 21and 28. Improvement and response were measured by using the Positive and Negative Syndrome Scale.
Conclusions: We will present novel data on this ongoing large-scale association study on response to haloperidol.

S-82
Newer antipsychotic drugs: From neuroplasticity to neurotherapy

S-82-001
Neuroplasticity and signaling in the action of atypical antipsychotic drugs: Implications for functional recovery

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Objectives: Antipsychotic drugs (APD) are the mainstay for the treatment of schizophrenia. These drugs are important for treatment as well as prevention, suggesting that they do not only interfere with mechanisms that are responsible for the acute manifestation of the disease but, more in general, the regulate brain function, through complex mechanisms that may have an impact on patient stabilization. Although a potential relationship between the receptor affinity of APDs and their therapeutic properties can be established, the picture is complicated by the observation that most drugs show very complex receptor profiles and synaptic mechanisms. On this basis, it is feasible to hypothesize that the functional outcome of these complex mechanisms is not the pure 'algebraic' summation of single mechanisms, rather is the consequence of their interaction down stream from receptors, at the level of second messengers, signaling proteins and transcriptional events. These events appear to be particularly relevant for the long-term changes brought about by APDs, possibly through adaptive mechanisms that improve core defects present in the brain of schizophrenics.
Methods: To this regard during the last decade a great deal of attention has been devoted to the modulation of neuronal plasticity as a suitable endpoint for psychotropic drug therapy. Schizophrenia can be associated with changes in neuronal plasticity and therapeutic agents can increase the expression and function of key proteins involved in such mechanisms.

Results: Accordingly, recent studies from our and other laboratories have demonstrated that some second generation APDs, including olanzapine and quetiapine, modulate the expression of the neurotrophin brain derived neurotrophic factor under basal condition or in response to stress, regulate the activity of intracellular signaling molecules and can promote hippocampal neurogenesis.
Conclusions: These adaptive events, occurring in key brain regions for mood disorders and cognitive function are believed to be important for functional recovery of schizophrenic patients.

S-82-002
Receptor neuroplasticity of newer antipsychotic drugs

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Objectives: Newer antipsychotic drugs (APDs), including asenapine (ASP), clozapine (CLZ), olanzapine (OLZ), quetiapine (QTP) and risperidone (RSP) all share their greater affinity for serotonin 5-HT2A than dopamine D2 receptors. In terms of their 5-HT2A receptor affinity, these APDs are ranked as ASP> RSP> CLZ> OLZ> QTP. In terms of their anti-D2 potency, they are ranked as ASP> RSP> OLZ> QTP> CLZ. ASP has high affinity for 5-HT2C receptors. CLZ, OLZ and QTP have high affinity for histamine H1 receptors, while both CLZ and OLZ have potent anticholinergic activity. This complex drug-receptor interaction pattern may contribute to their low risk of extrapyramidal side effects.
Methods: In a series of studies, we examined the effects of long-term administration of representative newer APDs (ASP, RSP, CLZ, OLZ, QTP) on neuroplasticity of dopamine, serotonin and glutamate receptor subtypes using quantitative autoradiography.
Results: We found that ASP, CLZ, OLZ and RSP increased abundance of D2 receptors in prefrontal cortex and D4 receptors in caudate-putamen of rat brain. Repeated treatment with ASP, CLZ, OLZ, RSP and QTP increased 5-HT1A and decreased 5-HT2A receptors in rat frontal cortex. In contrast, OLZ and RSP, but not CLZ or QTP increased D2 receptor levels in caudate-putamen. All newer APDs examined reduced NMDA receptor binding in caudate-putamen but failed to change D3 and kainate receptor binding in rat forebrain regions
Conclusions: Neuroplastic responses of cortical D2, 5-HT1A and 5-HT2A receptors and striatal D4 and NMDA receptors suggest that these sites mediate the beneficial therapeutic effects of newer APDs. Elevation of D2 receptors in caudate-putamen by both OLZ and RSP is consistent with the dose-dependent ability of both agents to induce some extrapyramidal side effects. Lack of significant changes in D3 and kainate receptors suggests that these sites are less crucial for the neuropharmacological actions of newer APDs.

S-82-003
Serotonergic properties of antipsychotic drugs: Relevance to neuroplasticity

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Objectives: Recent developments towards understanding the pathophysiology of schizophrenia highlight a growing emphasis on the potential involvement of dysregulated neuronal connectivity and synaptic plasticity as well as alterations in neurotransmitter activity. Thus, it has been speculated that brain structure changes observed in patients may, at least in part, be a consequence of diminished neurogenesis and neuroplasticity. This suggests that molecular approaches directed towards modulating these cellular processes may find some utility in the pharmacotherapy of schizophrenia. Indeed there is emerging evidence that some antipsychotic drugs may facilitate regulation of brain plasticity. The receptor mechanism(s) underlying the neuroplastic effects of atypical antipsychotic requires further clarification; however, their serotonergic properties could be an important driver. This is based on accumulating evidence suggesting interaction between the serotonin and growth factor systems but also perhaps direct modulation, by certain 5-HT receptor subtypes of signalling pathways considered to be relevant in mediating neuroplasticity. An overview and a critical evaluation of this topic in the context of mode of action of antipsychotic drugs will be presented.

S-82-004
Neuroplasticity as a Target for Innovative Treatments. Effect of Clozapine in Two Animal Models of Schizophrenia

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Objectives: Carlsson's accelerator/brake hypothesis of schizophrenia (Biological Psychiatry, 1388, 1999) which proposes the loss of a frontal cortical brake on ventral tegmental area (VTA) dopamine was tested in the socially isolated and maternally deprived rat models of schizophrenia by investigating the activation of the medial prefrontal cortical (mPfc) D2 receptor on VTA glutamate and GABA transmission.
Methods: Intra-mPfc and VTA microdialysis was employed to investigate the effects of intra-mPfc pergolide (1 μM, 60 mins) on dialysate VTA glutamate and GABA release, alone and in the presence of chronic clozapine (5 mg/kg i.p. daily, 10 days).
Results: Basal dialysate glutamate levels were similar in all three groups while GABA was reduced by 55% in the isolated rat (p=0.0066 v's social control). Clozapine had no effect on basal dialysate glutamate or GABA levels. Intra-mPfc pergolide rapidly reduced VTA glutamate by -96% (p<0.001 v's non-treated control) and VTA GABA by -24% (p=0.023) in the social control rat but increased VTA GABA by +90% in the isolated rat (p=0.016 v's control). Clozapine counteracted the intra-mPfc pergolide-induced reduction in VTA glutamate from -32% to +9% (v's basal) in the social control rat (p=0.0103 v's vehicle-treated group, ANOVA) while it reversed the intra-mPfc pergolide-induced increase in VTA glutamate to a decrease (i.e. from +23% to -21%, p=0.0085) in the isolated rat. Clozapine also reversed the intra-mPfc pergolide-induced increase in VTA GABA in the isolated rat from +99% to -9% (p=0.0324).
Conclusions: The findings confirm the cortical brake on the VTA in the social control rat operating via a frontal D2 receptor-mediated inhibition of both corticofugal glutamate and local interneuronal VTA GABA release - which is abnormal or absent in the two animal models. Furthermore, the ability of clozapine to reverse the pergolide effect in the social controls and normalize it in the isolated rat suggests a role for clozapine in maintaining this brake on the VTA. These findings demonstrate the ability of both environment and antipsychotic drugs to shape brain plasticity.

S-12
Impulse disorders – categorical versus dimensional approaches: State of the evidence

S-12-001
Fractionating impulsivity: Neural and neurochemical perspectives

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Objectives: To analyze the construct of impulsivity in psychological and neural terms, in order to test the hypothesis that it is not unitary, and also to distinguish it from the construct of compulsivity. To characterize the different forms of impulsivity, for example, arising from motivational, motor or perceptual processes, so as to determine the optimal pharmacological therapy for impulsive behavior.
Methods: We employed three major paradigms in rats to assess impulsivity; temporal discounting of reward; premature responding on the 5 choice serial reaction time task and stop-signal inhibition. We also used the latter task to measure impulsivity in humans. Finally, for comparison with other tasks requiring response inhibition, we employed reversal learning as a test of compulsive behavior. We used a mixture of pharmacological, lesioning and neuro-imaging approaches to dissociate performance on these tasks.
Results: Motivational forms of impulsivity engaged neural circuitry including the amygdala, ventral striatum (nucleus accumbens) and orbitofrontal cortex. This contrasted with evidence for motor inhibition (stop-signal task) including inferior frontal cortex, dorsal striatum and sub-thalamic nucleus. The selective norepinephine re-uptake blocker atomoxetine remediated impulsivity in all three impulsivity paradigms. 5-HT2 agents further dissociated impulsive behavior from compulsive behavior.
Conclusions: Impulsivity can be dissociated from compulsivity and general mechanisms of behavioural inhibition, as well as fractionated into several distinct forms. Notwithstanding the separable neural systems underlying impulsivity, a drug such as atomoxetine can reduce impulsivity in several domains, with implications for the treatment of attention deficit hyperactivity disorder and other syndromes in which impulsive behavior is a prominent symptom.

S-12-002
Brain circuitry and neuromodulators in impulsive aggressive personality disorders

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Objectives: The purpose of the study was to define the brain circuits involved in the disinhibition of aggression in patients with personality disorders marked by impulsive aggression, particularly borderline personality disorder, and to characterize the role of neuromodulators that alter the activity of these circuits. PET FDG imaging, functional MRI, and neurochemical imaging of the serotonin transporter in 5HT2a receptor were utilized to define brain circuitry and characterize the serotonin system in patients with these disorders.
Methods: Subjects in these studies met criteria for intermittent explosive disorder-revised and a personality disorder, usually borderline personality disorder, obtained from clinical referrals and advertisements.
Results: FDG PET studies suggest reduced baseline activation in prefrontal cortex, particularly anterior cingulate and orbital frontal cortex at baseline and in response to serotonergic probes that normally activate these areas. FDG PET imaging during a laboratory aggression task suggests amygdala hyperactivation, broad prefrontal hypoactivation with compensatory hyperactivation of orbital frontal cortex, and reduced sensory association regions activation. Negative stimuli in the form of words or pictures tend to facilitate startle responses and increased amygdala responding and differentially activate cortical regions consistent with self preferential processing and more reflexes of reactivity to the stimuli. Reciprocal activity of limbic and cortical regions are disrupted in borderline personality disorder patients with aggression as determined by correlations between these regions.
Conclusions: Impulsive aggressive personality disorders are characterized by reduced cortical activity in orbital and cingulate cortex and heightened amygdala responsiveness with disruption of normal inhibitory controls. Limbic hyperactivation can occur in response to negative salinence stimuli consistent with hypersensitivity to noxious environmental events in conjunction with the reduced prefrontal inhibitory controls.

S-12-003
Functional neurocircuitry and neuropsychopharmacology of pathological gambling and the ICD's

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Objectives: To examine the role of the dorsal (cognitive) and ventral (emotional) anterior cingulate cortex (ACC) in impulsivity in patients with impulse control disorders (ICD's) such as pathological gambling (PG) and healthy controls (HC). To examine the impact of treatment with mood stabilizers on impulsivity and ACC activity in PG.
Methods: FDG-PET was conducted pre- and post lithium treatment in PG subjects. fMRI on noGo-Go tasks were conducted in PG and HC. Neurocognitive and temperament/personality tests of impulsivity were administered to PG subjects, and correlated with BOLD signal in ventral ACC. Placebo controlled trials with lithium carbonate and topiramate were conducted in PG
Results: PG patients vs HC had frontal and ACC deficits in metabolism at baseline. Lithium treatment increased metabolism in ventral (BA25) and dorsal ACC. PG patients had decreased BOLD signal in dorsal ACC on fMRI response inhibition tasks. Increased ventral ACC activity correlated with increased severity on impulsivity measures. Mood stabilizers (topiramate; lithium) were superior to placebo on PG and impulsivity measures.
Conclusions: Dorsal (cognitive) and ventral (emotional) ACC modulated different aspects of impulsivity in PG, and were modulated by mood stabilizer treatments of impulsivity.

S-12-004
Is ADHD the prototypical impulse control disorder or impulsive facet in ADHD a semantic mistake: Clinical and neuropsychological arguments

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S-14
Psychiatric disorders and thyroid axis functioning across lifecycles

S-14-001
Thyroid and developing brain

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Objectives: To assess the impact of maternal thyroid dysfunction during gestation on fetal brain development
Methods: Review of the (recent) literature. Apart from overt (clinical) maternal thyroid dysfunction (TSH and FT4 outside reference range), several other examples of maternal thyroid dysfunction have been described: sub-clinical hypo/hyperthyroidism (TSH outside reference ranges with normal FT4), hypothyroxinemia (FT4 in lower 5th or 10th percentile with normal TSH) and elevated concentrations of thyroid-peroxidase antibodies (TPO-Ab).
Results: Overt maternal thyroid dysfunction (especially hypothyroidism) during gestation has clearly been related to impaired fetal brain development. Several pathways can be discriminated. Firstly, maternal thyroid hormone during gestation is crucial for fetal neuron development. Secondly, maternal hypothyroidism often results in preterm birth which in turn is major risk factor for immature developed brain.

Finally, maternal hypothyroidism may result in obstetric complications which are risk factors for peri-natal morbidity, including brain damage. Subclinical hypothyroidism has clearly been associated with impaired fetal neurodevelopment. On the contrary, sub-clinical hyperthyroidism is not related to impaired fetal development or obstetric problems. Several studies showed significant IQ delay in children of mothers with hypothyroxinemia during gestation while others did not. A possible explanation might be the iodine intake in the different areas of research. Elevated titers of TPO-Ab (often with higher TSH concentrations) have clearly been shown to be related to obstetric problems (miscarriage, pre-term birth) and as such are a risk factor of impaired fetal neurodevelopment.
Conclusions: Although the literature concerning this topic is increasing, most studies lack epidemiological power, use definitions of impaired maternal thyroid function which are difficult to compare or different assessment points during gestation. Moreover, longitudinal studies are urgently needed to evaluate whether (subtle) neuro-developmental delay at early age persist into the second decade.

S-14-002
Thyroid hormones in treatment of mood disorders

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Objectives: Several lines of evidence support a relationship between thyroid gland function and affective illness. Interest in the use of thyroid hormones as a treatment for affective disorders dates back many decades, arising from associations observed between psychiatric symptoms and thyroid disease states.
Methods: An up-to-date review on the use of thyroid hormones in the treatment of mood disorders.
Results: Both thyroid hormones, triiodothyronine (T3) and levothyroxine (L-T4) have been used to augment the action of antidepressant and prophylactic mood stabilizing drugs in euthyroid patients. Meta-analyses support an effect of T3 to potentiate the therapeutic action of tricyclic antidepressants in treatment-refractory patients and to accelerate the onset of antidepressant effects. One approach for refractory bipolar disorder is to supplement standard treatment regimens with L-T4. Open-label studies have consistently demonstrated that augmentation with L-T4 can improve the course of affective illness. Specifically, adjunctive treatment with supraphysiological doses of L-T4 may be an effective and well-tolerated strategy in the maintenance treatment of patients with rapid cycling and otherwise prophylaxis-resistant bipolar disorders. Additionally, recent evidence has shown that supraphysioloigcal doses of L-T4 may also be an effective augmentation agent for acute intervention in unipolar and bipolar patients with a treatment-resistant major depressive episode. Progress in molecular and functional brain imaging techniques (e.g., PET) has provided a new understanding of these phenomena, illuminating the relationship between thyroid function and mood modulation.
Conclusions: Thyroid hormones are valuable augmentation agents in refractory mood disorders. Results from brain imaging studies suggest that thyroid hormones produce mood improvement by actions on specific limbic and subcortical circuits that have been implicated in the pathophysiology of mood disorders. Reference: Bauer M, Goetz T, Glenn T, Whybrow PC (2008) The thyroid-brain interaction in thyroid disorders and mood disorders. Journal of Neuroendocrinology 20:1101-1114

S-14-003
PMDD and thyroid functioning

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USA

Objectives: Premenstrual Dysphoric Disorder (PMDD) affects 5-10% of reproductive age women and consists of the cyclic recurrence of affective symptoms associated with functional impairment. Studies of thyroid hormones (TH) find that PMDD women do not differ in mean THs, but they exhibited greater variability in thyroid stimulating hormone (TSH) and thyroxine (T4), suggesting there may be some PMDD women for whom THs are clinically relevant.
Methods: We began to assess histories of sexual and physical abuse (SA/PA) in women with PMDD who were free of current Axis I disorders, and not taking any medications, including thyroid supplements.
Results: We found that PMDD women have more SA (35% vs. 11%) and PA (50% vs. 22%) than controls. We also showed that the greater variability in TSH resided exclusively in the SA - PMDD women, who also had levels 75% greater than non-abused women.. SA-PMDD women showed a unique TH profile, with elevated total triodothyronine (TT3), thyroid binding globulin (TBG), and greater ratios of TT3/FT4 and FT3/FT4, consistent with increased peripheral conversion of T4 to T3. Greater TT3 predicted more severe symptoms.
Conclusions: We hypothesized that the elevated TT3 seen in SA-PMDD women is a marker for increased arousal since, in combination with increased TSH and TT3, they have greater BP and HR responses to stress. Current research will extend the prior work by recruiting non-PMDD women with SA to assess whether the TH disturbance in SA is unique to PMDD.. In addition to BP and HR, we are assessing PMDD and abuse-related differences in plasma norepinephrine (NE) and β-adrenergic receptor (AR) responsivity as related to TT3 since catecholamines, via β-AR stimulation, increase the conversion of T4 to T3. These results will advance our understanding of the pathogenesis of PMDD by identifying clinically distinct subgroups, thereby informing intervention efforts targeting PMDD women with SA.

S-14-004
Thyroid functioning and mental disorders

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Objectives: To review recent findings on thyroid functioning in mental disorders.
Methods: Literature review
Results: Thyroid hormone (TH) is critical for the proper development of different tissues, especially the development of the brain. TH also plays an important role for the functioning of the matured brain. Mental symptoms, notably cognitive dysfunction and depression, are common expression of the thyroid diseases. On the other hand, sufficient evidence suggests that there are abnormalities in TH metabolism and thyroid immunity in primary mental disorders, especially in mood disorder. Intracellular action of T3 in the brain is determined by complex of factors, including circulating concentrations of thyrotropin, T4 and T3; concentrations of TH binding proteins and availability of free hormone; activity of TH transporters and deiodinase enzymes; and, finally, activity of thyroid receptors (TRs).
Conclusions: Individual genetic variations and mutations of thyroid axis related transporters, enzymes and receptors influence thyroid function, including T3 activity in the brain and may contribute to presentation of psychiatric disorders, as well as to response to psychiatric treatments. Better understanding of molecular mechanism related to genetic alterations in TH transport in and out of the neuron, intracellular TH metabolism in glia cells and neurons, as well as polymorphism in TRs, opens new venues for better understanding of TH effects in the brain as well as for finding new targets and genetic markers for the treatment of mental disorders.

S-26
New approaches to diagnostics and treatment in personality disorders

S-26-001
Changes in classifying personality disorders: New from the DSM-V task force

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Objectives: In this contribution, the current developments toward a new classification of personality disorders in DSM-V will be summarized.
Methods: The changes in DSM-V are primarily focused on enhancing the system's clinical utility. The threshold for change in DSM-V will not be as stringent as in DSM-IV. Changes result from a response toward current criticisms, a concept of clinical utility, literature reviews, and field trial results.

Results: The currently proposed model consists of 4 parts: (1) generic criteria for the presence or absence of a personality disorder, (2) severity rating of personality disorder, (3) prototype ratings of 5 specific personality disorders, and (4) dimensional ratings on various personality traits in 6 domains.
Conclusions: The currently proposed model can be considered a dramatic departure from the exclusively categorical approach of DSM-IV. The work group Personality and Personality Disorders expect DSM-V to be more easily applicable and clinically useful than DSM-IV.

S-26-002
Schizotypal personality disorder: New data on imaging, genetics, and treatment

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Objectives: The purpose of this presentation is to present new findings regarding cognitive status, underlying genetics, relevant imaging studies, and interventions designed to improve cognition of schizotypal personality disorder (SPD).
Methods: All subjects, who were recruited from both advertisements and clinical settings, were evaluated and studied at Mount Sinai Medical Center. Patients completed a neurocognitive battery including the modified AX CPT, DOT test, PASAT, and other tests of working memory. Subjects were genotyped at David Goldman's laboratory using PCR methods. fMRI studies were used for functional imaging and D1 binding and raclopride displacement by amphetamine were assessed in neurochemical PET imaging studies at the Columbia PET Center. Interventions with guanfacine and pergolide were evaluated to assess their effects on cognitive performance.
Results: Patients with SPD showed a pattern of cognitive impairment that suggested problems in context processing and working memory. These deficits were associated with the Val allele of the Val 158 Met COMT polymorphism. fMRI data suggests inefficient cortical processing during a working memory task with compensatory activation of superexecutive areas including BA 10. Neurochemical imaging studies suggest alterations in abnormalities in D1 receptor binding and in raclopride displacement by amphetamine. Both pergolide and guanfacine resulted in interventions resulting in improvement in cognition, particularly working memory.
Conclusions: These results suggest that SPD patients show a cognitive impairment similar but attenuated from that of schizophrenia that may be more specific for working memory and can be related to genetic factors and associated with altered brain activation in dopaminergic parameters. Guanfacine, an alpha2 adrenergic agonist, and pergolide, a D1/D2 agonist, improve cognitive performance in SPD suggesting that catecholaminergic modulation of this cognitive deficit.

S-26-003
Differentiating subtypes of antisocial personality disorder by functional neuroimaging

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Florian Schlagenhauf, Lars Schulze, Christoph Berger, Knut Vohs, Karlheinz Hauenstein, Gregor Domes, Kristin Prehn

Objectives: Criminal offenders with antisocial personality disorder (APD) are a heterogeneous group composed of distinct subtypes. We know of those who are highly irritable, explosive and risk-seeking and often fulfill the criteria of borderline personality disorder (BPD) in addition to APD while others, often termed psychopaths, are prominently characterized by particularly low anxiety and deficient affective experiences. In the high-impulsive risk-seeking group functional neuroimaging data point to low orbitofrontal activity with insufficient top-down control on amygdala activity, e.g. when inhibition of emotions is challenged. The other group presents poor autonomic responses and amygdalar as well as insular hypoactivity in response to emotional stimuli.
Methods: We were interested how subtypes of criminal offenders all of them diagnosed with APD make decisions that bear a certain degree of uncertainty regarding potential gains and losses. For this we chose a game paradigm, the Behavioral Investment Allocation Strategy task (Kuhnen & Knutson, 2005); in this task, participants were required to choose between two stocks and a bond, one stock being randomly assigned to be the "good" (+10 €), the other the "bad" (10 €) one.
Results: Different from the prominent strategy of healthy controls, criminal offenders with BPD did not prefer bonds (i.e. safe responses) when uncertainty was high. Their risk-seeking behavior was accompanied by less activity in the inferior frontal gyrus before choosing the bond in contrast to controls. Psychopaths differed from controls by decreased activity in rACC reflecting a deficit to emotionally represent uncertainty.
Conclusions: These results support the theory that criminal offenders with psychopathy are characterized by a lack of emotion, whereas criminal offenders with BPD show a more pronounced deficit in behavioral control to adjust their choices in the face of higher risk.

S-26-004
Psychotherapeutic treatment guidelines in personality disorders

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Objectives: Psychotherapy is of central importance in the treatment of personality disorders including Borderline Personality Disorder (BPD). There are several available psychotherapeutic treatment approaches for BPD, e.g. dialectical behaviour therapy, schematherapy, mentalization based therapy, cognitive behavioural therapy, transference focussed therapy and emotion regulation group therapy.
Methods: We performed a systematic review and a metaanalysis of psychotherapeutic approaches for the treatment of BPD.
Results: From the searches up to December 2008, 19 randomized controlled trials were identified which investigated the effectiveness of psychotherapy as compared to treatment as usual. The detailed results of this systematic review and metaanalysis will be presented at the congress. It turns out that the best evidence of effectiveness is provided for dialectical behaviour therapy, but single studies also provide evidence for effectiveness of schematherapy, mentalization based therapy and other more short-term trials. Up to date, transference focus therapy currently lacks high level evidence of effectiveness.
Conclusions: Psychotherapy is effective for the treatment of BPD with best evidence for dialectical behavior therapy.

S-33
Peripartum mood disorders: From physiological to pathophysiological adaptations

S-33-001
Adaptations of stress responses in peripartum women: Implications for psychiatric illness

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Objectives: Most women tolerate the large hormonal changes during pregnancy and postpartum with little or no mood changes. However, women with a history of depression or anxiety often experience exacerbation of symptoms during pregnancy, postpartum or after weaning. Biological factors which may contribute to symptom exacerbation are not well understood.
Methods: Cerebrospinal fluid and blood samples were obtained at the time of spinal anesthesia for elective caesarian section in 22 healthy pregnant women who were at term but not in labor, and during the early follicular phase of the menstrual cycle in 20 healthy non-pregnant women. Hormones and peptides were measured by radioimmunassay and neurotransmitters by HPLC.
Results: Pregnant women had elevated levels of CSF corticotropin releasing hormone and decreased levels of CSF GABA. In addition CSF prolactin levels were markedly elevated. Despite elevated plasma levels oxytocin during pregnancy, brain levels of oxytocin were not elevated.

Conclusions: Healthy pregnant women have changes in brain neurochemicals similar to changes that occur in depression. For women with a vulnerability to depression, these changes may contribute to the risk of relapse of a depressive episode during pregnancy or postpartum. In addition, because hormonal changes that occur during pregnancy are maintained by lactation, vulnerable women who do not breastfeed, or who wean abruptly may be at increased risk of relapse of depression and anxiety postpartum.

S-33-002
Late pregnancy thyroid status: Relationships to perinatal depression in women and a rat model

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David Overstreet, Maria Boccia, Lesly Marson

Objectives: Our goals were to 1) examine relationships between prepartum thyroid status and pre and postpartum depression in women and 2) test in rats whether simulating the pattern of change in estrogen and progesterone levels during human pregnancy produces depression and anxiety-like behavior.
Methods: In euthyroid women (N=31), thyroid measures were obtained on pregnancy weeks 32-35, 36, and 37 as well as Edinburgh Postnatal Depression Scale (EPDS) and Beck Depression Inventory (BDI) self-ratings at prepartum time points and every other week postpartum (weeks 2-24). Nulliparous female rats were injected daily with progesterone (P,4mg/day sc x 22 days) and estradiol benzoate (E,2.5µg/day [days 1-16], 50µg/day {days 17-22]). Some received desipramine 5mg/kg/day ip on days 16-22. Control animals were injected daily with sesame oil. At 2, 48 and 72 hr after the last injection, rats were tested in the social interaction test followed by a 5-min forced swim test.
Results: Mean prenatal total and free thyroxine concentrations correlated significantly and negatively with mean pre and/or postpartum EPDS and BDI scores. E+P-treated rats exhibited significantly greater swim test immobility and less social interaction at 2 hr (analogous to late pregnancy) and 48 and 72 hr (analogous to the postpartum period), changes that were prevented by desipramine treatment. Total and free thyroxine concentrations at 2 hr were significantly lower in E+P-treated animals.
Conclusions: Our findings have several important implications. Measuring thyroxine concentrations during late pregnancy may help identify women at greater risk of developing perinatal depression. Thyroxine supplementation of women with low prepartum concentrations may decrease that risk. Variability in prenatal thyroid status may contribute to differences in vulnerability to mood disturbance by the large perinatal shifts in E and P concentrations. We have also developed a rat model of perinatal depression and anxiety with thyroid changes similar to those in perinatal depressed women.

S-33-003
Chronic psychosocial stress in pregnancy: Towards an animal model of postpartum depression

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Objectives: The time around birth is accompanied by behavioural and neuroendocrine adaptations of the mother. The responsiveness to stressors is attenuated due to increased activity of stressprotective neuropeptides. However, these complex adaptations are not only important for the offspring, but also for the mental well-being of the mother.
Methods: Chronic psychosocial stress (restraint, overcrowding) in pregnancy partly prevents important neuronal/behavioural adaptations, lowers body weight gain and increased adrenal weight in all stressed groups, verifying the chronic stressor. Further confirmation of the stressor was achieved by demonstrating that offspring of mothers exposed to stress during pregnancy emitted significantly more ultrasonic vocalizations and were more anxious and depressed in adulthood.
Results: Chronic stress in pregnancy prevented the lactation-induced elevation in basal corticosterone; although did not affect the hyporesponsiveness to stressors in lactation. Chronic stress attenuated the upregulation of OXT mRNA in early lactation, whereas CRH mRNA expression within the PVN was unchanged. Moreover, chronic stress prevented the anxiolytic phenotype observed in lactation and increased the activity during swimming, which alterations of the noradrenergic system. Contrary to expectations, stressed dams displayed more maternal care consistent with our observations of a direct link between dam's anxiety and the quantity of maternal behaviour.
Conclusions: The chronic psycho-social stress paradigm has revealed important consequences of pregnancy stress on the maternal behavior and physiology. Thereby, these results increase our understanding of the brain mechanisms involved in the development of mood disorders during pregnancy and in the postpartum period [Supported by Volkswagenstiftung and DFG grant NE 465/16-1].

S-33-004
Social support, stress perception and maternal depressive symptoms during pregnancy: Effects on fetal health

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Objectives: High stress perception is frequently mentioned when discussing causes of infertility and unexplained reproductive failures. However, less severe pregnancy outcomes are of particular importance to population health. An emerging area of research called 'developmental origins of health and disease' currently focuses on the identification of environmental insults during pregnancy. Such environmental insults have been proposed to induce permanent functional changes to the offspring, causing an increased susceptibility to develop chronic disease later in life. The scientific hypothesis behind this paradigm has primarily been developed from epidemiological studies, focusing on environmental insults such as altered maternal nutrition, pollution and infection, which could then be linked to a higher prevalence of e.g. low birth weight. More recently, the list of programming agents during pregnancy and early childhood has been amended, and maternal stress perception during pregnancy has been confirmed as a potent environmental factor which can program the fetus leading to chronic diseases such as schizophrenia or depression later during post-natal life. Disorders of the immune system leading to chronic inflammatory disease also merit consideration since epidemiological data evidence a steady rise in the incidence of such disorders over the past five decades.
Methods: Employing cohort studies and fundamental research in mice, we aimed at identifying psychosocial, biological and sociocultural parameters during early pregnancy and evaluate these as factors to interfering with fetal development.
Results: Our research pursued to date reveals insights on how maternal stress perception during pregnancy generates a risk for the offspring to develop chronic diseases in later life, such as allergies and anxiety-like behaviour. Low levels of progesterone during early pregnancy along with poor social support and high stress seem to be central in impairing fetal health.
Conclusions: The identification of relevant mechanisms involved in stress-induced altered fetal/neonatal development will subsequently allow the development of primary prevention strategies aiming to abrogate the effect of maternal stress on the developing fetus.

S-72
Recent advances of psychoneuroimmunological study of psychiatric disorders

S-72-001
Anti-inflammatory effects of antidepressants: Implications for pathophysiology of depression

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Objectives: Increasing evidence indicates that microglial activation and inflammatory processes play important roles in the pathogenesis of neurodegenerative disorders such as Alzheimer's disease and Parkinson's disease. So far, there is no direct evidence that activated microglia are involved in the pathogenesis of depression. However, there is circumstantial evidence of its role from recent studies. It has been suggested that impaired hippocampal neurogenesis contributes to the pathogenesis of depression. A recent study has demonstrated that neuroinflammation inhibits hippocampal neurogenesis while minocycline, a specific inhibitor of microglial activation, can restore the impaired neurogenesis. Pro-inflammatory cytokines and free radicals, both of which are released from activated microglia, have been reported to block hippocampal neurogenesis. Increased pro-inflammatory cytokines also lead to the reduced availability of serotonergic neurotransmission through the activation of indoleamine 2,3 dioxygenase (IDO).
Methods: We investigated whether or not antidepressants can inhibit microgliala activation in vitro.
Results: Several kinds of antidepressants inhibited the release of pro-inflammatory cytokines and free radicals from activated microglia. Interestingly, some antipsychotics, which are also used for treatment-resistant depression, had similar effects on microglial activation.
Conclusions: The above results suggest that microglial activation may play an important role in the pathophysiology of depression.

S-72-002
The mild encephalitis-hypothesis – new findings and studies

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Objectives: In a subgroup of affective and schizophrenic spectrum disorders an underlying low level CNS inflammatory process, termed mild encephalitis (ME), may be core to induce severe psychiatric disorder.
Methods: We collected evidence that in a small number of cases Borna Disease Virus (BDV) may be an initiating or causal agent. In other single cases we identified a streptococcal infection associated autoimmune process probably underlying chronic depression. But various infectious agents and autoimmune mechanisms are assumed to be involved, eventually representing a diverse spectrum of specific causes with common pathogenetic pathways. Age-related variance of pathogenicity of infectious agents could explain age-related variance of disease onset. Gene-environment-immune interaction is the paradigm in autoimmune disorders in general, and fits ME hypothesis. In such scenario also non-specific treatments can be useful, but in therapy resistant cases only differentiating specific causes respectively pathogenetic mechanisms may lead to improved therapies.
Results: The ME hypothesis was supported by the observation that therapy resistant cases of major psychosis impressively improved with cerebrospinal fluid filtration (CSFF). CSFF was an immune modulatory treatment previously shown effective in Guillain-Barré syndrome, an autoimmune neurological disorder. Furthermore, we recently found by CSF cell subtypings in a considerable subgroup of affective and schizophrenic spectrum disorders presenting an inflammatory pattern of T cell subtype distribution similar to that found in neurological patients with meningoencephalitis or chronic inflammatory neurological disorders, though with overall normal CSF cell numbers in the psychiatric patients.
Conclusions: The ME hypothesis appears an attractive explanatory new model for understanding the onset and course of severe psychiatric disorders in a multiconditional framework but with relevant single causal factors. Bechter K: Mild encephalitis underlying psychiatric disorder – A reconsideration and hypothesis exemplified on Borna disease. Neurol Psychiatry Brain Res 2001; 9:55-70

S-72-003
The role of antiinflammatory therapy in psychiatry

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Objectives: COX-2 inhibition seems to balance the type-1/type-2 immune response, possibly via inhibition of prostaglandin E2. COX-2 inhibition reduces proinflammatory cytokines. COX-2 inhibition has an impact to the glutamatergic neurotransmission and influences the tryptophan/kynurenine metabolism: all three components seem to be involved in the pathophysiology of psychiatric disorders, particularly in schizophrenia and major depression.
Methods: Due to the increase of proinflammatory cytokines and PGE2 in depressed patients, antiinflammatory treatment would be expected to show antidepressant effects. In schizophrenia, therapeutic effects of COPX-2 inhibitors would be expected, too.
Results: An own randomized double blind pilot add-on study using the selective COX-2 inhibitor celecoxib in MD showed a significant therapeutic effect of the COX-2 inhibitor on depressive symptoms. Although those preliminary data have to be interpreted cautiously, those results are encouraging for further studies dealing with the inflammatory hypothesis of depression. Secondly, we and other research-groups performed several studies of COX-2 inhibitors in schizophrenia. In a prospective, randomized, double-blind study with the COX-2 inhibitor celecoxib in acute exacerbation of schizophrenia, a therapeutic effect of celecoxib was observed. The finding of a clinical advantage of COX-2 inhibition could not be replicated in a second study. Further analysis of the data revealed that the efficacy of therapy with a COX-2 inhibitor seems most pronounced in the first years of the schizophrenic disease process.
Conclusions: It has to be considered, however, that therapy with COX-2 inhibitors is currently under discussion - as therapy with other non-steroidal antiphlogistics - due to cardiovascular side-effects.

S-72-004
Stress and immune markers in depression

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Objectives: Major depression with melancholic features is consistently associated with elevated cortisol and the cytokines tumor necrosis factor-alpha (TNFα) and interleukin (IL)-6. The acute phase protein CRP, whose elevation is reported to increase the risk of cardiovascular disease, is also frequently elevated in depression. There is evidence that increased inflammatory activity contributes to treatment non-response and studies suggest that ω-3 fatty acid supplementation is effective in antidepressant non-responders. We tested the hypotheses that in major depression (1) the plasma ω-6:ω3 fatty acid ratio is greater in antidepressant non-responders than responders (2) higher ω6:ω3 ratios are associated with a pro-inflammatory cytokine profile.
Methods: Patients with major depression together with matched healthy controls were recruited. ELISA assays and gas chromatography were used for plasma analysis.
Results: Arachidonic acid (AA) levels were elevated in both the responders and non-responders. IL-6 was elevated in a similar manner. The eicosapentaenoic acid (EPA):AA ratio in the three groups was as follows: controls 0.08±0.01; responders 0.08±0.01; non-responders 0.04±0.01. These differences are significant ($p<0.001$). AA and IL-6 were highly correlated in both responders and non-responders but not in healthy volunteers.
Conclusions: Major depression has a pro-inflammatory profile with elevations in both cytokines and AA. The role of toll-like receptors in the pro-inflammatory profile of depression will be explored.

Workshops

W-06
Animal models of major psychiatric disorders

W-06-001
Animal models for anxiety and depression related diseases

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Objectives: Mood and Anxiety disorders are serious, growing medical problems that remain poorly understood and inadequately treated. The complex interaction between stress and genetics that leads to the manifestation of such disorders in certain susceptible individuals is one of prime interest in neuroscience. This is paralleled with efforts to develop novel pharmacological strategies to counteract the deleterious effects of stress. However, psychiatry has proven to be among the least penetrable clinical disciplines for the development of satisfactory in vivo model systems for evaluating novel treatment approaches. With the explosion in the use of genetically modified mice, enormous research efforts have been focused on developing mouse models of psychiatric disorders. The success of this approach is largely contingent upon the utility of available behavioural paradigms for modelling depression- and anxiety-related behaviours in mice. There are key issues facing drug discovery as it endeavours to identify "translational models" for depression and anxiety. Whilst numerous attempts have been made to create rodent models of depression, or at least models of the symptoms of depression there are no satisfactory animal models of depression available. More recently, there is currently a shift away from these traditional animal models to more focused research dealing with an endophenotype-style approach, selective breeding programs and incorporation of new findings from human neuroimaging and genetic studies. Additionally, recent emphasis has also been placed on developing mouse models of the early-life origins of anxiety as childhood trauma and neglect exert a profound and pervasive influence on risk for anxiety and mood disorders. Endophenotype-based modelling of depression and anxiety disorders is opening up more tractable avenues for understanding the neurobiological and genetic basis of these disorders. The need for improved animal models to identify new antidepressant and anxiolytics and to provide insights into the neuropathology underlying the disease is critical.

W-06-002
Animal models for gene X environment interactions shaping adult psychopathologies

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Gregers Wegener, Inga D Neumann

Objectives: Pathophysiologies of major psychiatric diseases, e.g. depression, anxiety and schizophrenia have not been clarified. Nevertheless, the role of genetic factors is extensively documented in epidemiologic and twin studies, while clinical studies indicate that psychosocial factors are also of importance.
Methods: Although rodent behaviour and neurobiology can not be directly translated to human diseases, in particular schizophrenia, animal models with a degree of face-, predictive-, and construct-validity have been developed in order to contribute to elucidation of disease etiology & pathology as well as identification of novel targets of pharmacological treatments. Genetic animal models have been established by selective breeding and specific defects/traits have been recreated by selective gene-knockouts. On the other hand, myriad experiments have explored consequences of environmental events, such as prenatal and early life stress/trauma. Thus far, most animal experiments have been carried out in normal animals, thereby omitting to take into account the role genetic loading may play in animals exposed to a variety of acute/chronic deleterious conditions. However, research in the past decade has shown that gene-environment interaction often is the crucial determinant of human disease.
Results: Focusing on genetics, our groups have investigated two inbred rat models: the high anxiety-like behaviour (HAB) and their controls, the low anxiety-like behaviour (LAB) rats, and the "depression" Flinders sensitive line(FSL) and their controls, the Flinders resistant line (FRL) rats. Subsequently, in order to enable investigations of gene-environment interplay, which is central to psychiatric pathology, we have constructed new paradigms by subjecting the HAB/LAB and FSL/FRL strains to prenatal or postnatal stress (early life maternal deprivation). Behaviour, neurochemistry, endocrinology and cell proliferation were assessed both under baseline conditions and following stress.
Conclusions: Utility as well as shortcomings of these models to enhance understanding of disease pathology and develop new treatments will be discussed.

W-12
Is there still a place for unipolar depression?

W-12-001
Genetic differences between unipolar and bipolar depression

Alejo Corrales
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Objectives: Affective disorders are complex genetic disorders. Genetic epidemiological studies have reported that both Bipolar and Major Depressive Disorder have a genetic component, however the role of genetic factors seems to play a smaller role in depression. Environmental factors are considered to be more of an influence (e.g., early traumatic events) in Major Depressive Disorder. Studies in genetic epidemiology of mood disorders report differences in concordance rates and heritability in twin studies between these two different disorders. We will discuss current available data about the genetic differences in both disorders.

W-12-002
Clinical differences between unipolar and bipolar depression

Jose Luis Ayuso-Gutierrez
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Objectives: There is some evidence that bipolar and unipolar depressed patients may differ over a wide range of clinical features. Results could have implications not only for clinical and genetic studies, but also for treatment (mood stabilizers versus antidepresants). Consequently, an early distinction between bipolar and uinipolar disorder is of utmost importance for the treatment of these illnesses.
Methods: The object of this presentation is to reveal the factors that distinguish between unipolar and bipolar depression by means of a retrospective and prospective study (time of follow-up: 9 years) on patients' files at San Carlos Hospital in Madrid. It includes 200 in-patients divided according to DSM IV criteria into two groups: patients with bipolar disorder type I and patients with recurrent depressive disorder. In addition to the longitudinal pattern of the disease in the two samples of the follow-up study, we also have analysed the symptomatic profile of both subtypes using the Hamilton Rating Scale for Depression.
Results: Our study has revealed that bipolar I disorder differs significanftly from unipolar disorder in the following aspects. age at the onset of illness, mean number of episodes, mean duration of episodes and mean duration of free intervals. As far as the symptomatic profile is concerned, we have found significant differences between both goups of depressed patients on the following items: guilt feeling, suicide behavior, somatic anxiety, psychic anxiety, loss weight and obsessive symptoms.
Conclusions: i spite of the fact that both groups of depressed patients have a large clinical heterogeneity, there is evidence of symptomatic and course differences between unipolar and bipolar subtypes.

W-12-003
Psychoneuroimmunoendocrinological differences between unipolar and bipolar depression

Andrea Lopez Mato
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Objectives: To determine if unipolar and bipolar depression are a unique disorder or different entities from a psychoneuroendocrinological (PNIE) point of view. Genetic, clinical and therapeutical differences will be reviewed by other co-speakers
Methods: Several PNIE challenges were performed in different drug free patients, on a clinical open basis, in the Biological Institute of Psychiatry sited in Buenos Aires, under the author chairship. Unipolar and bipolars underwent a clinical diagnose based on DSM IV criteria and special mood questionaries
Results: TRH/TSH test showed a blunted response in nearly 30 % of unipolar patients as a trait marker: None presented hyper response and other group remained normal. Bipolar patients presented a clear hyperresponsive result to the challenge in 30 % of the population, behaving as a state marker, with normalization after recovery, Dosage of antiperoxidase antibodies were extremely high compared to normal population (30% vs. 8%) accounting for a probable thyroid sub clinical disease. None of them had received lithium for more than a year. Dexamethasone suppression test (DST) revealed no suppression both in unipolar and bipolars with a robust tendency to more altered results related to the severity of clinical presentation or risk for psychotic symptoms. Disturbances of circadian rhythm were observed in unipolar depression. Blunted response to hypoglycaemic challenge, represented by low Growth Hormone release was reserved for unipolars Urinary excretion of Pheniletilamine, Phenilacetic acid, Serotonine, 5 HIAA, Dopamine, Norepinephrine o Epinephrine were similar in both groups but Metoxiphenilgicol excretion was much lower in bipolar patients
Conclusions: In spite of the fact that our patients population can not be compared as clearly as in a double blind randomized study, some observations may lead to some general remarks towards the PNIE difference between unipolar and bipolar depression. Neurobiological findings still mark an important and clear-cut space for unipolar depression.

W-12-004
Therapeutical differences between unipolar and bipolar depression

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Objectives: The aim of this part of the workshop is to discuss the differences in the treatment between unipolar and bipolar depression
Methods: We review the WFSBP Guidelines for Biological Treatment of Unipolar Affective illness and for Biological Treatment of Bipolar Disorders, especially part I: Treatment of bipolar depression (2002) and add the results of a literature research using Medline in the last five years.
Results: Antidepressants are the fist line treatment in unipolar depression, but the use in bipolar depression has raised some controversy, especially in weighing the impact of switch and suicide risk. In 2002, the Task Force on Treatment Guidelines for Bipolar Disorders spoke about combining the treatment with a mood stabiliser (Lithium, antiepileptic medications as lamotrigine, valproate, carbamazepine) and antidepressant, preferably a modern, non-TCA antidepressant was the first line approach, at least for patients with moderate and severe bipolar depression meanwhile in severe and/or psychotic depression may be needed a TCA or irreversible MAOI. Today the use of antidepressants in bipolar depression continues being controversial. Atypical antipsychotic of second generation (olanzapine, risperidone, quetiapine) or third generation are recommended as adjunctive treatment in bipolar depression and for prophylactic efficacy. Electroconvulsive therapy in bipolar depression has a relative high switch risk. Psychoeducation, interpersonal psychotherapy and cognitive-behavioural therapy combined with pharmacological treatment are a very useful option in both kind of depressions, but we must have in mind the different strategies in each case.
Conclusions: Psychiatrics must know the different treatments for unipolar and bipolar depression.

W-08
Mastering the challenges in conducting multinational child and adolescent psychopharmacology trials

W-08-001
Ensuring data quality and consistency in multinational clinical trials

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W-08-002
Ethical, clinical and practical considerations in designing clinical trials in paediatric psychopharmacology

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Objectives: To understand the ethical, clinical and practical considerations in designing clinical trials in paediatric patient populations and the differences compared to adult programmes
Methods: There has been recently an obvious increase in the number of clinical trials in the field of psychopharmacology. With the European Paediatric Regulation that had entered into force in 2007, more research will be performed. The authors will share some lessons learned from trials already conducted.
Results: Ethical concerns have to be reassessed from a paediatric perspective; furthermore specific cultural consideration have also to be taken into account and different practices in different countries may complicate the assessment as evidenced for instance by the different views on placebo use. It is therefore critical to adhere to high ethical standards. It is also important to understand that what has been successful in adult populations may no longer be appropriate for children and adolescents. Study design must be clinically and scientifically sound and cannot simply be an extrapolation from successful adult trials. The diagnosis might be assessed in a different way than with adult patient populations. There is still limited accepted endpoints and validated suitable assessment tools. Involving parents/caregivers should be involved as the study design must not constitute a burden for parents/caregivers or children, therefore practical considerations are of paramount importance including for instance determining an age appropriate drug formulation or avoiding frequent blood sampling.
Conclusions: Designing a successful clinical programme and clinical trials in a paediatric population remain a challenge and requires taking into account specific ethical, clinical and practical considerations.

W-10
New tools for cognitive remediation in schizophrenia

W-10-001
Symptom oriented cognitive remediation in RECOS

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Objectives: The Programme de Remédiation Cognitive pour patients présentant une Schizophrénie ou un trouble associé (RECOS – Vianin, 2007) is a program which is specifically aimed at providing individualized cognitive remediation therapy for patients with schizophrenia. Before treatment, the patients were evaluated with a large battery of tests in order to determine in which of the five specific training modules they would participate. The study was designed to evaluate benefits of the RECOS program by comparing cognitive functioning before and after treatment.
Methods: 28 patients participated in one to three cognitive modules. The functional outcome of the cognitive deficits was considered for the selection of the training modules. The patients participated in 20 sessions of training (one session per week) per module. As executive functioning has been shown to be important in predicting functional outcome, techniques of remediation were those used for dysexecutive syndrome. At the end of the training period, the cognitive functioning of each patient was reevaluated by using the same neuropsychological battery.
Results: The results showed a greater improvement in the modules for which training had taken place as opposed to the modules where no training had taken place. However, an improvement was observed in both types of module, indicating a learning transfer effect. Moreover, by considering results of the Wisconsin Cards Sorting Test, a superior effect size has been observed with the RECOS program than with a cognitive remediation program which does not target the deficits of each participant (REHACOM®).
Conclusions: This study confirms that the great heterogeneity of the observed cognitive deficits in schizophrenia necessitates a detailed neuropsychological investigation as well as an individualised cognitive remediation therapy. These results need confirmation however, by using a larger sample of patients.

W-10-002
Cognition rehabilitation in schizophrenia: Costs and effectiveness

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Vyv Huddy, Caroline Cellard

Objectives: Cognitive impairments in people with schizophrenia are known to be related to poor functional outcome and can interfere with the success of rehabilitation programmes. The costs of supporting individuals with a diagnosis of schizophrenia are higher if they have a cognitive difficulty (1). This study investigates Cognitive Remediation for Schizophrenia (CRT) is efficacious and whether it is cost-effective.
Methods: A meta-analysis of CRT studies was carried out also investigated the methodological adequacy of the studies. In addition the costs of the provision of CRT and the costs of services were investigated in a large methodologically adequate randomised control trial (RCT) of CRT.
Results: The methodological adequacy of CRT studies is variable and therefore assessments of effect size may have been inflated. The effect size is likely to be modest but still important. In the RCT investigated in detail, CRT improved working memory at post treatment and follow-up compared to a control group. These improvements are achieved at no increases in costs at post-treatment. At follow-up the gains in cognition were achieved at a small cost (2). However, detailed assessments suggest that for this study which was independent of an active functioning rehabilitation programme, there was no evidence to support long term cost efficiency (3).
Conclusions: Conclusions: CRT can improve cognition and in the presence of rehabilitation programmes can significantly improve real life functioning. However, the programmes vary considerably in assumptions, methods and methodological rigour of their evaluation. CRT is cost-effective in the short term compared to treatment as usual and shows gains in both costs and cognition. In the longer term it is probably that CRT will improve costs when provided in a comprehensive rehabilitation programme. 1 Wykes et al Schizophrenia Research, 2003 2 Wykes et al British Journal of Psychiatry, 2007 3 Patel et al., under review

W-11
Pharmacological management of schizophrenia in pregnancy and the puerperium

W-11-001
Antipsychotic therapy in pregnancy

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Objectives: The age of onsets of psychotic disorders is usually before or during the childbearing years. Treating pregnant women with psychotic disorders is a challenge. The benefits of pharmacological treatment have to outweigh the possible teratogenic /developmental risks for the foetus. Today no single optimal treatment option is available and neither of the typical or atypical antipsychotic drugs is approved for use during pregnancy. Nevertheless, they are by clinical necessity frequently taken by reproductive-age women world-wide. The paucity of reproductive safety data is problematic with post marketing surveillance limited to small series or case reports whereof many lack vital information such as correct diagnosis (mother and infant), dosage of drug, length of treatment, and possible concomitant medication. Typical antipsychotics cause hyperprolactinaemia which in turn may lower fertility. Such side effects are less likely to appear with the prolactine-sparing atypical antipsychotics with the exception of risperidone. Consequently, over time more women suffering from psychotic illnesses may become pregnant. Atypical antipsychotics, however, are associated with substantial bodyweight gain with an increased risk for adverse effects of adiposity on glucose and lipid metabolism; risk factors to develop hypertension and gestational diabetes and also to affect pregnancy outcome including some congenital malformations.

W-11-002
Antipsychotic therapy in breast-feeding

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Objectives: To analyse infant safety during antipsychotic-exposure via maternal milk.
Methods: A systematic computerized search was carried out on Medline/PubMed/TOXNET/EMBASE covering the period between 1980 and January 2009.
Results: Information on the safety of FGAs (haloperidol chlorpromazine, trifluoperazine, zuclopenthixol and flupenthixol) for the breastfed infant is scarce. Human data on SGAs are also very limited or absent. However, it should be highlighted that olanzapine shows both the highest number of reassuring reports and the highest number of drug-induced neonatal extrapyramidal symptoms.
Conclusions: Postpartum psychosis is a relevant clinical concern, since it may affect a relatively high proportion of women, especially those with a history of previous postpartum psychotic episodes. Thus, antipsychotic therapy is mandatory in all patients with postpartum psychosis. In fact, this disorder is likely to have a devastating impact on the quality of mother-infant bonding. Moreover, mothers suffering from postpartum psychosis and showing cognitive disorganization are likely to neglect infant needs and indulge in unsafe practices. Unfortunately, however, neither FGAs nor SGAs have demonstrated specific, definitive advantages in safety during puerperium.

W-14
Prefrontal cortex-relevance in psychiatry

W-14-001
Prefrontal cortex – functional neuroanatomy

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W-14-002
Prefrontal cortex – relevance to psychiatric disorders

Venkat Subramaniam
Nat. Inst. of Mental Health, and Neurosciences (NIMHANS), Bangalore, India

W-01
What can genetics tell us about psychiatric disorders I: Focus on copy number variants

W-01-001
Recurrent deletions and duplications associated with schizophrenia

David St. Clair
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W-01-002
Copy number variation in schizophrenia. Fact and fiction

Michael O'Donovan
Cardiff University, School of Medicine, United Kingdom

W-01-003
Genomic variation at the neurexin locus in schizophrenia

David A. Collier
King's College London, Inst. of Psychiatry, United Kingdom

W-01-004
Genomic structural variation, bipolar disorder and psychosis

Nick Craddock
Cardiff University, Dep. of Psychological Medicine, United Kingdom

W-03
What can genetics tell us about psychiatric disorders II: Focus on endophenotypes

W-03-001
Genes to biology in the major psychoses – the use of neuropsychological and neurophysiological endophenotypes

Michael Gill
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Objectives: Genetic variation contributing to schizophrenia and related diagnostic categories is likely to operate through intermediate traits or endophenotypes because of their role in underlying brain systems.
Methods: To develop an understanding of the function effects of genetic variation contributing to risk for the major psychoses, we have assessed cognitive and neuropsychological, neurophysiological and neuroimaging measures in a large sample of patients with schizophrenia and related disorders. We have used this approach to interrogate risk variants at candidate genes and DNA variants emerging from Genome-wide Association Studies (GWAS).
Results: We have shown that Dysbindin risk variants affect clinical symptom measures, spatial working memory, early processing of visual information, and brain structure. We have examined gene variants identified in recently reported GWAS study suggesting variants at NOS1 contribute to risk for schizophrenia and related disorders. A main effect of NOS1 genotype on verbal IQ and working memory was observed in both our Irish sample, and a replication sample from colleagues in Germany, with carriers of the GG risk genotype performing below other genotype groups. In the German sample, non-verbal and full scale IQ, and visual memory were also associated with NOS1. The effects of NOS1 genotype was evident in both patient and control samples.
Conclusions: These studies suggest Dysbindin risk genotype affects aspects of visual information processing and that lowered cognitive ability is likely to be at least part of the mechanism by which NOS1 confers increased risk, consistent with the idea of 'cognitive reserve' as a risk factor for psychiatric disorders. As the results from collaborative GWAS studies emerge, endophenotype studies will be an essential part of understanding the functional consequences of risk variants.

W-03-002
Are there brain imaging measures useful as endophenotypes for schizophrenia?

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Abstract: The concept of an "endophenotype" has been recently used in many different ways, but originally was defined to provide a label for a biological or other marker that could be measured, and that is intermediate between the cause of a psychiatric disorder (most often schizophrenia) and its clinical characteristics. The endophenotype is thus a factor that is found to differentiate patients from controls, is shown to be highly heritable, and within families segregates with illness. A controversy exists, however, about the so called "well relatives" of affected individuals. In some applications of the word "endophenotype", investigators insist that if the factor is an endophenotype, it must be present in well relatives as well as those affect. The original definition however does not require this, but suggests that it is more likely than chance, given that some of the "well" individuals will eventually develop the illness or may have a milder presentation of its pathology. Unfortunately many current "endophenotype studies" erroneously short cut the initial characteristics and only report whether well relatives can be differentiated from controls. In the use of brain imaging measures, particularly regional structural volumes, a series of early twin and family studies particularly of brain ventricular size satisfied some of the above measures, although did not agree on the well relative concept. Recently, however, there have been several studies that show structural brain and other abnormalities in well relatives of people with schizophrenia. Few studies have been capable of showing that the abnormalities segregate with illness within families since families with a high density of illness are difficult to find and to bring to MRI scanners. The observation that brain structural changes progressive over the course of the illness can make many of the above studies invalid, although excessive change in brain structure in itself may be an endophenotype for illness, as suggested by one twin study. All the above studies reported since the early 1980's to the present will be reviewed and conclusions drawn about specific structures. The usefulness of brain imaging phenotypes will depend on whether they can be used to predict who among people at genetic high-risk for illness eventually become ill, whether they can be used as phenotypes in searches for candidate genetic mechanisms, and whether ultimately they can used as targets for the effectiveness of a new generation of drug treatments.

W-03-003
Tardive dyskinesia as an endophenotype of schizophrenia: molecular genetic findings

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Clement Zai, Arun Tiwari, Renan DeSouza, Herb Meltzer, Jeff Lieberman, Daniel Mueller

Objectives: Identification of core subphenotypes (endophenotypes) of schizophrenia that have more homogeneous etiology may be of considerable help for understanding the disease. In this regard, administration of antipsychotic medications 'reveals' the distinctive phenotype of abnormal involuntary movements (tardive dyskinesia) in 25 to 30% of patients. It is plausible that examination of tardive dyskinesia (TD) in schizophrenia may identify a genetically more homogeneous subgroup of the illness. Our objective is to dissect the dopamine system in TD using molecular genetic tools.
Methods: We examined dopamine system genes in 240 schizophrenia patients chronically treated with traditional neuroleptics who were assessed using the Abnormal Involuntary Movement Scale (AIMS).
Results: Our newest data suggest involvement of a haplotype of DRD3 promoter markers (p=0.01 with TD diagnosis; p=0.008 with quantitative AIMS score). In addition, we have typed markers in the DRD2 gene that have not previously been tested in TD, finding significant association (p=0.03). Most recently we examined seven markers across the gene AKT1, biologically linked to dopamine receptor signaling, and initial results are mostly negative, although one marker shows a trend (p=0.06) to predict TD. Furthermore, given the biological interaction between D3 and BDNF, we have also examined their gene-gene interaction, with some intriguing positive results.

Conclusions: Our data point to an important role of the dopamine system in risk for TD. The challenges remaining include assessing the subtypes of TD itself (oro-facial versus truncal). Overall, we need to understand our findings in the context of the larger population of TD susceptible versus TD resistant schizophrenia patients. Future tasks include searching for correlations between possession of genetic risk variants for TD and other clinical characteristics of schizophrenia, in order to define the boundaries of a putative "TD endophenotype".

W-03-004
Endophenotypes in psychiatry: Pro's and Con's

Michael J. Owen
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W-09
Molecular genetics of adult ADHD

W-09-001
Genetic studies in IMPACT, the international multi-centre persistent ADHD collaboration

Barbara Franke
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Objectives: Attention-deficit hyperactivity disorder (ADHD) is observed in children and adults with a prevalence of 5-12% and 2-4%, respectively. More than 20 twin-studies confirm the high heritability of this neuropsychiatric disorder, which is estimated at about 76%. Importantly, the heritability of the persistent form of the disorder in adults appears even higher. Molecular genetic studies aiming at identifying the genes involved in ADHD, including linkage and candidate-based association studies, have been rather disappointing. Very little overlap in linkage regions identified in the different studies has been observed, and only few genes showed significant association in meta-analyses. The studies have mainly been based on childhood ADHD, only few genetic studies have looked at patients with the persistent form of the analysis, so far.
Methods: To perform and promote genetic studies in persistent ADHD, we founded the International Multicenter persisting ADHD CollaboraTion (IMpACT) in 2008.
Results: During the representation, we will give an overview of genetic studies in ADHD, thus far. We will discuss the results of linkage and association studies in children and adults. In particular, the results of the first genome-wide association studies in (children with) ADHD will be summarized. Also, the prerequisites for successful genetic analyses in adult ADHD will be part of the discussion, including a discussion of endophenotypes, which are heritable traits related to ADHD, that might be less genetically complex than the clinical disorder and its symptoms.
Conclusions: With the advent of genome-wide association studies, the IMpACT collaboration can provide well-characterized samples for the identification of new genes for the persistent form of ADHD.

W-09-002
Functional studies of candidate genes involved in adult ADHD

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Objectives: Attention-deficit hyperactivity disorder (hyperkinetic disturbance; ADHD) is a common psychiatric disorder diagnosed in children, adolescents and adults. Attempting to discover susceptibility genes for ADHD, molecular genetic studies are currently being performed in patient samples across the world. These studies have provided tentative evidence for genetic association of ADHD with several genes, but none of the findings have reached robust statistical significance across populations, possibly due to genetic heterogeneity and lack of statistical power. To increase samples sizes and facilitate international collaboration, the IMPACT (International Multicenter Persisting ADHD CollaboraTion) consortium was formed in 2008. IMPACT is actively recruiting patients in six countries and already has access to genetic and clinical data for >2,000 well-described adult ADHD cases along with their respective controls.
Methods: In addition to clinical and genetic studies, IMPACT partners are also performing functional studies on ADHD candidate genes at the molecular, cellular or organism level, both in humans and experimental animals. Such studies are mandatory (i) to identify candidate genes in chromosomal regions indicated by linkage or association studies (ii) to determine how genetic variants may influence the function of these genes and (iii) to establish genotype-phenotype relationships across different diagnostic categories.
Results: In this presentation, methodological issues will be discussed. Examples will be provided of molecular and cellular studies of genetic variants of proteins involved in monoamine signalling in the brain and how these variants relate to risk of developing psychiatric disorders. Thus, it will be shown that alterations in brain serotonin levels strongly influences the risk of developing ADHD related symptoms, as well as other psychiatric disorders.
Conclusions: Despite promising results, functional studies of ADHD related genes are still in its infancy and much larger emphasis must be placed on developing robust and reproducible assay systems to keep up with the pace of recent high-throughput technology in genetic research.

W-04
Clozapine and lithium – gold-standard or outdated treatment?

W-04-001
Current use of lithium

Michael Bauer
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Objectives: Lithium was discovered almost 200 years ago and has been used in medicine in one form or another for almost 150 years. Since its introduction into psychiatry in 1949, many new aspects of its use in psychiatry and the neurosciences have been discovered in basic and clinical research. Lithium is intriguing for several reasons. It is a simple element easily found in the periodic table, yet it has demonstrated a unique, striking efficacy in many patients with bipolar and unipolar mood disorders.
Methods: This workshop provides an up-to-date description and recent discoveries of clinical research relevant for the use of lithium in mood disorders. Practice guidelines for the efficacious and safe use will be provided.
Results: Although its value has now been established for several decades, its clinical use varies markedly among different countries. Its value as an effective augmentation agent in depression and a suicide-preventing agent is being increasingly recognized and has spurred new interest in lithium's use. The ability of lithium to significantly reduce suicidal risk distinguishes it from other mood stabilizing agents that are available today. Furthermore, basic research has recently revealed that lithium may possess demonstrable neuroprotective properties.
Conclusions: Lithium is one of the "oldest" medications in psychopharmacology. 60 years after its discovery in modern psychiatry, lithium is still one of the most important medications with striking efficacy in mood disorders. Reference: Lithium in Neuropsychiatry-The Comprehensive Guide. Informa Healthcare UK Ltd, 2006 (M Bauer, Paul Grof, Bruno Müller-Oerlinghausen, eds),

W-04-002
Current use of clozapine

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W-13
Drugs, hormones and psychoneuroimmunoendocrinology

W-13-001
Stress, the immune system and depression

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Abstract: Stress causes maladaptative changes in the neurotransmitter, immune and endocrine systems which, as a result, play a major role in causing physical ill-health and depression.
In recent years, there has been a paradigm shift in our understanding of the inter-relationship between the HPA and the immune axes. Thus activation, rather than suppression, of important aspects of the immune system occur following chronic stress and depression. A primary cause of this is ascribed to the glucocorticoid induced apoptosis of hippocampal neurons together with a desensitisation of cortical and peripheral glucocorticoid receptors. This chronic, low grade inflammation results and this is now considered to be central to the pathogenesis of depression and top diabetes, cancer, asthma, arthritis and cardiovascular disease that are often co-morbid with depression.

Evidence in support of the macrophage hypothesis of Smith (Med.Hypoth.35,298-306,1991), which postulates that the symptoms of depression arise from a stress/genetically programmed activation of peripheral and central (astrocytes and microglia) macrophages, is provided by the elevation of pro-inflammatory cytokines (IL-1,IL-6,TNF,IFN etc) in the plasma and to some extent in the CSF. Acute phase proteins are also elevated in the plasma of untreated depressed patients. In short, in depression there is an imbalance between the pro-inflammatory (Th1) and anti-inflammatory (Th2) arm of the immune system. Effective antidepressant treatment largely restores the balance within the immune system.
The rise in pro-inflammatory cytokines also results in the activation of the tryptophan-kynurenine pathway whereby tryptophan is shunted away from the synthesis of serotonin to the formation of kynurenine and its end products following the activation of indoleamine dioxygenase. The activation of this pathway in depression results in an imbalance between the neuroprotective end product, kynurenic acid, and the neurodegenerative end products 3-hydroxykynurenine and quinolinic acid in favour of the highly neurotoxic neurodegenerative products In addition, in the brain the pro-inflammatory cytokines activate cyclo-oxygenase 2 and inducible nitric oxide synthase to produce prostaglandin E2 and nitric oxide. These add to the inflammatory stress (see Leonard and Myint: Neurotox. Res.10,149-160, 2006).

Thus in chronic depression the inflammatory changes, coupled with hypercortisolaemia that blocks the synthesis of neurotrophic factors that normally repair damaged dendrites, a situation arises whereby the neurodegenerative pathways predominate over the neuroprotective pathways. As there is increasing clinical and epidemiological evidence linking chronic depression with the likelihood of dementia, there is increasing evidence how this may occur. Indeed, all of the changes that occur in depression are even more prominent in dementia.
Thus depression and dementia are part of a continuum in which chronic stress is a common factor.

W-13-002
Psychopharmacology on the feminine vital cycle

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Objectives: Psychopharmacology in the feminine vital cycle L Rendon, Hospital Psiquiatrico - Catholic University Asunción, Paraguay Several stages of the woman's reproductive cycle, corresponding to hormonal changes, are closely related to psychiatric manifestations, (Premenstrual Dysphoric Disorder PMDD, Postpartum Depression PPD and Menopausal state). A review of the current literature of the evidence-based psychopharmacological options for management of these dysfunctions will be presented. Since treatment modalities are increasingly based on pathophysiological hypotheses concerning possible underlying biological mechanisms: mostly ovulation-related hormonal changes, serotonergic dysfunction and modulation of GABA action at GABAA receptors by neuroactive steroids; there is a need to examine highlighted issues regarding the available options. The session will follow whit a review of these data: The implication of neurosteroids in the action of antidepressants. Pulsatile hormonal interaction with alcohol, tobacco and drugs, modulate their effects and increase use patterns during the premenstruum. First-line therapy in the treatment of PMDD, and their effective dosing regimens. Menopause onset increases the incidence of depression in women, but the involved mechanism is poorly understood, having correlation with decreased estrogens (ER) levels, the current findings suggest a reduced sensitivity of the aged brain to gonadal steroids. The highly relevant interaction between ER and the serotonin system concerning to mood disorders will be discussed, as well as the reduced response to antidepressant drugs by a chronic hypoestrogenic state and the influence of estradiol levels on the cognitive function. The postpartum is a period of heightened vulnerability for recurrence of mood and psychotic episodes, preliminary evidence linked PPD to bipolar disorder, often misdiagnosed and inappropriate treated. Although the pharmacological treatment during pregnancy and breastfeeding poses major clinical and ethical dilemmas, it should be considered that untreated psychiatric illnesses at those periods are not without its own risks since mothers may lead to suicide attempting or infanticide. Acute and Maintenance treatment option for PPD will be presented.

W-13-003
Psychiatric effects of hormones

Andrea Lopez Mato
University of Buenos Aires, Psychiatry, Argentina

Objectives: To show that hormonal drugs may have psychopharmacological effects in different psychiatric entities
Methods: Unipolar and bipolar depressives receiving thyroid hormone add-on therapy Females with menopausal depression receiving oestrogen, progestin, tibolone or soy bean supplementation Male andropausic patients receiving DHEA supplements Chronic fatigue syndrome and related entities patients medicated with FDA approved drugs plus DHEA Melancholic depressives receiving cortisol synthesis inhibitors
Results: Treatment refractory unipolar depressive patients on add-on T3 supplementation therapy showed a robust response compared to those on classical antidepressants There was not a clear difference in remission rates. This expresses T3 action in the desensibilization of adrenergic receptors which alteration accounts for many depressive symptoms and for drug-related adverse effects of classic antidepressants. Bipolar patients, overall rapid cycling type (correlated with TRH/TSH test hyper response) showed normalization of endocrine challenge and clinical stabilization. T4 was selected due to the potential hypomania T3 may trigger. Depression in perimenopause was improved with tibolone, a recombinant drug with estrogenic, progestin an testosterone action with remarkable cognitive impairment enhancer properties DHEA improved cognitive and physical symptoms in PADAM with special emphasis in amelioration of libido, strength and vitality loss. DHEA showed the same effect in many involution states. Patients with central sensitivity syndromes such as CFS, fibromialgia, and various algid syndromes responded to DHEA as an add-on treatment due to its immunological enhancement properties and its psychostimulant properties No improvement was observed with cortisol inhibitors in major depression
Conclusions: Hormones or endocrine enhancers can boost or augment psychopharmacological action of traditional drugs in several psychiatric illnesses by direct action on the receptors involved or as an add-on effect on other organic systems related. When used adjunctively their action is boostered This paves the way to a new concept in the treatment of psychiatric illness, reconceptualised as psychoneuroimmunoendocrinologycal alterations

W-13-004
Hormonal Effects of Psychiatric Drugs

Raquel Teresa Zamora-Cabral
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Objectives: The aim of this part of the workshop is to discuss the adverse hormone effects of some drugs that the psychiatrics habitually prescribe.
Methods: Literature research using Medline and different clinical handbooks of psychotropic drugs.
Results: Prolactin level may be elevated as endocrine effects, that is habitually produced by neuroleptics or conventional antiypsychotics, some "second generation" antipsychotics, some antidepressant drugs. High prolactin levels may be associated with sexual side effects, menstrual disturbances, infertility, bone density reduction. In women breast engorgement, lactation, amenorrhea, menstrual irregularities, changes in libido. In men: gynecomastia, rarely galactorrhea, decreased libido and erectile or ejaculatory dysfunction. Disturbance in antiduretic hormone function (vasopresine), hyponatremia with polydipsia and polyuria, reported to occur in 6-20% of chronic patients using conventional antipsychotics. Risk increase in smokers and alcoholics. Hyperglycemia, glycosuria and high or prolonged glucose tolerance tests, especially with clozapine, but also reported with risperidone, quetiapine and olanzapine. Hyperlipidemia, increases in cholesterol and triglyceride levels, greatest increases seen with clozapine and olanzapine, ziprasidone reported to lower levels of cholesterol and triglycerides independent of changes in body mass index. Increase appetite and weight gain are habitual in patients receiving clozapine, olanzapine and others antypychotics drugs, lithium, some anticonvulsants (valproate), Some antidepressants (paroxetine, tricyclics) are associated to carbohydrate craving that may result in weight gain. Subclinical hypothyroidism (high TSH and normal free T4) found in 25% patients on lithium. Clinical hypothyroidism as a long term effect, may be more common in regio of high dietary iodine.
Conclusions: All clinic psychiatric may be informed about the endocrine effects of the psychotropic drugs for management if they appear in the patients.

W-02
New frontiers in partnerships for research – building friends, breaking barriers

W-02-001
Perspectives from private psychiatry

Rajesh Nagpal
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Objectives: Perspectives from the private sector The private sector, in India delivers 70% of the total mental health care. Traditionally, however, the only component is services with training in some pockets. Research with the exception of drug trials is uniformly sketchy. Biotechnology is the sunrise sector, private sector is also changing it's perspective and as a natural corollary, private sector now feels the need to be involved. The advantage of public private sector joint participation, is expansion of a more heterogeneous patient pool and cross pollination of ideas.
Conclusions: In this Indo US collaboration, the financing arm of the project (US) is cognizant of the need of adequate monetary compensation. Further, the project also envisaged capacity building, both factors have led to an enduring relationship

W-02-002
Bottlenecks to collaborative research

Smita Deshpande
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Conclusions: Bottlenecks to collaborative research It is difficult to carry out research in a setting not specifically geared to it. During the Nehruvian era, in the 60s, scientific research was separated from academics. Hence basic science received a setback. The same to some extent happened for basic and applied health research. Research and education became confined to the ivory towers of medical colleges, while most hospitals carried out clinical care. When we began background work to collect data on schizophrenia genetics in India in 1988, these were the bottlenecks we faced: 1. The idea of international collaborative research between previously untested individuals was new in the India-US context. 2. The hospital- patient care, with little or no medical education or students- was novel. 3. There were no ethical committees in place; they had never been needed in my hospital. Government regulations mandating for ethics committees in all hospitals had never been implemented. 4. The hospital had no staff with any research background. They found it strange that anyone wanted to carry out research at all! They thought basic research with no immediate benefits was of very limited or no use. 5. There was no trained research staff. 6. We were one of the first groups to root for subject payment for research participation. 7. The concept of private-public research partnerships- we approached all psychiatrists in Delhi for research subjects, notwithstanding their place or work- was new. We broke though mutual paranoia in this regard, and proved that private practitioners were fully alive to the importance of basic research in emerging psychiatric fields. A lot passion and personal effort and time were the keys to open this door and minimize the bottlenecks. Today we ourselves are facilitators for research in this hospital, where the atmosphere has changed totally. My talk will focus on these and other relevant issues.

W-02-003
University colleges & international research

Osama El-Boraie
Manobal Klinik, Psychiatry, New Delhi, Egypt

W-02-004
Satellite centers or transfer of technology? Developing competencies in middle income countries

Vishwajit Nimgaonkar
Manobal Klinik, Psychiatry, New Delhi, USA

Objectives: To describe enabling collaborations between centers
Conclusions: Vishwajit L Nimgaonkar, DPhil, MRCPsych; Professor of Psychiatry and Human Genetics, University of Pittsburgh School of Medicine, Pittsburgh PA, USA Our group is currently collaborating with eight US and three international groups as part of our research in psychiatric genetics. This work has been in progress for over seventeen years. It is focused on endophenotypes associated with schizophrenia and bipolar disorder. I will review the trials, tribulations and rewards of our work. The difficulties encountered include administrative burdens, funding difficulties, personality issues and cultural differences, as well as logistical issues such as time zone differences. These difficulties can be overcome with patience, persistence and good humor. The payoffs include multiplication of resources, tremendous leaning opportunities and the opportunities to test gene-environment interactions. The long term rewards are twofold: the excitement of scientific discovery and the gratification of training. I will share our experiences and offer lessons learnt during the course of this work.

W-05
The development of biological psychiatry in the developing world

W-05-001
Teaching and training of biological psychiatry in the developing world

Saroja Krishnaswamy
Penang Medical College, Department of Psychiatry, Malaysia

W-05-002
The progress of biological psychiatry in the asian subcontinent

Anu Kant Mital
Manobal Klinik, Psychiatry, New Delhi, India

W-07
Exploring mental disorders in evolutionary perspective

W-07-001
Is clinical neuroscience's brain evolutionarily informed?

Horacio Fabrega
University of Pittsburgh, School of Medicine, USA

W-07-002
Darwinian psychiatry as an antidote against medicalization of human diversity

Alfonso Troisi
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Objectives: Labeling a psychological or behavioral condition as sick may have serious individual and social consequences, including self-reproach and social stigmatization. During the past 2 decades, psychiatric epidemiological studies have contributed a rapidly growing body of empirical knowledge on the prevalence data for mental disorders. The implausibly high prevalence rates found by these studies have led to concerns about the validity of the current methods of psychiatric diagnosis and have reinvigorated the debate about the concept and definition of mental disorder. According to many, current methods of psychiatric diagnosis are overinclusive and produce a high number of false positive. In this paper, I discuss the concept of mental disorder from the perspective of Darwinian psychiatry.
Methods: According to Darwinian psychiatry, the validity of the conventional criteria of psychiatric morbidity is dependent on their association with functional impairment. Suffering, statistical deviance, and physical lesion are frequent correlates of mental disorders but, in absence of dysfunctional consequences, none of these criteria is sufficient for considering a psychological or behavioral condition as a psychiatric disorder.
Results: The Darwinian concept of mental disorder builds from two basic ideas: (1) the capacity to achieve biological goals is the best single attribute that characterizes mental health; and (2), the assessment of functional capacities cannot be properly made without consideration of the environment in which the individual lives. These two ideas reflect a concept of mental disorder that is both functional and ecological.
Conclusions: Redefining an undesirable condition as a normal variant is more than an academic exercise. Since a major contribution of Darwinian psychiatry is the insight that diversity and individual differences are core evolutionary features of any animal species, including Homo sapiens, the clinician should share such an information with the patient, not underestimating its reassuring and emancipating potential.

W-07-003
Gene-environment interaction in psychiatry: An evolutionary approach

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Objectives: In the last years gene environmental interaction studies have been of particular relevance in psychiatric genetics. The main idea of most of these studies is that there is an additive effect between genetic and environmental risk factors in the origin of mental illness. Interestingly long time ago evolutionary theory propose that the mechanism for evolutionary changes lies in genetically influenced variations in the adaptations of organism to their environment.
Methods: We present two longitudinal studies of gene environmental interaction. One related with post partum depression (N=1880) and other about the influence of mother genotype on infant (N=320) temperament.
Results: The same genotype ("s" allele in 5-HTTLPR) was a significant protective factor for post-partum depression but a risk factor for infant irritability.
Conclusions: We interpreted our results in the light of evolutionary theory. Our findings suggest that there are no 'bad' or 'good' genotypes, at least for common genetic variants (like 5-HTTLPR). Some genotypes might be "risk" or "protective" factors depending on the environmental conditions.

W-07-004
Exploring social brain dysfunction in evolutionary perspective

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Objectives: The term "social brain" has been coined as a metaphor for the way primate and human brains preferentially process information. It basically suggests that, during primate including human evolution, selection has operated on the recognition, processing and computation of social stimuli to maximise an individual's inclusive fitness, i.e. survival and reproductive success. Indeed, there is good evidence that brain enlargement in primates and humans emerged as a result of selection for social information processing. It is therefore intuitively plausible to propose that superior social information processing is associated with greater inclusive fitness, and that between-individual differences exist with regards to social cognition within populations. Contrariwise, one can assume that individuals with social ineptness may have such behavioural deficits because they are specifically impaired in social information processing rather than non-social information processing. In fact, such disorders of the "social brain" have been extensively discussed, above all with regards to autism and schizophrenia.
Methods: Survey of the existing literature.
Results: Both autism and schizophrenia are characterised by profound difficulties in social interaction and poor reproductive fitness, and impaired social cognition has repetitively been demonstrated in either disorder. Whether and how these deficits are compensated for by superior skills in other domains is still a matter of debate.
Conclusions: This controversy notwithstanding, we must not overlook the fact that we as clinicians and neuroscientists have an observational bias due to our own preferences for recognising social deficits. Thus, in a sense seeing mental illnesses as disorders of the "social brain" is perhaps too vague a concept as it seem to apply for virtually all kinds of psychological disturbances.

Young Scientists Award Session

YS-01
Brain Function

YS-01-001
Amygdala hyperactivity in social anxiety disorder induced by facial attractiveness

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Objectives: Various studies reported a hyperactivity of the amygdala within anxiety disorders during specific emotional stimulation with angry facial expressions [1]. The aim of this study was to assess whether this hyperactivity is also associated with facial attractiveness.
Methods: 28 healthy subjects (17 female), aged 27.5±7.1 (mean±SD) and 10 patients (1 female) aged 28.6±4.3 with social anxiety disorder underwent functional MRI. The visual paradigm introduced here comprised highly attractive and highly unattractive faces (stimuli rated by an independent group) with a neutral emotional expression where subjects were instructed simply to distinguish between both genders. Within this paradigm, parametric maps represent the signal change between faces of the *opposite* gender against baseline. For comparison, a well-established paradigm [2] was conducted, which consisted of a face-processing task matching emotional expressions (anger, fear, sadness, disgust, happiness) to a target expression. Differences between patient and control group were calculated by conducting an independent samples T-test in SPM5 separately for each paradigm.
Results: Amygdala hyperactivity in patients compared to healthy controls were more pronounced within the paradigm containing attractive and unattractive faces (Figure 1; hottest voxel left: t=4.67; right: t=4.35; both: p<0.0001 uncorrected, p<0.05 FDR) than for the one with the expression of facial emotions (left: t=2.86; right: t=2.46; both: p<0.01 uncorrected, not significant after FDR-correction).
Conclusions: To our best knowledge, this is the first study demonstrating an association of amygdala hyperactivity in anxiety disorders with processing of facial attractiveness. Moreover, the results suggest that this hyperactivity is even stronger within highly attractive and unattractive stimuli [3] compared to emotional expressions [1, 2]. To conclude, the amygdala might play a critical role in processing of arousing stimuli independent of valence.
References: [1] Stein et al., 2002. Arch Gen Psychiatry 59(11):1027-34. [2] Hariri et al., 2002. NeuroImage 17:317-23. [3] Winston, et al. 2007. Neuropsychologia 45:195-206.

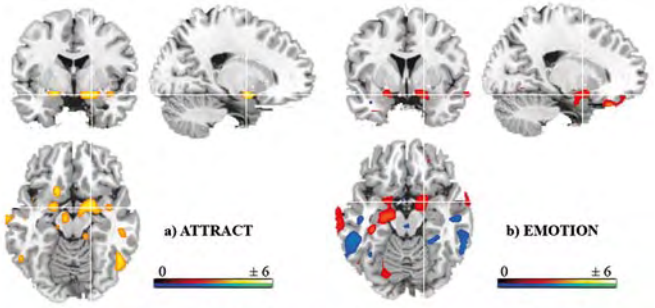

Figure 1: fMRI hyperactivity in social anxiety patients vs. healthy controls for the paradigm a) containing attractive and unattractive faces (t >3.33, p<0.001) and b) matching emotional expressions (t >1.69, p<0.05). Crosshair indicates right amygdala.

YS-01-002
Interleukin-6 is elevated in the cerebrospinal fluid of suicide attempters and related to symptom severity

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Objectives: Depressive disorders are associated with immune system alterations that can be detected in the blood. Cytokine concentrations in cerebrospinal fluid (CSF) and their relationship to aspects of suicidality have previously not been investigated. The aim of this study was to investigate associations between CSF levels of proinflammatory cytokines and multiple aspects of suicidality. We also analyzed the relationship between the cytokines, monoamine metabolites and psychiatric symptoms.
Methods: We measured Interleukin-1β, Interleukin-6 (IL-6), Interleukin-8, and Tumor necrosis factor-α (TNF-α) in CSF and plasma of suicide attempters (n=63) and healthy controls (n=47). Patients were classified according to diagnosis and violent or non-violent suicide attempt. We evaluated suicidal ideation and depressive symptoms using the Suicide Assessment Scale and the Montgomery – Åsberg Depression Rating Scale (MADRS). We also analyzed the relation between cytokines and monoamine metabolites 5-hydroxyindoleacetic acid (5-HIAA), homovanillic acid (HVA) and 3-methoxy-4-hydroxyphenylglycol (MHPG) in the CSF, as well as the integrity of the blood brain barrier as reflected by the CSF/serum albumin ratio.
Results: IL-6 in CSF was significantly higher in suicide attempters than in healthy controls. Patients who performed violent suicide attempts displayed the highest IL-6. Furthermore, there was a significant positive correlation between MADRS scores and CSF IL-6 levels in all patients. IL-6 and TNF-α correlated significantly with 5-HIAA and HVA in CSF, but not with MHPG. Cytokine levels in plasma and CSF were not associated, and patients with increased blood-brain barrier permeability did not exhibit elevated cytokine levels.
Conclusions: We propose a role for CSF IL-6 in the symptomatology of suicidal behavior, possibly via mechanisms involving alterations of dopamine and serotonin metabolism.

YS-01-003

Are atypical antipsychotics "fire extinguisher" in the brain? The effect of atypical antipsychotics on microglial activation induced by interferon-gamma in vitro

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Objectives: Microglia, a mediator of neuroinflammatory/neuroimmunological responses via the release of cytokines and free radicals such as nitric oxide (NO) and superoxide in the CNS, play an essential role in the pathology of neurodegenerative diseases such as Alzheimer's disease and Parkinson's disease. The pathology of schizophrenia remains unclear, while, recent brain-imaging studies have proved neurodegenerative processes such as volume loss and microglial activation in schizophrenia. Dopamine system dysfunction has been mainly hypothesized in schizophrenia, and D2 receptor (D2R) antagonism against dopamine neurons has been believed to the primary therapeutic target for schizophrenia. While, atypical antipsychotics (APDs) with multiple-receptor-affinity are becoming standard drugs for schizophrenia due to less adverse effects and more effectiveness for the negative symptoms of schizophrenia such as cognitive dysfunction.

Methods: We thus hypothesized that atypical APDs may have protective effects directly on microglia. Primary rat microglial cells and mouse 6-3 cells are used in this study. We investigated the effects of atypical APDs on the generation of NO and inflammatory cytokines such as tumor necrosis factor (TNF)-alfa by interferon-gamma-activated microglia in vitro. NO and cytokines were measured by Griess method and ELISA, respectively.

Results: Not only atypical APDs with D2R antagonism such as risperidone and quetiapine, but also aripiorazole, which is a new atypical APD with D2R partial agonism, significantly inhibited the release of NO and TNF-alpha from the interferon-gamma-activated microglia in vitro.

Conclusions: Atypical APDs revealed to have significant anti-inflammatory effects via the inhibition of microglial activation (Kato T et al: Schizophrenia Research 2007, Kato T et al: Journal of Neurochemistry 2008, Bian Q et al: Prog Neuropsychopharmacol Biol Psychiatry 2008). Atypical APDs may therefore have therapeutic effects on patients with schizophrenia by reducing the microglial inflammatory reactions, which has put forward a novel hypothesis beyond dopamine/neuron doctrine in the field of schizophrenia research.

YS-02
Genetics

YS-02-001
Interaction of psychological, neurocognitive and genetic risk factors in the background of suicidal behaviour

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Objectives: Many investigations identified social, psychological and environmental risk factors of suicide. Recently, neurobiological researches revealed the dysfunction of the ventromedial prefrontal cortex with the impairments of decision-making skills. In addition, these were associated with genetic variants of the serotonergic system. This ongoing study aimed to find an explanatory model of suicidal behaviour through the integration of the approaches above. Interactions between personality character traits, ventromedial cortex function and genetic polymorphisms were examined.
Methods: 30 suicide attempters (SA) and 28 controls received the Temperament and Character Inventory (TCI), Barratt Impulsivity Scale (BIS) and were asked to perform the computerized Iowa Gambling Task (IGT). Affective status was measured with the Beck Depression Inventory and the Hamilton D-17 Scale. Serotonin transporter, brain-derived neurotrophic factor, tryptophan hydroxylase and catechol-o-methyl-transferase gene variants were examined. Two-tailed t-test, Pearson correlation and - due to the small sample size - Kruskal-Wallis analysis was used to compare results and explore relationship between IGT performance, genetic and personality.
Results: SA scored higher on all BIS scales ($p<0.01$). Significant difference was measured on self-directedness, social deviance, harm avoidance ($p<0.001$), cooperation ($p=0.019$) and transcendence ($p=0.003$) scales of TCI. SA selected less advantageous desks on both reward and punishment sensitive tasks of IGT ($p<0.001$). In addition, punishment sensitivity correlated with novelty seeking in SA and self-directedness in controls. Planning impulsivity scores and serotonin transporter genotype were related in SA (Kruskal Wallis test=10.11, df=2, p= 0.006), but not in controls.
Conclusions: This study supports the notion that impairments of the ventromedial cortex play an important role in suicidal behavior. Furthermore, we demonstrated relation between this alteration and specific personality traits. Preliminary data about the genetic basis of these traits were also provided. Our investigation may constitute to an explanatory model of suicide which could help us to broaden our knowledge and develop new prevention strategies.

YS-02-002
Association of a serotonin receptor 2A gene polymorphism on cognitive function in early-onset schizophrenia and their unaffected relatives

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Objectives: To investigate the association between the T102C polymorphism on the 5-HT2A gene and cognition in individuals with early onset schizophrenia (EOS; onset of psychotic symptoms before the age of 18) and their relatives.

Methods: Fifty-three EOS probands and 117 of their first-degree relatives were examined on a comprehensive neuropsychological test battery. The Wechsler Memory Scale-Revised (WMS-R) and California Verbal Learning Test (CVLT) was used to measure memory function and verbal learning and recognition, respectively. Visual information processing was measured with the Span of apprehension test (SPAN). The degraded-stimulus continuous performance test (DS-CPT) was used to measure sustained attention. Executive function was measured using the Wisconsin card sorting test. The Structured Clinical Interview yielded four diagnostic groups: EOS probands; relatives with Mood Disorders; Other Axis I diagnoses; and no Axis I diagnosis (healthy relatives). Analysis of co-variance was performed, with diagnostic status and genotype as fixed factors and age as covariate.
Results: Results showed a significant main effect of genotype in which individuals with the rs6313 CC genotype had poorer memory performance on all composite WMS-R indices than those with either TC or TT genotypes [P=0.01]. A differential effect of 5-HT2A variants was found on verbal learning and recognition, in which rs6313 TT homozygozity produced a greater number of perseverations than the CC genotype [P=0.04]. There was no effect of genotype on any executive function measures [P=0.42]. In the SPAN alone, there was a significant effect of genotype whereby homozygotes with the rs6313 C allele produced fewer correct responses and more false alarms than heterozygotes with the rs6313 T allele [P=0.04].
Conclusions: The findings of our study suggest that the rs6313 C allele, which has been associated with measures of clinical severity in schizophrenia, may impact on specific cognitive processes in individuals with genetic predisposition to schizophrenia regardless of diagnosis.

YS-02-003
A genetic modifier of human aggression and anger control

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Objectives: Monaminergic neuromodulation, particularly via noradrenaline, dopamine and serotonin, has been associated with aggressive behavior in animals and humans. Monoamines in the human brain activate G-protein-coupled receptors (GPCRs), which in turn exert relatively long-lasting effects on neuronal mechanisms.
Methods: Here we investigated the influence of a common genetic variation in a postsynaptic adapter molecule involved in GPCR signaling on human aggression and anger traits in a cohort of 532 young, healthy participants. We further investigated the effects of the polymorphism on emotional capture of attention, using event-related functional magnetic resonance imaging (fMRI) while subjects performed a modified version of the Eriksen flanker task with task-irrelevant emotional background pictures (angry faces). Immunohistochemistry was used to assess the distribution of the corresponding protein in the human brain.
Results: In the Buss and Perry Aggression Questionnaire (BPAQ), carriers of the rare allele scored significantly lower in physical aggression. Carriers of this variant also had significantly higher scores in the anger control dimension of the State-Trait Anger Expression Inventory (STAXI). In the fMRI study, carriers of the rare variant showed significantly higher activation of the dorsal anterior cingulate (dACC) in the high interference condition with emotional distracters, which in turn predicted shorter reaction times. Immunohistochemical investigations revealed that the corresponding gene product is expressed at high levels in human dACC neurons.
Conclusions: Taken together, we could demonstrate that the rare variant was associated with both lower physical aggression and higher control of anger as indexed by self-report measures and fMRI during emotional interference. More generally, our results suggest that human aggression and anger might be modulated by genetic variations not only in the molecules directly related to monoaminergic signaling, but also by polymorphic variants of interacting intracellular signaling molecules.

YS-03
Psychotic Disorders I

YS-03-001
Plasmatic Glutathione levels and their relationships with clinical and therapeutic features in schizophrenic patients

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Objectives: Altered glutathione (GSH) systems are suggested to participate in the pathophysiology of schizophrenia. The aims of this study were to determine plasma glutathione levels in patients with schizophrenia compared to healthy controls and to examine the relationships between glutathione levels and clinical and therapeutic features of schizophrenic patients
Methods: It was a case-control study carried out on eighty-eight patients with schizophrenia according to DSM-IV-TR criteria (58 men and 30 women, mean age= 30.8 ± 8.25 years) and forty six healthy control subjects (32 men and 14 women, mean age =29.7 ± 5.23 years). All patients were assessed by Clinical Global Impressions-severity (CGI-severity) and Global Assessment of Functioning (EGF). The most of patients (60%) were under first-generation antipsychotics with a mean daily dosage of 403 ± 205 mg Chlorpromazine equivalents. Forty percent of patients were antipsychotic-free for at least three months prior to the study. Plasmatic glutathione levels (total glutathione GSHt, reduced glutathione GSHr, oxidized glutathione GSSG) were determined by spectrophotometry. Statistical analyses were carried out as appropriate using SPSS.11. for Windows.
Results: GSHt and GSHr levels were significantly lower in schizophrenic patients than in controls with respectively p= 0.003 and p=0.001. A positive correlation was found between age of disease onset and GSHt and GSHr levels. No correlation was observed between GSH levels and both clinical sub types of schizophrenia and EGF-scores. However, GSHt and GSHr levels were inversely correlated with CGI-severity scores. According to therapeutic status, there were no significant differences concerning GSH levels. In addition, there was no correlation between GSH levels and daily dosage of neuroleptic treatments in medicated schizophrenic patients
Conclusions: These findings suggest that decrease in glutathione levels in patients with schizophrenia is not related to neuroleptic treatments and could be used as biological markers of severity of schizophrenia symptoms.

YS-03-002
What can the N170 tell us about face processing in schizotypy?

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Objectives: Deficits in facial affect discrimination in schizophrenia may reflect inadequate configural processing. It has been proposed that the event-related potential (ERP) known as the N170 reflects the process of encoding facial information to form a structural representation. We investigated whether configural processing was behaviourally and/or neurophysiologically different in persons with high schizotypy.
Methods: Healthy individuals (N = 28) were assigned to either high or low schizotypy extremes defined by the Oxford Liverpool Inventory of Feelings and Experiences (O:LIFE; Mason, Claridge & Jackson, 1995). Two stimulus types were presented in both an upright and inverted orientation; Mooney stimuli (configural information only), and photographic stimuli (both featural and configural). These were compared with non-face stimuli and participants were required to make face/non-face judgements. N170 latency and amplitude were submitted to separate repeated measures analysis of variance with the following within subject factors; orientation (two levels, upright and inverted), hemisphere (two levels, left and right), and electrode (three levels, P7/P8, PO7/PO8, CB1/CB2). Group sizes were too small to detect differences. Correlations of the O-LIFE scores with amplitudes for each electrode were then run.
Results: Accuracy and reaction times did not differentiate the schizotypy groups, however O-LIFE scores correlated significantly with N170 amplitudes ($p < .05$). Assessment of group waveforms revealed that high schizotypy showed a trend for reduced N170 amplitudes to both face orientations, relative to the low group.
Conclusions: Reduced amplitudes in high schizotypy indicate impoverished facial information during face processing. Face processing impairment in schizophrenia may instead be attributable to a global reduction in the quality and/or quantity of fine detailed information. Determining the aetiology of face processing deficits will have a significant impact on the management of social distress experienced in schizophrenia, and subsequent treatments may help to reduce delusions of a social/persecutory nature.

YS-03-003
Identification of novel Clozapine interactions with the Phosphatidyl Inositol 3-Kinase (PI3K)/Insulin signaling pathway in a Caenorhabditis elegans model system

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Objectives: Clozapine has superior therapeutic efficacy and a unique side effect profile as an antipsychotic agent, but the mediators of these effects are not known. We used C. elegans as a model system to identify previously undiscovered mechanisms of drug action. C. elegans provides a versatile system that can be used to identify novel targets and pathways modulated by psychoactive drugs, as many gene systems of interest in psychiatric illnesses are conserved between C. elegans and mammals.
Methods: We studied behavioral and developmental effects of clozapine in C. elegans vis-à-vis other antipsychotics to discover clozapine-specific phenotypes. We then screened for mutant worms that suppressed the clozapine-specific effects in order to dissect pathways modulating clozapine's effects on these phenotypes.
Results: We observed that clozapine, but not other typical or atypical antipsychotic drug tested, induced developmental arrest in early larval stages in C. elegans in a dose-dependent manner. Experiments with mutants deficient in neurotransmitter biosynthetic pathways showed that clozapine-induced larval arrest was not dependent on dopaminergic or serotonergic systems. We discovered that age-1 mutants, which have a mutation in the gene coding for phosphatidyl inositol 3-kinase (PI3K), suppressed clozapine-induced larval arrest, and these mutant worms continued to develop onto adulthood. We studied the nuclear/cytoplasmic localization of the transcription factor DAF-16, which is the downstream effector in the PI3K/insulin signaling pathway. DAF-16 localization studies indicated that clozapine-induced larval arrest results in activation of the insulin signaling pathway.
Conclusions: We discovered that clozapine has unique interactions with the PI3K/insulin signaling pathway in C. elegans. This is intriguing in the context of recent human genetic studies pointing to an association between the PI3K target AKT-1 and schizophrenia. Our findings of a drug-specific novel interaction between clozapine and the PI3K pathway in C. elegans holds important implications for understanding the unique therapeutic and/or side effects of clozapine in humans.

YS-04
Other

YS-04-001
Affective symptoms and body mass index (BMI): A life course approach

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Objectives: The association between depression and obesity became a focus of research interest due to the rapidly increasing prevalence of both disorders in children and adults. However, there is lack of information about this relationship across the life course. We investigate the association of longitudinal profiles of affective symptoms with BMI trajectories.
Methods: We use data from the MRC National Survey of Health and Development, a 1946 birth cohort (Wadsworth et al, 2003). We applied multilevel random-coefficient models for longitudinal data with BMI (age 15-53) as the outcome. Longitudinal profiles of depression and anxiety symptoms, previously derived using latent class analysis (Colman et al, 2007), were used. Four affective symptoms profiles were considered: absence of symptoms (n=2038), repeated symptoms with adolescent onset (n=1596), adolescent-onset symptoms with good adult outcome (n=269) and adult-onset repeated symptoms (n=656).
Results: Men with adolescence-onset affective symptoms had significantly lower BMI over all ages compared to those with an absence of symptoms ("control" group). This association was largely explained by their lower BMI at age 11. After adjusting for BMI at age 11 and childhood socioeconomic position, women with adolescent-onset symptoms with good adult outcome had lower BMI at age 15 and a greater rate of BMI increase over the life course than controls. This resulted in them having higher BMI than the controls by age 53 years. A similar pattern was seen for women with repeated symptoms with adolescent onset although there increase in BMI was only slightly faster than controls. Those with adult-onset symptoms did not have significantly different BMI compared with controls at any age in either men or women.
Conclusions: There is no evidence that affective symptoms are associated with obesity. The association of affective symptoms with BMI varied across the life course and depends on gender and age of onset of symptoms.

YS-04-002
Mental disorders and suicidal ideation in primary care patients

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Objectives: To evaluate the prevalence and relationship of mental disorders with suicidal ideation in primary care patients
Methods: All adult patients consecutively admitted to the primary medical care center during one month period were asked to participate in the study.502 patients, 135 (27%) men and 367 (73%) women, were included in the study. Patients were evaluated for mental disorders twice, first time by family physician (FP) and the second time by trained investigator, using standard instrument, Mini International Neuropsychiatric Interview (MINI).
Results: Mood and anxiety disorders were diagnosed for 14.3% of patients by FP and for 36%, using M.I.N.I. ($p<0.001$). According to the MINI, depression was diagnosed for 22.4% vs. 3.8% of patients, diagnosed by FP ($p<0.001$); anxiety disorders, 29.1% vs. 3.8%, respectively ($p<0.001$). FP has not recognized suicide ideation in any patients, when using MINI suicidal ideation was found in 3.8% of patients. We found no significant gender differences in suicide ideation. However, suicide ideation was associated with MINI diagnoses of depression and Post-traumatic stress disorder.
Conclusions: The results of this study indicate that FPs recognize only minority of patients with mood and anxiety disorders, and suicide ideation is hardly identified at all. Depression and Post-traumatic stress disorder are significant risk factors for suicide ideation in primary care patients.

YS-04-003
Emotional interference in obsessive-compulsive disorder: A neuropsychological study using optimized emotional stroop test

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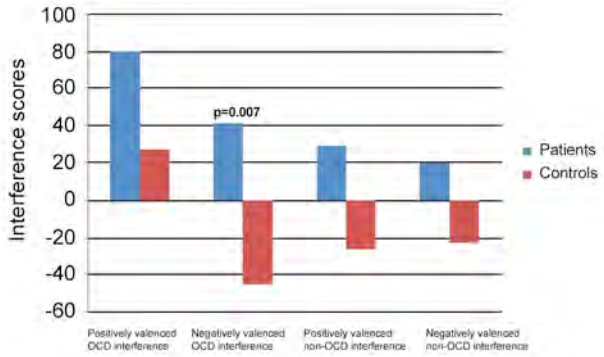
Objectives: Evidence for emotion and attention processing abnormalities in Obsessive-compulsive disorder (OCD) using emotional stroop test is equivocal. Some of these discrepancies could be due to methodological issues, mainly differences in lexical characters of words which potentially influence word processing speed and smaller sample size. In addition, potential effect of symptom status and subtype of OCD on emotion and attention processing are yet to be explored systematically. We aimed to study emotional interference in obsessive compulsive disorder using an optimized emotional stroop test.
Methods: We for the first time examined a large sample of OCD patients (both symptomatic and remitted) using a methodologically superior optimized version of emotional stroop test. We optimized the test by matching the words on all lexical characters namely length, frequency, orthographic neighborhood and used a complete automated test administration. Color stroop test was also administered to examine color word interference. 50 patients satisfying DSM-IV criteria for OCD (23 washers and 27 checkers; 24 symptomatic and 26 remitted) and 50 age, handedness and sex matched healthy controls were examined.
Results: OCD patients as a group had significantly higher 'negatively valenced OCD interference score' ($t=2.764$; $p=0.007$) but did not differ in other emotional interference scores. A novel finding of the study was only symptomatic patients had significantly higher negatively valenced OCD interference score ($p=0.009$), but not remitted patients in comparison to controls. Checkers had a significantly higher color-word interference score than healthy controls ($t=2.01$; $p=0.05$), but washers did not differ. There were no significant correlations between other illness related variables (age at onset, illness duration, medication dose) and stroop test performance.
Conclusions: Study findings suggest presence of selective emotional bias for OCD-relevant stimuli in these patients. This bias is a potential state marker (i.e., related to symptomatic status). The observations are in tune with the threat relatedness hypothesis.



OTHER - Young Scientists Award Session

YS-04-004

Deficits in implicit but not explicit reversal learning indexed by novel tasks in patients with obsessive-compulsive disorder

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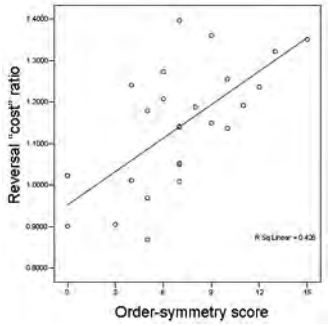
Objectives: To determine whether patients with Obsessive-Compulsive Disorder (OCD) show deficits in reversal learning and set-shifting using tasks that assess implicit and explicit learning mechanisms, and to explore relationships between performance and OCD symptom dimensions.
Methods: 27 patients with OCD recruited from a hospital in-patient unit and a community support group, and 27 matched healthy controls completed a clinical interview and questionnaires, followed by computerised tests measuring reversal learning and set-shifting. Explicit learning was examined using the Concept Formation Task (Oades, 1997) with sequential stages examining errors-to-criterion for reversal, intra- and extra-dimensional shifts. A more implicit form of reversal learning was measured using a novel cued target detection task based on a validated learned irrelevance paradigm (Young et al., 2005). Here, reversal learning was indexed by a reaction time 'cost' to detect targets in reversal, relative to acquisition, blocks. Both the explicit and implicit learning tasks had variants composed of neutral stimuli, and salient affective stimuli. Data were compared between groups using ANOVA, and relationships with OCD symptoms (measured using the D-YBOCS and OCI-R) were explored using correlations and multiple regressions.
Results: OCD patients showed poorer reversal learning than controls on the more implicit, but not explicit, task (group difference in reversal 'cost' $F(1,53) = 4.5$, $p < 0.05$). This deficit was strongly associated with order-symmetry symptoms in OCD patients ($r = 0.65$, $p < 0.001$; figure), even when controlling for other clinical and demographic factors. OCD patients also showed poorer extra-dimensional set-shifting than controls in the explicit task ($F(1, 52) = 6.32$, $p < 0.05$) but this did not correlate with any variables. Significant effects were limited to the task variants involving salient, affective stimuli.
Conclusions: These data reveal task-specific deficits in cognitive flexibility in OCD patients that are partly related to order-symmetry symptoms, and may provide promising endophenotype measures.



YS-05
Psychotic Disorders II

YS-05-001
Spatial reference in schizophrenia

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Objectives: The capacity to adapt different viewpoints in space allows seeing the world through the eyes of others. Self-disturbances in schizophrenia might be the result of a perturbed capacity to adopt a non-egocentric point-of-view.
Methods: We tested 24 chronic schizophrenic patients (SZ) (DSM-IV) and 25 healthy controls (C) matched for age and years of study in a visual viewpoint changing task. Participants had to adopt a viewer-center (egocentric), an object- or a landmark-centered (both allocentric) perspective estimating distances of two trash cans to oneself, a ball, or a palace.
Results: We found that reaction time (RT; t(47)=1.664; p=.11) and RT-decrease associated with task progression (r's>.50; p's<.01) was similar in the egocentric condition in both groups. Patients showed significantly increased RT in the object- (t(47)=2.430;p=.02) and landmark-centered condition (t(47)=2.091;p=.04) without RT improvement associated with task progression (p's>.15). Finally, switch cost was elevated in patients when changing from the egocentric to the landmark condition, while it was diminished when changing from the landmark to the egocentric condition (p's<.015). In fact, patients did not benefit from the non-switch landmark-centered condition as did controls (tC(24)=-3.375;pC=.0003;tSZ(24)=-1.056;pSZ=.302).
Conclusions: The results implicate that schizophrenia patients' adoption of an egocentric perspective is preserved. However, adopting an allocentric point of view and switching between egocentric and landmark-centered perspective are impaired. Distinguishing between ego- and allocentric space allows to associate patients' deficits in visuo-spatial and theory-of-mind tasks with spatial perspective taking deficits. Patients fail to accomplish an efficient transfer between different referential systems and instead maintain a more costly egocentric visuo-spatial position that might lead to deficits in self-experience, as well as social and empathic functioning.

YS-05-002
Schizophrenia: GSK-3ß and PLA2 dysregulation

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Nádia Raposo

Objectives: Evidence suggests that GSK-3β and PLA2 bears a close relation with the neurodevelopmental hypothesis for schizophrenia, which is an extremely disabling psychiatric disease. Reduced levels of GSK-3 β and increased PLA2 activity were found in schizophrenia. In this study we investigated the levels of pGSK-3β and GSK-3β (by ELISA) and PLA2 activity (by radioenzymatic assay) in platelets of schizophrenic patients.
Methods: The study was performed at the Department and Institute of Psychiatry of the University of São Paulo. The sample comprises of 14 drug naïve schizophrenic patients (age 30.5±9.3 years) and 20 healthy individuals (age 28.5±9.0 years). Schizophrenic patients were diagnosed using the Structural Clinical Interview for DSM-IV. All patients were reevaluated after 8 weeks under treatment with olanzapine (mean daily doses of 9.5±7.5 mg).
Results: It was found that platelets of schizophrenic patients had a 40% reduction in the levels of pGSK-3β and GSK-3β compared with the control one, this reduction is accompanied by high PLA2 activity (36% higher than control subjects). After 8 weeks on antipsychotic treatment, olanzapine promoted a substantial increase (80±20%) in pGSK3β in platelets of schizophrenic patients and PLA2 activity was reduced (355±115 before, 267±39 after, p=0.001).
Conclusions: Thus, these findings suggest that GSK-3 β and PLA2 dysregulation are crucial to Schizophrenia and that platelets may be useful to quantify these altered biomarkers and one of the greatest advantages is that it does not require brain biopsies.

YS-05-003
Delusions in bipolar disorder: Similarities and differences with schizophrenia

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Objectives: Delusions are common during acute psychotic periods in both schizophrenia and bipolar disorder. There has, however, been little research on the phenomenology of delusional beliefs in bipolar disorder, other than investigations that have suggested that delusional beliefs are more likely to be mood-congruent in bipolar disorder. This study sought to examine the phenomenology of delusions in bipolar disorder, specifically whether there were differences in severity, frequency and types of delusion experienced in bipolar disorder. Further, what differences exist between those currently experiencing delusions and those whom have experienced them in the past.
Methods: 40 patients with bipolar disorder, 54 schizophrenia patients and 44 healthy controls were administered the Peters Delusional Inventory (PDI), a 21 item questionnaire examining the endorsement rates of a range of delusional beliefs. Preoccupation, distress and convictional intensity were also recorded for each endorsed item. Additionally a full SCID interview was administered to the patients to obtain their other symptom characteristics.
Results: Acutely psychotic schizophrenia patients and bipolar patients endorsed the same number of delusional beliefs, and were equally distressed and preoccupied by them. Interesting when delusions subsided in bipolar disorder they were no longer convinced their delusional ideas were true, where this was not the case in schizophrenia who continued to show high conviction levels.
Conclusions: This study provides descriptive data regarding cross section frequency and phenomenological characteristics of delusions in bipolar disorder. Despite similarities to schizophrenia when acutely unwell, bipolar patients achieve better symptom remission.

Free Communications

FC-01
Affective Disorders (Unipolar) I

FC-01-001
The effect of cortisol suppression on emotionasl stress responses in depressives and controls

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Objectives: Since Piazza & Le Moal (1996) had demonstrated the mediating role of cortisol on motivational behaviour in drug addicted animals, the question was raised if the release of cortisol in stress conditions is also the mediator of psychological stress responses.Since depressives are known to have blunted cortisol responses to stress accompanied by higher emotional stress sensitivity and since smoking is used by them to modify stress responses, the present study investigated the effects of cortisol suppression on emotional stress responses before and after smoking in depressive and non-depressive smokers.
Methods: 80 male smokers divided according to questionnaire scores into high and low depressives were subjected to one of the 4 combinations of stress +/- and cortisol suppression +/-. Stress was induced by a task of public videotaped arithmetics performance and cortisol suppression was achieved by 1000 mg (4 dosages) of metyrapone. versus placebo After the stressor they were allowed to smoke two cigarettes. Plasma cortisol and questionnaire based emotional responses were recorded four times during a 4 hour experiment
Results: Results obtained by three-factorial analyses of variance revealed that metyrapone successfully reduced cortisol levels and stress responses and prevented the drop in wakefulness seen with placebo. After smoking subjects felt more alert in the metyrapone than in the placebo group. Interactions between drug, stress and depression revealed that in depressives cortisol blockade combined with smoking could counteract their higher stress induced emotional arousal and drop in wakefulness
Conclusions: It must be concluded that cortisol suppression has a beneficial effect on activation possibly due to an antagonism of cortisol to noradrenergic cortically arousing processes. In depressives the beneficial effect of smoking on alertness could not counteract stress induced exhaustion. However, again,cortisol suppression helped to restore activation indicating the mediator role of cortisol with a possibly inverted u- shaped function for subjective activation.

FC-01-002
Cortical inhibitory deficits in major depressive disorder

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Objectives: Several lines of evidence suggest that major depressive disorder is associated with deficits in γ-aminobutyric acid (GABA) inhibitory neurotransmission. Cortical inhibition represents a neurophysiological process in which GABAergic inhibitory interneurons selectively attenuate the activity of other neurons in the cortex. Transcranial magnetic stimulation represents a noninvasive technique to measure cortical inhibition. Objective: To measure cortical inhibition in medicated patients with treatment resistant major depressive disorder, unmedicated patients with major depressive disorder and medicated euthymic patients with a history of major depressive disorder and compare them to healthy subjects. It was hypothesized that patients with major depressive disorder would demonstrate inhibitory deficits compared to healthy subjects and that symptom severity would be related to inhibitory deficits.
Methods: Cortical inhibition was measured using transcranial magnetic stimulation paradigms known as short interval cortical inhibition and the cortical silent period, which index GABAA and GABAB receptor mediated inhibitory neurotransmission, respectively. All of the participants were recruited and evaluated at the Centre for Addiction and Mental Health. 25 patients with TRD, 16 unmedicated patients with major depressive disorder, 12 medicated euthymic patients with previous major depressive disorder (i.e., HAMD17<8) and 25 healthy subjects were enrolled.
Results: All major depressive disorder patient groups demonstrated significant cortical silent period deficits compared to healthy subjects. By contrast, only treatment-resistant depressed patients demonstrated significant deficits in short-interval cortical inhibition compared to healthy subjects, medicated euthymic major depressive disorder patients and unmedicated major depressive disorder patients. Further, across all major depressive disorder patients there was significant correlation between short-interval cortical inhibitory deficits and the severity of depressive symptoms.
Conclusions: Our findings suggest that GABAB neurophysiological deficits are closely related to pathophysiology of major depressive disorder. Our findings also suggest that more severe illness is selectively associated with GABAA receptor mediated inhibitory deficits.

AFFECTIVE DISORDERS (UNIPOLAR) - Free Communications

FC-01-003

Increased self-focus in major depressive disorder is related to neural abnormalities in subcortical-cortical midline structures

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Objectives: Patients with major depressive disorder often show a tendency to strongly introspect and reflect upon their self which has been described as increased self-focus. While subcortical-cortical midline structures have been suggested to mediate the "core self" in healthy subjects, the neural correlates of the abnormally increased self-focus in MDD remain unclear. The aim of the study was therefore to investigate the neural correlates during judgment of self-relatedness of positive and negative emotional stimuli.
Methods: Using fMRI, we investigated 27 acute MDD patients and compared them with healthy subjects employing a paradigm that focused on judgment of self-relatedness as compared to mere perception of the very same emotional stimuli.
Results: Behaviourally, MDD patients showed significantly higher degrees of self-relatedness of specifically negative emotional stimuli when compared to healthy subjects. Neurally, MDD patients showed significantly lower signal changes in various subcortical and cortical midline regions like the dorsomedial prefrontal cortex (DMPFC), supragenual anterior cingulate cortex (SACC), precuneus, ventral striatum (VS) and the dorsomedial thalamus (DMT). Signal changes in the DMPFC correlated with depression severity and hopelessness while those in the VS and the DMT were related to judgment of self-relatedness of negative emotional stimuli.
Conclusions: In conclusion, we here present first evidence that the abnormally increased self-focus in MDD might be mediated by altered neural activity in subcortical-cortical midline structures.

FC-01-004

Altered negative bold responses in the default-mode network during emotion processing in depressed subjects

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Objectives: Studies using functional magnetic resonance imaging (fMRI) show predominant negative blood oxygenation level-dependent (BOLD) responses (NBRs) in regions of the default-mode network such as the pregenual anterior cingulate cortex, the ventromedial prefrontal cortex, and the posterior cingulate cortex. Patients with major depressive disorder (MDD) show emotional-cognitive disturbances, which have been associated with alterations within the default-mode network. However, it remains unclear whether these default-mode network alterations are related to abnormalities in NBRs.
Methods: Using an event-related fMRI design we investigated neural activity in the default-mode network during different emotional tasks in patients with MDD.
Results: MDD patients showed significantly reduced NBRs in several regions of the default-mode network. Decreased NBRs in MDD patients correlated with depression severity and feelings of hopelessness.
Conclusions: Findings demonstrate that default-mode network NBRs are reduced in MDD and modulate these patients' abnormally negative emotions.

FC-02
Other I

FC-02-001
Thai psychiatrists views on ICD-10, DSM -IV, and biological aspects of psychiatry

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Objectives: Background:The Thai Ministry of Public Health request psychiatrists give coded diagnoses for their patients' disorders according to the International Classification of Diseases (ICD). The current version used is the ICD-10 TM (Thai Modification). However, the classification system of the American Psychiatric Association (DSM-IV) is also popular, and frequently used nationwide.
To survey the opinions of Thai psychiatrists toward the current classification systems used, both the ICD-10 and DSM-IV
Methods: A questionnaire, adapted from that of Prof. G Mellsop et al. was sent by post to members of the Psychiatric Association of Thailand.
Results: A total of 84 questionnaires were returned and completed for the first round of the survey. Those respondents who routinely used DSM-IV Axis I was 86.9% while those who routinely used ICD-10 was only 52.4%. A multi axial approach of DSM-IV was less routinely used from Axis I to Axis V, the percentage of respondents was 86.9, 59.5, 52.4, 33.3 and 29.8, respectively. Respondents' first choices for the purposes of a classification system were "as a reliable inter-clinician communication tool" (33.3%), "to facilitate clinician and service user communication" (31.0%), and "to inform the service user/patient management plans" (20.2%). Most respondents (81%) viewed the current classification as not over-embedding European derived cultural concepts or values and 68% did not agree that where clinician were of different cultures the current classifications were unreliable or inappropriate. Regarding the biological aspects of psychiatry, most respondents viewed the classification as not helping them to differentiate between disorders that did or did not need biological treatment and most mental illnesses usually deserved a combination of both biological and psychological interventions.
Conclusions: Thai psychiatrists' views are consistent with colleagues from New Zealand, Singapore, Malaysia and Indonesia. However, from a cultural point of view more Thai psychiatrists felt that the systems were universally useful than did their New Zealand counterparts.

FC-02-002
Human imprinting and oral tactile fixation on a decoy

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Objectives: To analyze past theories of causality of thumb and dummy sucking and to propose and find evidence for a more logical explanation for the emotional oral tactile sucking fixation on thumbs or dummies in early infancy.
Methods: By literature search over a 30 year period evidence for the proposal of the existence of human imprinting has been sought. Dissemination of the proposal of human imprinting and its evidence is thus undertaken for the purpose of seeking contrary argument or evidence.
Results: Across the mammalian spectrum there is evidence for fixated oral tactile sucking on nipple decoy objects when there has been maternal deprivation in early infancy. Only those mammals who have the benefit of human intervention in the presence of an inanimate decoy usage or self imprint decoy will survive.
Conclusions: Infants exhibit great emotional distress when their fixated sucking comfort object is not available and as Lorenz noted in his search for visual mammalian imprinting, replacement fixated sucking objects are at first rejected and there is great emotional distress before a switch is achieved. Freudian displacement behaviour is thus supported but it is not a sucking need as only the fixated object at any one time suffices. Other mammals being more flexible have more choice than human newborn and will use tail, penis or the genitalia or ears of other grouped newborn, such as happens in the cattle industry. Hunger is rejected as a causality as infants non-nutritively suck after feeds, when they are distressed and preceding sleep. Thumbsucking is unkown or rare in cultures where the breast remains uncovered.

FC-02-003
Gray matter changes in adolescents with Anorexia Nervosa restrictive type: A Voxel-Based-Morphometry study

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Objectives: A limited number of studies have used Voxel-Based Morphometry (VBM) to examine brain structure in patients with Anorexia Nervosa. The purpose of the present study was to investigate gray matter changes in a sample of Anorexia Nervosa restrictive type (AN-r) adolescent patients in the early stages of the illness, using VBM.
Methods: Participants were 18 AN-r female patients (without any other psychiatric disorders) whose AN-r had been in progress for less than 12 months and 18 age-matched healthy female control subjects. All subjects were scanned using a high-resolution T1-weighted magnetic resonance imaging (MRI) sequence. Images were preprocessed with the software package SPM2 according to the optimized VBM method, and statistically analyzed. An analysis of global and local GM volumes was performed in order to assess any significant difference between both groups.
Results: The analyses yielded a significant global GM decrease in the AN-r patients; furthermore, a significant region-specific decrease in GM volume was found in the left and right middle cingulate cortex, the left and right precuneus, and the left and right inferior and superior parietal lobules.
Conclusions: The findings revealed a global GM decrease and a precocious bilateral GM decrease in the middle cingulate cortex, precuneus, inferior and superior parietal lobules among AN-r adolescent patients. These findings suggest that there might be a region-specific GM vulnerability in these areas and that they could be involved in the pathophysiology of AN-r. Given that these regions are also involved in the manipulation of mental images and mental representation of the self, this might explain the presence of a distorted body image in such patients. Further research is necessary in order to confirm these results, and to identify the causes, specific roles, and consequences of such structural modifications.

FC-02-004
Enhancing the clinical utility of testing for drug metabolising enzyme (dme) status in real world psychiatric settings

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Objectives: To consider ways to enhance the clinical utility of testing for drug metabolising enzyme (dme) status in real world psychiatric settings.
Methods: The cytochrome P450 2D6 activity of patients who were being prescribed risperidone was made available to clinicians in Mental Health Services in the Auckland region. Along with the actual genotype a description was given as to the likely impact of this genotype on enzyme activity and consequent blood levels of the drug. The impact on prescribing behaviour was assessed by both quantitative (doses used) and qualitative (how useful the clinician thought the test was).
Results: Though clinicians believed that it was useful to receive this information regarding the likely drug metabolism of the patient the dosage data did not support this with a non-significant difference between those who had normal metabolism compared to those who had reduced rates of metabolism. Twenty percent of the sample of 97 patients had dme status that was other than "normal" (extensive).
Conclusions: This study confirms views expressed regarding the necessary and sufficient criteria to achieve change in the prescribing behaviour of clinicians, namely that just making a test result available will not have the desired effect. This paper will expand on system issues that are likely determinants, including the design of and access methods for laboratory test information (both electronically and in paper form), the attitudes of clinicians to screening tests, the fragmentation of care systems and presence of multiple decision makers, and the conservative nature of medical practitioners. The number of subjects with other than expected dme status would suggest that there is definite benefit that could accrue from the regular use of such assay. Finding ways to incorporate that into standard practice is a substantial challenge for psychiatric practice.

OTHER - Free Communications

FC-02-005

Changes of affinity of autoantibodies against alpha-melanocyte-stimulating hormone are involved in the mechanisms of anorexia nervosa and bulimia

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Objectives: α-Melanocyte-stimulating hormone (α-MSH) is a key molecule signaling satiety. Autoantibodies (autoAbs) directed against α-MSH have been identified in humans, while their levels were associated with psychopathological traits in anorexia nervosa and bulimia. Furthermore, an increase in affinity of α-MSH autoAbs in a rat model of repeated mild stress was associated with a switch of the functional role of α-MSH autoAbs from an agonist to antagonist of α-MSH-mediated satiety and anxiety. In the present work, we tested our hypothesis that affinity of α-MSH autoAbs can be altered in anorexia nervosa or in bulimia which might be responsible for differential alteration of appetite in these two forms of eating disorders.
Methods: Total IgG and IgM were isolated from sera samples of patients with anorexia nervosa restrictive type, bulimia or healthy controls. Affinity of IgG and IgM autoAbs for α-MSH was measured using BIAcore equipment. Effect of IgG autoAbs to affect binding of α-MSH-I125 to melanocortin MC4 receptors was studied in transfected cos-7 cells. To determine the effect of α-MSH autoAbs on feeding and anxiety, we developed a rat model of passive transfer of affinity purified IgG α-MSH autoAbs from patients with anorexia or bulimia into the hypothalamus of rats.
Results: An increased affinity of IgG autoAbs for α-MSH was found in subjects with bulimia, while affinity of IgM autoAbs was lower in both anorexia nervosa and bulimia vs. healthy controls. AutoAbs of higher but not of lower affinity were able to block α-MSH-I125 binding on MC4 receptors. Passive transfer of high or low affinity α-MSH autoAbs into the rat hypothalamus resulted in increased and decreased food intake and body weight, respectively, and reduced anxiety in both groups.
Conclusions: These results provide the first evidence that pathological changes in affinity of α-MSH autoAbs may underlie biological mechanisms of anorexia nervosa and bulimia.

FC-02-006

Cyclooxygenase-2 (COX-2) gene polymorphism and the risk of mild cognitive impairment in a Southern Chinese community

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Objectives: Mild cognitive impairment (MCI) is a high risk condition for conversion to clinical dementia. Annual conversion rates of 10%-15% have been reported in some studies. Constitutional factors are important determinants of Alzheimer's disease. Genetic susceptibility may play a role in modulating the development of MCI and also subsequent conversion to clinical dementia. Our preliminary study indicated that one polymorphism (rs689466) in cyclooxygenase-2 (COX-2) gene may be associated with the cognitive deterioration in Chinese older persons. The present study is to further explore whether COX-2 gene polymorphism was associated with MCI and further cognitive decline.
Methods: 450 Chinese subjects (264 cognitively intact and 186 mild cognitive impairment) were followed up with a mean (SD) duration of 21.62 (3.94) months. Association between the COX-2 gene polymorphism (rs689466) with MCI and two year cognitive deterioration were evaluated.
Results: rs689466 was associated with the risk of MCI in subjects older than 70 (Pearson $\chi 2$ =8.16, df 2, P=0.017). At follow up, 326 (72.2%) subjects were reassessed. Twenty two MCI patients progressed to clinical dementia, while 115 had improved or remained stable. rs689466 status did not affect the conversion (Pearson $\chi 2$ =0.487, df 2, P=0.784). Baseline age and MMSE scores are associated with conversion.
Conclusions: COX-2 gene may be involved in the pathophysiology of MCI. Its role in subsequent cognitive deterioration requires further assessment and evaluation.

FC-03
Psychotic Disorders I

FC-03-001
Bringing 'dealing with stigma' into clinics: Why should 'stigma' not be a part of routine clinical assessment in schizophrenia: Need for objective assessment and quantification

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Objectives: One of the most significant researches and public health initiatives that have been launched in recent times is the program for dealing with stigma and discrimination. We have reached to a point where psychiatry is ready with therapeutic tools; which provide appropriate, effective and safe treatment for most of the mental disorders resulting in excellent outcomes. These often turn out to be better that many treatments for physical disorders. Ironically, most patients do not receive treatment. The paper discusses the concept of quantification and integration in routine clinical practice. Our objective wa sto explore if quantifaication of stigma as a clinical domain if possible and helpful in clinical care or not.
Methods: We reviewed the litreture on Stigma to study the impact & source. The study tested a semi-structured Interview schedule for quantification and to assess reliability & utility in Clinical care..
Results: The most impressive finding is that stigma is universal and that it's everybody's problem. The stage is now set for taking a step forward: by providing information about objective assessment and quantification of stigma. This is a reasonable and important research priority; If there is an answer to stigma, (which all of us believe there is), we need to apply that knowledge as soon as possible, before all the negative experiences are deep rooted into patient's personalities that make them decompensate from their own self esteem. main finding emerges that stigma is also a risk factor responsible for consequences of illness. It is related to duration of untreated psychosis, Increased Suidality, domestic violence, developmet of chronicity & noncompliance.
Conclusions: The paper concludes that assessment of stigma needs to a routine part of clinical care assessment. It needs to be quantified for all its domains and be addressed on individual as well as family level. it appears that quantification is possible and feasible. It also appears that such attempts have clinical utility to improve outcome and reduce diability.

FC-03-002
Differences among bipolar disorder and schizophrenia: Less and less feasible – breaking a dogma (Kraepelin´s dichotomy)

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Objectives: Following the recent progress mainly in the fields of genetics and neurobiology, the validity of the diagnostic distinction between bipolar disorder and schizophrenia is receding.
Methods: Review the MEDLINE from 2000 to 2008 the differences and similarities genetic, neurobiological and brain function between schizophrenia and bipolar disorder.
Results: Evidence for basic neurobiological processes common for both disorders is expanding with regard to (a) susceptibility genes (whit neuroregulin-1 in 8p22; dysvidin in 6p22; G72/G30 in 13q32; COMT in 22q11-13 and chromosome 15q26), (b) neurodevelopment (Reported on the down regulation of key oligoendrocyte and myelination genes for both disorders. The critical period for myelination is the adolescence and early adulthood. Thus, white matter abnormalities might be present before the onset of the disorder and might induce cognitive deficiencies. GABAergic interneurons, cell density is decreased in both. Expression of glutamatergic NMDA receptors.) and (c) brain functions (cognitive deficits, sensory gating, P-50 ratio, P300, visuospatial achievement, frequency of leading saccades).
Conclusions: The etiological and/or pathopsysiological findings are unable to differentiate between bipolar disorders and schizophrenia.

FC-03-003
Sensitivity to expressions of pain by schizophrenia patients – neurocognitive and symptoms correlates

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Bernardo Moura

Objectives: Recognition of emotional facial expressions has been described as impaired in patients with schizophrenia. However, to our knowledge no study has addressed whether these patients have also impaired sensitivity to expressions of pain. Our goal was to test schizophrenic patients' sensitivity to facial expressions of pain, compared to a healthy group. We also addressed whether this performance correlated with positive symptoms, neuro-cognitive variables and with the recognition of other basic emotions.
Methods: We applied a battery of tests composed of: Comprehensive Affect Testing System (CATS), Sensitivity to Expressions of Pain (STEP), Toulouse-Pierón (TP), Stroop and Digit Span (DS) to two groups of individuals, 23 patients with the diagnosis of schizophrenia and 26 healthy volunteers, matched for age, education and gender. On the clinical group, symptoms were assessed using Brief Psychiatric Rating Scale (BPRS).
Results: Performance on the STEP task was impaired in the patients group, on all variables tested although no bias was detected. STEP performance was correlated with basic emotion recognition in general and more specifically with recognition of disgust and neutral expressions. In the schizophrenia group, but not in the healthy group, STEP performance was correlated with working memory. Also, the group of patients with more severe unusual thought content symptoms had a significantly lower sensitivity in the discrimination between no-pain and moderate pain expressions. Finally, working memory was negatively correlated with severity of unusual thought content and hallucinations.
Conclusions: Because STEP task might imply a delay between stimuli and response, our hypothesis is that because of less efficient and perhaps slower early processing of emotional faces, patients' performance was more dependent upon working memory. Because working memory is also impaired, patients have higher rate of misperceptions and misinterpretations that might give rise to positive symptoms.

FC-03-004
The navel hypothesis of schizophrenia: The meaning of schizophrenia: Synishophrenia instead of schizophrenia?

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Conclusions: In this presentation I argue that it is not possible to understand the meaning of schizophrenia within a medical model (approach) only but from an evolutionary perspective too. Like the navel on our body as the sign of one's previous development, schizophrenia stands as the sign of one's previous development of complex cortical interconnectivity (in particular frontal-temporal circuits). It is a well accepted fact that schizophrenics have a lower fertility and increased early mortality. Therefore the disorder is maladaptive and, according to the laws of natural selection, should have disappeared from the gene pool long ago. In this context I argue that prevalence rates which are approximately 1% in most of the surveyed actually represent a standard deviation (error) rate in composing a division of cerebral circuits partly modified by environmental factors / prenatal, fetal, post-partial, infectious, trauma, social, family etc./ That and not only a stigmatisation of the name schizophrenia is the reasoning to propose the term synishophrenia as the one that shows the real nature of the disorder - the problem of composing the division of cerebral circuits.

FC-03-005
Longitudinal assessment of adolescents with 22q11.2 Deletion Syndrome: Cognitive and cerebral correlates to enhanced risk for psychosis

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Objectives: The objective of this study is to examine cognitive and cerebral development that may contribute to the expression of positive psychotic symptoms in 22q11.2 Deletion Syndrome (22q11DS). A number of reports suggest that positive symptoms appear during childhood and adolescence, and approximately 30% of adults with 22q11DS meet the diagnostic criteria for schizophrenia. Here, we investigate cognitive and neuroanatomical alterations, which during adolescence may set the stage for increased vulnerability to schizophrenia in this neurogenetic disorder.
Methods: Thirty adolescents underwent two MRI scans at an interval of approximately three years. First, we evaluated the unfolding of psychotic symptomatology in participants with 22q11DS, and examined the evolution of performances on standardized neuropsychological testing. Second, we calculated cortical folding measures (LGI; local gyrification index) derived from an automated technique measuring LGI. In addition, we examined cortical thickness by delineating the cortical mantle and external plane to reconstruct 3D surfaces, thus enabling the precise estimation (~150 000 points) of the cortical sheet.
Results: Assessments of psychotic symptoms in participants with 22q11DS reveal that more than two thirds of the sample report positive symptoms of psychosis. Memory skills such as those involved in source monitoring show deficits thought to contribute to the maintenance of positive symptoms such as auditory hallucinations. Finally, the neurodevelopmental trajectory of LGI and cortical thickness early alterations that can affect participants reporting psychotic symptoms. More specifically, gyrification alterations can be observed in the left middle and inferior frontal gyri, and the right inferior frontal gyrus. Cortical thickness measures revealed late onset of cortical specialization and accelerated cortical thinning in the frontal lobes.
Conclusions: Longitudinal assessments of cognitive and cerebral development in 22q11DS suggest that early markers can help to identify increased risk for psychosis in this population. Results will be discussed in light of early identification and treatment strategies.

FC-03-006
Quantitative motor activity in psychotic disorders

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Objectives: Motor symptoms are frequent in schizophrenia and relevant for the diagnosis of subtypes. However, the assessment has been limited to observations recorded in scales and experimental designs. Additionally, cycloid psychoses are suggested to be an own category within psychotic disorders and different from schizophrenia. The aim of this study was to use wrist actigraphy to obtain motor activity data in three schizophrenia subtypes as well as in cycloid psychosis.
Methods: In two studies, we investigated hospitalized 92 patients using PANSS and continuous actigraphy for 24h. In the first study 36 paranoid, 11 catatonic and 13 disorganized schizophrenia patients were included. In the second, we compared 16 patients with cycloid psychoses with 16 patients with schizophrenia who were matched for age and sex. Data of the wakeful hours of the day were analyzed.
Results: Activity level, movement index, and mean duration of uninterrupted immobility were found to be only predicted by the schizophrenia subtype. Age, gender, duration of illness, and chlorpromazine equivalents did not contribute to the variance of the activity data. A MANOVA demonstrated the significant differences in the three parameters between schizophrenia subtypes ($P = 0.011$). Patients with catatonic schizophrenia had lower activity levels, lower movement index and longer duration of immobility than patients with paranoid schizophrenia. The patients with cycloid psychoses had higher levels of activity and proportion of active vs. inactive periods during waking hours compared with paranoid schizophrenia (both $p = 0.025$).
Conclusions: Schizophrenia subtypes can be differentiated using objective measures of quantitative motor activity. The increased duration of immobility appears to be the special feature of catatonic schizophrenia. Also, cycloid psychoses display higher motor activity compared with paranoid schizophrenia. As motor activity differs between these groups of psychotic patients, the underlying pathophysiology might differ as well.

FC-04
Addictive Disorders I

FC-04-001
Clinical characteristics of patients with cannabis dependence

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Marie-Odile Krebs, Xavier Laqueille

Objectives: To assess clinical characteristics in outpatients with cannabis dependence.
Methods: All consecutively outpatients seeking treatment for cannabis dependence according to the DSM-IV, in the substance abuse department of Sainte-Anne Hospital in Paris between June 2007 and december 2008 were included in the study (n=44). Patients with psychotic disorders, bipolar 1 disorders, current opioid or cocaine dependence were excluded. The patients were assessed using the Diagnostic Interview for Genetic Studies (DIGS 3.0; Nurnberger et al. 1994) which generate DSM-IV diagnoses, in particular alcohol and drug abuse or dependence.
Results: The mean age of the patients was 28 (±9.9) years; 82% were male, 18% were female; 45% of the patients had familial history of alcohol abuse, 34% familial history of depression. The mean ± SD age of onset of cannabis use, regular use and dependence were 15.9 ± 2.7 years, 19.0 ± 6.8 years, and 20.7 ± 8.1 years respectively. The mean number of cannabis cigarettes/day smoked was 6.3 ±3.4. The effects of recent cannabis intoxication reported by the patients included relaxation (93% of the patients), impairments in attention (73%), impairments in memory (73%), sensation of slowed time (52%), disorganized thoughts (50%), decreased mood (48%), euphoria (41%), dishinibition (32%), paranoia (25%), impaired motor coordination (25%), and hallucinations (11%). Eighty-four percent of the patients reported at least one symptom of cannabis withdrawal including insomnia (73%), anxiety (70%), sweating (34%), and tremors (25%). Regarding psychiatric comorbidity, 27% of the patients had a history of lifetime alcohol dependence, 14% had current alcohol dependence, 34% had a history of depression; 9% made at least one suicide attempt; 61% of the patients used cocaïne, without dependence, 52% used amphetamines, 25% opiates. All the patients smoked tobacco cigarettes every day.
Conclusions: Psychiatric induced symptoms and psychiatric comorbidities are common in patients with cannabis dependence.

FC-04-002
Attention Deficit Hyperactivity Disorder (ADHD) among cocaine / crack abusers: Descriptive study in Martinique (French West Indies)

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Objectives: Attention Deficit Hyperactivity Disorder (ADHD) is a frequent comorbidity in Substance Abuse Disorder (SAD) patients. The aim of this study is to establish the prevalence of this comorbidity among heavy cocaine users in Martinique.
Methods: During eight months all patients seeking treatment for cocaine abuse in a specialized center for drug users treatment were assessed for adult ADHD and epidemiological data were recorded. No patients have been excluded even when they presented organic or other psychiatric comorbidities. Diagnosis of substance abuse and ADHD where established using DSM-IV-R criteria for ADHD and the Wender Utah Rating Scale (WURS-25).
Results: At the end of the study 46 (44 men and 2 women) cocaine abuser patients have been included. Of those 10 (21.7%) patients met DSM-IV-R criteria for ADHD. There was a significant difference in the pattern of cocaine use: the cocaine abusers with ADHD spend nearly 3 times more money on cocaine per week, than those without ADHD (p=0.008). There was a significant difference in the administration route, all the cocaine abusers with ADHD used crack cocaine in pipe rather than in joint or than powder cocaine, on the other side, only 53% of the cocaine abusers without ADHD used crack cocaine in pipe (p=0.02). There was a tendency for cocaine abusers with ADHD to have an earlier onset of cannabis, 2 years earlier (p=0.27). The cocaine abusers with ADHD have one year less of education (p=0.21) and a higher rate of unemployment 70% versus 55% (p=0.43), but these differences did not reach statistical significance.
Conclusions: Our study has shown a prevalence of 21.7% of ADHD among cocaine abusers seeking treatment. A more severe pattern of cocaine use is observed in patients with this comorbidity: they spent 3 times more money on cocaine per week, which means they used a more important dose, and the route of administration allowed a greater absorption.

FC-04-003
Cortical inhibition in alcohol dependence – examination with the double-pulse transcranial magnetic stimulation

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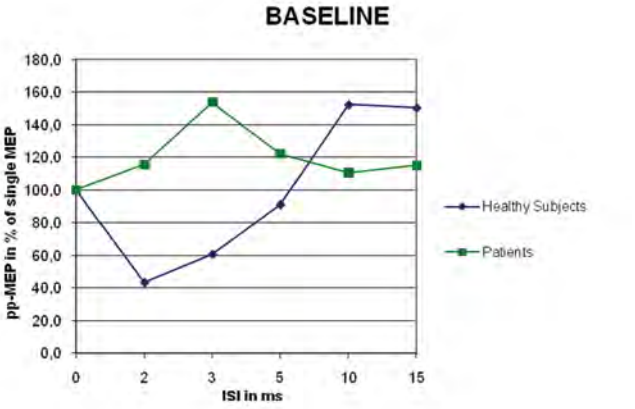
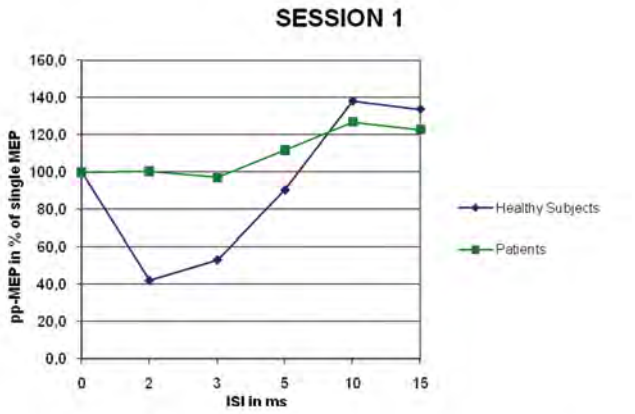
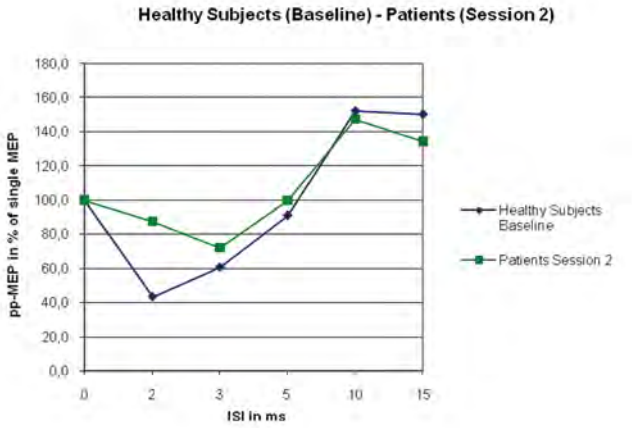
Objectives: Double-pulse transcranial magnetic stimulation (dpTMS) is a non-invasive tool for the investigation of the integrity and the excitability of inhibitory and excitatory neuronal circuits in cerebral cortex. We used dpTMS to test for functional changes in the motor cortex of patients with alcohol dependence.
Methods: Participants were 11 healthy subjects (49 ± 12 years, mean ± SE) and 10 patients (39 ± 12 years) with a DSM IV diagnosis of ethanol dependence. First, the motor threshold stimulation intensity was defined for the right abductor pollicis brevis (APB) muscle. Next, subjects underwent blocks of 10 trials delivered at short ISIs (2, 3, 5, 10 and 15 ms), 10 placebo trials and 20 single trials, conducted in random sequence at intervals of 200 ms. Patients were tested at entry, and at three and seven weeks after alcohol cessation, and control subjects were tested twice, at three weeks apart.
Results: At baseline the patients had a significantly higher amplitude of APB response at the inhibition ISIs of 2 ms ($p < 0.001$) and 3 ms ($p < 0.001$), and a significantly lower motor-evoked potential (MEP) at the facilitation ISIs of 10 ms ($p < 0.008$) and 15 ms compared to healthy subjects. At three weeks of cessation, differences were evident at 2 ms ($p < 0.001$) and 3 ms ($p = 0.01$), and at seven weeks only at 2 ms ($p = 0.003$).

Conclusions: Results show that the excitability and plasticity of the motor cortex changes during alcohol withdrawal. We speculate that attenuation of glutamatergic corticofugal pathways increased sensitivity of the striatal dopaminergic system, which contributes to the phenomenology of alcohol dependence and withdrawal. Perturbed cortical inhibition thus constitutes an endophenotype of altered glutamatergic transmission.







FC-04-004
Difference in reflection-impulsivity between pathological gamblers and healthy controls

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Objectives: Pathological gambling is classified as an Impulse Control Disorder in the DSM-IV-TR; however, few studies have investigated the relationship between gambling behavior and impulsivity.
Methods: The subjects performed the Matching Familiar Figures Test (MFFT). MFFT investigated the reflection-impulsivity dimension in pathological gamblers (PGs) (N=82), and demographically matched healthy subjects (N=82).
Results: Our study demonstrated that PGs had a significantly higher rate of errors than healthy controls (P =0.011) but were not different in terms of response time (P =0.487). PGs had a similar correct response time variability compared to the control group (P=0.357). However, the PGs were significantly more consistent in erroneous response time than healthy controls (P<0.0001).
Conclusions: Diminished MFFT performance in PGs as compared to controls supports findings of previous studies which show that PGs have impaired executive functions. Further controlled studies with a larger sample size which examine MFFT performance in PGs are necessary to confirm our results.

FC-04-005
Clinical aspects of dependence on the opioid tramadol

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Sepand Manouchehr

Objectives: German epidemiological data (Poser and Havemann-Reinecke 2002) showed 12% of all addicted treated patients in Lower Saxony being dependent from prescribed opioid analgesics. Here we report new clinical data of 150 patients being treated because of dependence on the opioid analgesic tramadol
Methods: Documents of these patients were evaluated to social-, family-, pain- and addiction development – data, psychiatric and somatic diseases; suicidality, source of tramadol (prescription: "legal", black market: "illegal"), withdrawl symptoms, therapy
Results: Of 140 patients (P) 123 P (87,9%) were "legally" dependent on tramadol (51,4% f, 48,6 m), 17 P (12,1%) "illegally" dependent (53,5% f, 46,5% m). The ages of "legally" dependent P were 20-80 years. In the group of "legally dependent" patients 20% were medical staff (16% nurses, 4% medical doctors), and 16% had academic professions; 75% of the "legally" dependent patients suffered from depression, 40 % had performed suicidal trial(s), 53% have had a somatic disease before the intake of tramadol, 17% after the treatment of tramadol dependence. 69% suffered from pain before intake of tramadol, 22% had no experience of pain before first intake of tramadol. 76% of the pain-patients were also ill with depression. 19.4% of the "legally" dependent patients suffered from addiction for the first time, 66,9% have had an addiction disease before. Seizures were documented in 23% of all patients with tramadol dependence/withdrawal as cause.
Conclusions: Pain, depression and pain, somatic diseases, previous addiction diseases, psychiatric family history, being a member of medical staff increase the risk to develop dependence to prescribed tramadol. Tramadol dependent patients show a high rate of suicidal trials and of seizures. The data will be discussed with respect to pathophysiological principles of analgesic and addiction effects of opioids.

FC-04-006

Changes in Cerebral type 1 Cannabinoid Receptor (CB1-R) availability in Ethanol-dependent patients after binge drinking and abstinence

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Objectives: The cerebral type 1 cannabinoid receptor (CB1-R) is assumed to play an important role in human addiction. This study investigates the in vivo cerebral CB1-R availability in alcoholic patients after an acute binge drinking episode and monitored abstinence, using positron emission tomography (PET) and [18F]MK-9470.

Methods: We investigated 16 male alcoholic patients (age range 34-61 years) without other psychiatric disorders, as assessed by the Structured Clinical Interview for DSM-IV (SCID). [18F]MK 9470 PET-scans were performed in an acute setting after hospitalization for binge drinking (acute condition, mean period between drinking and scan = 5±2 days) and after a monitored ethanol abstinence period of 4 weeks (chronic condition; 30 days ±5 days; n=12). The control group consisted of 15 male healthy volunteers (age range 21-49 years). Spatially normalized, parametric modified standardized uptake value (mSUV) images, reflecting receptor availability, were calculated. A predefined volume-of-interest (VOI; unpaired t-tests) statistical analysis was performed.

Results: In vivo CB1-R availability is globally decreased in grey matter regions (average: -8.7±2.2%) after binge drinking. Regional analysis (normalized to whole-brain activity) in the reward circuit showed that relative CB1-R availability was higher in insula (+2.4%; p=0.028) and nucleus accumbens (+4.5%; p=0.018). Chronic conditions showed a further decrease of global CB1-R availability (average: -14.8±1.6%). Regionally, relative significant increases in the nucleus accumbens (+5.4%; p=0.008) were observed.

Conclusions: In ethanol-dependent patients, a globally decreased CB1-R availability is observed in comparison to healthy volunteers, which is more pronounced after a period of abstinence. However, superposed on these global absolute decreases, relative increased uptake in the insula and nucleus accumbens was found. These results indicate that central CB1-R are altered in ethanol abuse giving a potential rationale for pharmacotherapy.

FC-05
Psychotic Disorders II

FC-05-001
The interhemispheric pathway in hearing: Relationship to auditory hallucinations in schizophrenia

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Objectives: Several studies suggest changes in the structural connectivity of auditory areas involved in the pathophysiology of auditory hallucinations in schizophrenia. Combining Diffusion Tensor Imaging (DTI) and fiber tractography provides a unique opportunity to visualize and to quantify entire trajectories of fiber bundles. We applied these techniques to quantify diffusion anisotropy of fibers interconnecting the auditory cortex with its corresponding contralateral area in patients with schizophrenia.
Methods: DTI images were used to investigate the fiber tracts of interconnecting homotopic auditory areas via the corpus callosum in ten patients with a first episode of paranoid schizophrenia and ten healthy controls, matched on age, sex and level of education. Subgroups of patients were created according to the presence of specific symptoms (commenting or conversing voices). Regions of interest were drawn manually, blind to group membership, to guide tractography, and fractional anisotropy (FA), a measure of fiber integrity, was calculated and averaged over the entire tract for each subject.
Results: There was no difference between FA-values in the interhemispheric auditory fibers between patients with schizophrenia and healthy controls. However, the subgroup of patients hearing conversing voices showed increased FA-values in comparison to patients without these symptoms (p=0.028) or healthy controls (p=0.038).
Conclusions: Specifically, our findings suggest a role of the interhemispheric pathway in the pathophysiology of auditory hallucinations in schizophrenia. Generally, DTI and tractography can be used to study white matter fiber tracts in vivo.

FC-05-002
Action of Psychotomimetic Ketamine on ongoing γ oscillations: EEG, network and cellular features

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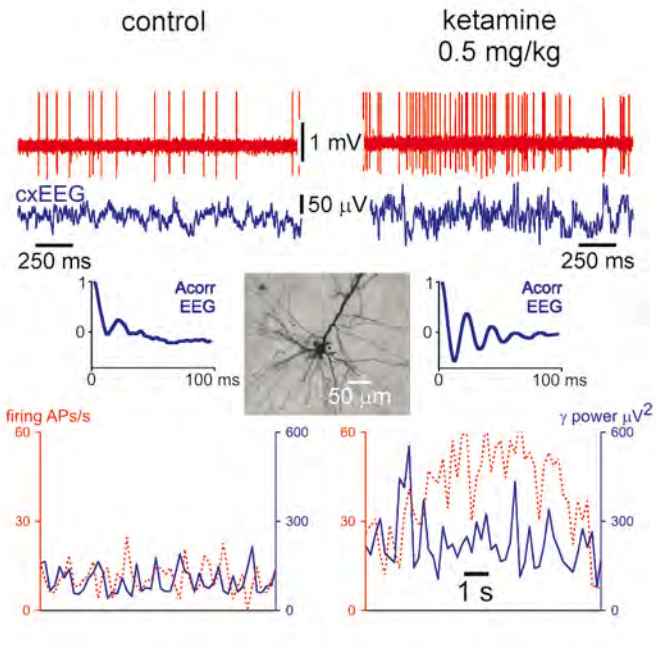
Objectives: Psychosis and cognitive impairment can be induced in humans following systemic injection of a single non-anesthetic dose of ketamine, a non-competitive NMDAr antagonist. In awaked rats, ketamine (<5 mg/kg) induces a peculiar brain state characterized by persistent aberrant γ frequency (30-80 Hz) oscillations in the frontoparietal cortical EEG. The aim of the present study was to understand the underlying cellular and network mechanisms.
Methods: Multi-site EEG and local field potential (LFP) recordings were performed in several structures, including the thalamus, in 16 freely moving and in 57 anesthetized rats. Juxtacellular and intracellular recordings of sensorimotor-related cortical and thalamic neurons were carried out along with LFP recording of the recipient network and with the corresponding cortical EEG.
Results: Ketamine (or MK-801)-induced aberrant γ noise also occurred in multiple cortical areas and subcortical structures, including the thalamus. The surface cortical EEG partly mirrored γ oscillations recorded in the underlying intracortical LFP. Ketamine significantly increased the power synchrony of the spontaneous γ noise between two highly and much less between two weakly interconnected structures. Juxtacellular and intracellular recordings of glutamatergic, corticofugal and thalamocortical neurons revealed that ketamine-induced aberrant γ EEG oscillations were associated with a significant modulation in their firing rate and membrane potential γ oscillations.
Conclusions: This study demonstrates that ketamine induces a pathological persistent brain state characterized, in cortical and subcortical networks, by a generalized aberrant γ noise. It reflects in part an increase of ongoing γ oscillations in the membrane potential of the corresponding glutamatergic neurons secondary to NMDAr blockade. Such abnormal cellular and network γ noise is a potential biomarker of psychotic states and might be responsible for cognitive disorders in schizophrenic patients. Supported by Inserm and Université de Strasbourg.



FC-05-003
Analysis of Single Nucleotide Polymorphisms (SNPs) of Serotonin receptors for schizophrenia in Malaysia population

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Objectives: Schizophrenia (SCHZ) is a psychiatric diagnosis that describes a mental illness characterized by impairments in the perception or expression of reality. Genetics factors are considered to be involved in the development of SCHZ. The role of the serotoninergic system has been implicated in the etiology of SCHZ and other behavioral disorders. Thus, serotonin receptor genes have been studied as candidate genes of these disorders.
Methods: In this study, the association between -1438G/A 5-HTR2A and TPH2 intronic rs1386494 single nucleotide polymorphisms (SNPs) and SCHZ were investigated in 124 schizophrenic patients and 102 healthy control subjects in Malaysia by using PCR-RFLP and deviation from Hardy Weinberg Equilibrium was determined.
Results: In this population based study, our results indicated that there was significant role for the -1438G/A SNP of 5-HTR2A in SCHZ in Malaysian population. However, there was no significant difference was found between genotype and allele frequency distributions between schizophrenic patients and control subjects for TPH2.
Conclusions: We believe that further studies are required to examine the relationship between serotonin-related genes and the behavioral phenotypes of SCHZ in the Malaysia population.

FC-05-004
Prenatal exposure to infection: A primary mechanism for abnormal dopaminergic development relevant to schizophrenia

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Objectives: Exposure to infection during critical periods of prenatal life is a notable environmental risk factor in the later development of schizophrenia and related psychotic disorders. The feasibility of a causal link between prenatal infection and higher risk of schizophrenia-related behavioral abnormalities in adulthood has also received considerable support from several experimental models established in both rats and mice. However, despite evidence for the existence of multiple adult brain and behavioral dysfunctions following prenatal immune activation, only little is known about the neurodevelopmental mechanisms underlying this association.
Methods: Using a mouse model of prenatal immune challenge by the viral mimic polyriboinosinic-polyribocytidilic acid (PolyI:C), we explored the effects of prenatal immune activation on the development of the central dopamine system, a neurotransmitter system known to be affected in schizophrenia and related disorders. Longitudinal structural investigations were conducted in the offspring from early fetal to adult stages of life using immunohistochemical stainings of the dopaminergic markers tyrosine hydroxlyase, dopamine transporter and dopamine D1 and D2 receptors. In addition, we conducted parallel behavioral and pharmacological investigations in order to ascertain the functional impact of abnormal dopaminergic development in prenatally immune challenged offspring relative to control offspring.
Results: Our study shows that prenatal immune challenge leads to dopaminergic mal-development starting as early as in the fetal stages of life and produces a set of postnatal dopaminergic abnormalities that are dependent on postnatal maturational processes. The postnatal structural deficits are paralleled by the existence of behavioral and pharmacological abnormalities known to be sensitive to dopaminergic imbalances, including sensorimotor gating deficiency and enhanced sensitivity to systemic amphetamine challenge.
Conclusions: Our results thus highlight that dopaminergic mal-development in general, and following prenatal immune activation in particular, may represent a primary etiopathological mechanism in the development of schizophrenia and related disorders.

FC-05-005
Attentional modulation of external speech perception in patients with hallucinations and delusions

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Objectives: A range of psychological theories have been proposed to account for the experience of auditory hallucinations and delusions in schizophrenic patients. Most influential theories are those implicating the defective monitoring of inner speech (Frith, 1992; Johns et al., 2006). However, there are other studies that measured response bias independently of self-monitoring and found the results inconsistent with defective self-monitoring model, but explained by an externalizing response bias (Allen et al., 2004). The aim of the present study was to identify the role of attentional biases in external misattribution of source by modulating participant's endogenous expectancies.
Methods: 23 paranoid schizophrenic patients and 23 healthy controls participated in 2 versions of the audio-visual task, which differed based upon level of the cue predictivness. Participants passively listened to recordings of single adjectives spoken in their own and another person's voice (alien) preceded by their own or another person's (alien) face and made self/nonself judgments about the source. The acoustic quality of recorded speech was experimentally manipulated by altering the pitch.
Results: In both versions of the task, patients showed increased error rates when listening to the distorted words spoken by themselves, misidentifying their own speech as spoken by someone else comparing to controls. However, patients made significantly more errors across all the conditions in which the cue was invalid, but were particularly prone to misidentify their own speech (original/distorted) as alien, when preceded by an alien face.
Conclusions: We confirmed the presence of the externalizing bias in patients listening to their own voice, that was moreover amplified when they were cued with the alien face. Patients seem to be less able than controls to alternate between strong inhibitory and strong facilitatory biases on a trial-by trial basis. This may reflect the a dominance of the top-down attentional mechanism in patients with halluciantions and delusions, responsible for the misattribution of the ambiguous sensory material.

FC-05-006
Prevalence of human parvovirus B19 infection in schizophrenia

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Objectives: Although autoimmune hypothesis has been assumed for many years in schizophrenia, reports are often conflicting. Some autoimmune viruses, such as Human Parvovirus B19 (B19) already incriminated in rheumatoid arthritis, are not yet investigated. This study aimed to assess prevalence of B19 infection in Tunisian schizophrenic patients.
Methods: Sera samples from sixty-nine patients meeting DSM-IV criteria of schizophrenia were analysed for the presence of anti-B19 antibodies (abs) with enzyme-linked immunosorbent assays (ELISA) commercial kits. Patients were recruited in Psychiatry Department of Sousse Farhat Hached hospital (Tunisia), during a twelve months period. As controls, we used sera samples from 97 healthy controls, with matched age and sex.
Results: The prevalence of B19 infection in schizophrenic patients was 79.7% (N=55) whereas it was 57.7% (N=56) in healthy controls. The difference was statistically significant between patients and controls (p=0.003). No correlation with any sociodemographic or clinical features was found in B19 seropositif schizophrenic patients.
Conclusions: To our knowledge, this is the first investigator-blinded study to document the high prevalence of B19 in schizophrenic peripheral blood. These data support the hypothesis of autoimmune pathogenesis in schizophrenia with a probable role of B19 infection. An additional biologic quantitative technique would be helpful to investigate any correlation between viral replication and the disease severity.

FC-06
Psychopharmacology I

FC-06-001
Effects of chronic lithium administration on renal function in the intellectually disabled

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Objectives: The purpose of this study is to study the rate of increases in creatinine and creatinine clearance activity in intellectually disabled adults in whom compliance was 100%.
Methods: The laboratory records of 57 intellectually disabled individuals receiving lithium over a 15 plus year period were reviewed to determine the incidence of changes in serum creatinine and creatinine clearance activity. A group of 57 individuals with intellectual disability not treated with lithium were used as controls. Individuals were treated with lithium for aggressive behaviors including injury to others and self injurious behavior. Most had a diagnosis of Bipolar Disorder. A creatinine level above l.5 or a creatinine clearance of 55 or less was considered pathologic.
Results: Approximately 20% of the studied individuals attained serum creatinine levels at or above l.5, with commensurate decreases in creatinine clearance rates. A control group of 57 intellectually disabled indivduals not treated with lithium showed no significant increases in serum creatinine levels or decreases in creatinine clearance over the study period. In those individuals in whom lithium as discontinued, serum creatinine levels and creatinine clearance activity reverted toward normal levels, but on average did not reach baseline levels. In no case did the parameters increase once lithium was withdrawn.
Conclusions: In a controlled study in which compliance was essentially l00 percent, lithium treated individuals showed a significant increase in serum creatinine and a decrease in creatinine clearance activity. Of significance, the renal changes did not progress once lithium was withdrawn, a reassuring finding.

FC-06-002
Baseline lipid levels and treatment response to paroxetine and tianeptine in depressed women

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Objectives: The role of plasma lipids in the pathophysiology and treatment of major depression is still unclear. The aim of the study was to compare baseline serum lipid levels and clinical outcome to 4 weeks treatment with paroxetine (20 mg/kg) or tianeptine (37.5 mg/kg) in depressed patients.
Methods: Serum total cholesterol, high-density-lipoprotein cholesterol (HDL-C), low-density-lipoprotein cholesterol (LDL-C) and triglycerides (TG) were determined in non-psychotic, non-suicidal female patients with major depression (DSM-IV criteria) before treatment with paroxetine (33 patients) or tianeptine (27 patients). The patients were categorized as responders or non-responders, according to 50% or less reduction in baseline 17-item HAMD scores, respectively.
Results: There were no signficant differences in demographic data and baseline lipid levels between patients treated with paroxetine or tianeptine. The frequency of responders and non-responders was similar in both treatment groups, with good therapeutic response observed in 22 (67%) out of 33, and 12 (44%) out of 27 patients treated with paroxetine and tianeptine, respectively. Baseline total cholesterol, TG, LDL-C levels and LDL-C/HDL-C ratio were significantly higher in non-responders than in responders to paroxetine treatment. There was no significant difference in baseline HDL-C levels and total cholesterol/HDL-C ratio between responders and non-responders to paroxetine treatment. In patients treated with tianeptine, no significant differences were found in baseline lipid levels and cholesterol/HDL-C and LDL-C/HDL-C ratios between responders and non-responders.
Conclusions: The results suggest that elevated total cholesterol, LDL-C, TG levels and LDL-C/HDL-C ratio are associated with non-response to treatment with selective serotonin reuptake inhibitor (SSRI) paroxetine, but not to treatment with selective serotonin reuptake enhancer tianeptine. Further studies with other SSRIs are needed to confirm that basal lipid profile could be used as a biological marker for clinical outcome in patients with major depression.

FC-06-003
Impact of escitalopram compared to amitriptyline on polysomnographically recorded sleep, daytime sleepiness and performance: A randomized, double-blind, placebo-controlled study in healthy male subjects

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Dieter Riemann, Kai Spiegelhalder, Bernd Feige, John-Peter Doerr

Objectives: Antidepressants differ as regards their impact on nocturnal sleep and daytime sedation. Up to now, data is not available for either amitriptyline (AMT) or escitalopram (ESC), with respect to the question whether the administration of these compounds has an impact on daytime sleepiness as measured by an objective test like the Multiple Sleep Latency Test (MSLT).
Methods: We investigated the effect of a single evening dose of 10 mg (ESC) on the polysomnographically recorded nocturnal sleep, daytime sleepiness, vigilance and cognitive performance in comparison to AMT 75mg and placebo (PBO). 12 healthy male subjects underwent 3 periods of 2 consecutive nights of polysomnography. The first night served as adaptation to laboratory conditions and was not included in the analysis. On the following day, subjective sleep parameters, a standardized test battery (d2 test, TAP, digit span) and the MSLT were conducted. ESC, AMT or PBO were given at 21:00 in the evening before the 2nd night in the sleep laboratory. One subject had to be excluded due to protocol violation.
Results: Both antidepressants caused a significant suppression of REM-sleep compared to PBO. Subjective sleep parameter data did not differ between AMT, ESC and PBO. Processing speed and performance were slightly, but significantly higher after ESC compared to AMT, but not compared with PBO. Daytime alertness was significantly impaired by AMT, but not by ESC. Daytime sleepiness, as measured by the MSLT, decreased significantly after the evening intake of ESC. In contrast, AMT led to a pronounced reduction of sleep latency measured by the MSLT. ESC had no effect on frequency of the number of periodic leg movements, whereas after AMT there was a significant increase.
Conclusions: This study demonstrated that a single evening dose of AMT or ESC, exhibit different effects on next day vigilance and alertness. A significant reduction of daytime vigilance was evident after AMT, but not after ESC.

FC-06-004
Enhancing effects of chronic lithium on memory in the rat

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Objectives: Despite recent enrichment of data establishing a neuroprotective role for lithium, its primary effects on cognition remain ambiguous. We examine chronic lithium effects on spatial working memory, long-term retention, on the ability to ignore irrelevant stimuli or on fear conditioning.
Methods: In three experiments, rats subjected to 30 daily intraperitoneal injections (2 mmol/kg) of lithium or saline (controls) were trained in 0-s delay T-maze alternation and then tested in 30-, 45- and 60-s delay (Experiments 1, 2, 3, respectively). Animals from Experiment 1 were further tested in passive avoidance under mild shock parameters. Retention was assessed 6h later. In Experiment 5, rats subjected to >30 daily injections of LiCl or saline underwent conditioned emotional response training after 40 pre-exposures either to the CS (latent inhibition-LiCl/latent inhibition-saline, n = 8) or to another stimulus (control-LiCl/control-saline, n = 8). In Experiment 6, eight LiCl and eight saline animals were trained in CER in the Skinner box.

Results: Lithium animals were indistinguishable from controls during 0-delay alternation baseline (Experiments 1–3, accuracy > 88%) but showed higher accuracy at 30- and 45-s delays (93% versus 85% and 92% versus 82%, Experiments 1 and 2, respectively). At 60-s delay this beneficial effect of lithium was no longer apparent (lithium and control accuracy = 78%). In Experiment 4, the shock used did not support 6h passive avoidance retention in controls, whereas lithium animals showed significant step-through latency increases. In Experiment 5, LiCl animals showed normal latent inhibition. In Experiments 5 and 6, their fear conditioning was unimpaired.
Conclusions: Chronic lithium enhanced spatial working memory and promoted long-term retention of a weak aversive contingency. The memory improvement under chronic lithium cannot be attributed to changes in the ability to ignore irrelevant stimuli or in fear conditioning. The results suggest that lithium may have potential as a cognitive enhancer.

FC-06-005
Immediate versus gradual suspension of previous treatments during switch to aripiprazole: Results of a randomized, open label study

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Objectives: Switching patients from one antipsychotic to another can lead to tolerability problems or transient symptom exacerbations. Up to recent years, however, switching from one antipsychotic to another has received scarce attention. The aim of the present work was to investigate possible differences in terms of efficacy and tolerability between different switching options to aripirazole.
Methods: In the present study, 77 subjects were randomly assigned to (1) aripiprazole (10mg) with simultaneous discontinuation of current antipsychotic; (2) aripiprazole (10mg) and tapering off current antipsychotic over 4 weeks with half dose after the first 2 weeks; (3) aripiprazole (10mg) and tapering off current antipsychotic over 4 weeks after maintenance of current dose for 2 weeks. Efficacy assessments included CGI-S, CGI-I, BPRS and SANS. Safety assessments included SAS, BAS and AIMS.
Results: Severity of symptoms significantly decreased from baseline over the 12 weeks of treatment. Patients switched to aripiprazole with immediate discontinuation of the previous antipsychotic (group 1) showed an increase of symptoms' severity at week 1. Moreover, these patients were slightly more likely to dropout, particularly because lack of efficacy. On the other hand patients with simultaneous tapering off the previous treatment (group 2 and 3) showed a steady improvement over time, though showing slightly more severe extrapyramidal symptoms at week 2. However, severity of side effects did not overall change significantly during the 12-weeks follow-up.
Conclusions: Previous treatment's tapering off strategy for switching patients to aripiprazole is preferable as compared to abrupt discontinuation, in order to prevent early worsening of symptoms and premature discontinuation of treatment.

FC-06-006
Reduced blood BDNF mRNA levels in depressed patients are normalized by antidepressant treatment

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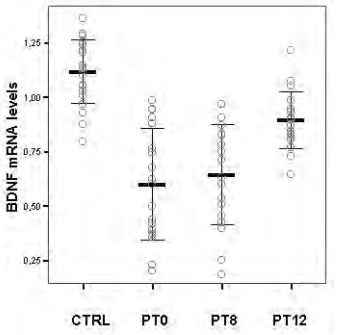
Objectives: Several preclinical and clinical studies have supported the involvement of brain-derived neurotrophic factor (BDNF) in both the pathophysiology and the treatment of Major Depression (MD). These data have shown a reduction in BDNF serum levels in depressed patients and a restoration following antidepressant treatment. However, to this point there is very little known about the central or peripheral origin of serum neurotrophin content.
Methods: In this study, we analyzed BDNF mRNA levels in leukocytes from 19 patients diagnosed with depression prior to and during treatment with escitalopram and from 21 control subjects, by using real-time PCR.
Results: We found that BDNF mRNA levels decreased in drug-free depressed patients (PT0) in comparison to controls (C) (PT0 = 0.64 ± 0.22, C = 1.17 ± 0.24, p = 0.002), whereas 12 weeks of escitalopram treatment reversed this reduction (PT12 = 0.84 ± 0.21, p = 0.004 versus PT0) (see Figure 1). Interestingly, mRNA levels in MD patients paralleled changes in serum BDNF levels during antidepressant treatment (p=0.001), and were correlated with symptoms improvement (p=0.044).
Conclusions: The study results indicate that the decrease in serum BDNF in MD patients may be, at least partially, due to an alteration in BDNF synthesis by leucocytes. Moreover, escitalopram treatment reverses this decrease, resulting in an increase in blood BDNF expression. In conclusion our findings point up a bridging link between the brain and body, suggesting that in addition to reflecting what happens in the brain, the peripheral tissues may also play an active and central role in the MD etiopathogenesis and in the action mechanisms of antidepressant drugs.



FC-07
Psychotic Disorders III

FC-07-001
Can the writing of patients with schizophrenia be identified by means of automated computer-aided analysis?

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Objectives: Prominent formal thought disorder, expressed as unusual language in speech and writing, is often a central feature of schizophrenia. Since a more comprehensive understanding of phenomenology surrounding thought disorder is needed, this study investigates these processes by examining writing in schizophrenia by novel computer-aided analysis.
Methods: Thirty-six patients with DSM-IV criteria chronic schizophrenia provided a page of writing (300-500 words) on a designated subject. Writing was examined by automated text categorization and compared with non-psychiatrically ill individuals, investigating any differences with regards to lexical and syntactical features. Computerized methods utilized included extracting relevant text features, and utilizing machine learning techniques to induce mathematical models distinguishing between texts belonging to different categories.
Results: Observations indicated that automated methods distinguish schizophrenia writing with 86% accuracy.
Conclusions: Results reflect underlying impaired processes including semantic deficit, independently establishing connection between primary pathology and language.

FC-07-002
The relation between the general intellect of schizophrenic patients and psychopathological deterioration

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Objectives: The aim of the study was to examine whether the postpsychotic decline in IQ during schizophrenia coincides with psychopathological deterioration or it is a state-independent premorbid impairment.
Methods: The IQ score of 32 schizophrenic patients and 25 normal comparison subjects were evaluated three times during an average of 4,5 years, after short (mean 2,3 years) and long (mean 4,6) follow-up periods. The results were examined and related to changes of negative and positive symptoms of the illness.
Results: The schizophrenic group had lower IQ score at baseline than the normal comparison subjects but showed comparable stability over time. The total IQ score slightly increased in both groups in follow-up period. No significant correlations were found between IQ score changes and, improvement or worsening of the clinical symptoms.
Conclusions: The IQ score of patients with schizophrenia appears to remain stable regardless of psychopathological decline, and even could be improved by learning and rehearsal.

FC-07-003
Cannabis use and cognitive functioning in schizophrenia

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Objectives: Research examining the neuropsychological functioning in cannabis users with schizophrenia over the past decade suggests that cannabis use is associated with altered cognitive functioning. The relationship to age and extent of use however remains unclear. This study examines the relationship between neuropsychological performance and indices of cannabis use such as frequency and recency of use in persons with schizophrenia.
Methods: The study recruited 40 males with schizophrenia (SCZ), 20 who have a history of cannabis use (FH+) and 20 without a history of cannabis use (FH-). The groups are matched for age, years of education and premorbid IQ. Medical history, substance use and psychiatric symptoms are assessed. A neuropsychological battery is administered and a urine drug screen is performed to confirm reported substance.
Results: The study results suggest cannabis use in the schizophrenia population is associated with improved cognitive functioning. This has been demonstrated in the domains of memory, processing speed and executive functioning. We further propose that these neuropsychological changes are related to the extent and recency of cannabis use. Results for this hypothesis will be presented at the conference.
Conclusions: This study furthers our understanding of the neuropsychological sequelae of cannabis use in the schizophrenia population and suggests further investigation into the potential therapeutic effects of cannabinoids in schizophrenia may be warranted.

FC-07-004
Effects of cannabis use on cognitive deficits in first-episode psychosis

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Objectives: This study examined the effects of cannabis use on cognitive deficits in first-episode (FE) psychosis.
Methods: Cognitive performances of 59 FE patients who did not use substances, 26 FE patients who use cannabis and healthy controls were compared with a neuropsychological battery targeting verbal memory, visual memory, processing speed, working memory, planning and reasoning and general intelligence.
Results: While substance nonuser FE patients were impaired in all domains, cannabis using FE patients were impaired in selective domains (processing speed, verbal memory and general intelligence). Some aspects of spatial working memory, visual memory and planning ability differentiated between FE patients. A cluster analysis based on spatial working memory performance suggested that cannabis using FE patients were consisted of two groups (cognitively impaired and unimpaired). Unimpaired group had a significantly earlier onset of cannabis use and had their first-episodes younger. These patients were not cognitively different from controls except general intelligence and processing speed.
Conclusions: Results of this study suggest that cannabis use in early ages can cause psychotic disorders in vulnerable individuals, despite the fact that cognitive deficits associated with late neurodevelopmental changes are not observed in this group.

FC-07-005
Association between neurocognitive factors and homicide in schizophrenia: A systematic review

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Objectives: Schizophrenics are at increased risk of violence and of committing homicide compared to the healthy subjects. The objective of this systematic review was to examine which factors were associated with schizophrenia, and to explore specific role of neurocognitive factors to explain this tendency.
Methods: A systematic English-French Medline literature search of controlled trials, cohort studies, case-control studies and transversal studies published from January 1990 to December 2008 was performed combining the MeSH terms "schizophrenia","homicide","violence","mental process","cognition","psychological phenomena and processes","risk", "risk factors", "prevention and control". Abstract selection was based on the STROBE checklist for observational studies and on the consort statement for clinical trials. Exclusion criteria were homicide-suicide and wartime homicide.

Results: Of the 187 selected studies, 100 observational and 12 interventional studies met the selection criteria and were included in the final analysis. Firstly, we highlighted that male gender, young age, low socioeconomic status, history of violence and alcohol abuse could be considered as general homicide-related factors, while clinical paranoid, delusions of persecution or thought insertion, disorganized thinking, long duration of untreated psychosis, stopped monitoring or treatment were more schizophrenia-specific factors for homicide. Secondly, our results suggested that schizophrenics with a history of aggressive behaviour compared to those who had not, had better performance on global neuropsychological tests exploring executive functions but performed more poorly while considering orbitofrontal functions. In addition, they had fewer neurological soft signs, displayed more orbitofrontal structural abnormalities and decreased hippocampal hypotrophy.
Conclusions: Homicide-related factors in schizophrenia are numerous, either general or specific, and closely interlinked. Our results raise a number of issues that mainly concern the role of neurocognitive factors: low capacity for insight, impaired neuropsychological tests for frontal functions and related neurological damage. Thus, we suggest that every comprehensive psychiatric assessment should explore the risk of homicide, especially through the history of violence. Key words: Homicide, schizophrenia, prevention, criminology

FC-07-006
Parameters of quantitative EEG correlate with negative symptoms in neuroleptic-naive patients with first episode schizophrenia

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Objectives: While several studies showed an association of QEEG band power with negative symptoms in patients with schizophrenia, this has not yet been investigated in a sample with neuroleptic-naïve first episode patients (NNFE) up to now. From literature we hypothesized delta (0.5-4 Hz) and theta (4-8 Hz) power to be augmented and alpha (8-12 Hz) power to be diminished with increased negative symptoms in NNFE. We expected no relationship of positive symptoms with EEG power.
Methods: The sample consisted of 27 NNFE. Psychopathology was rated with the Scale for the Assessment of Negative Symptoms (SANS) and the Brief Psychiatric Rating Scale (BPRS). EEG was recorded from 8 electrodes with the 10/20 system. Spectral analysis was performed in seven frequency bands after artefact removal. Linear regressions were calculated with log transformed power as dependent, psychopathology as independent and medication, drugs, age, sex, education, day time of EEG recording as confounding factors.
Results: A positive correlation of SANS global score with power in delta and theta frequency bands could be confirmed in NNFE. The negative correlation of alpha power density with the SANS score could not be detected. Beta1 (12-15 Hz) power also correlated positively with SANS. No relationship of BPRS summary score and EEG power could be found.
Conclusions: The present results confirm the correlation of negative symptoms with power of slow frequency bands. In addition to previous studies, the effect was shown in NNFE, which is compatible with augmented slow wave power being a marker for negative symptoms in schizophrenia.

FC-08
Anxiety I

FC-08-001
Neural and physiological phenotypes in zebrafish models of stress

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Objectives: To validate the experimental utility of zebrafish (Danio Rerio) in stress research, and explore the correlation between physiological and neural/behavioral stress responses.
Methods: Behavioral data in the novel tank test translates zebrafish stress/anxiety into quantifiable endpoints (latency to enter the top half of the tank, number of entries, time spent exploring the top half of the tank, fear-like erratic movements, and freezing bouts). As a corresponding physiological measure of stress, whole-body cortisol levels were assessed using ELISA.
Results: Chronic administration of the SSRI antidepressant fluoxetine [for 2 weeks] reduces anxiety behavior and lowers whole-body cortisol levels. To induce an anxiogenic response, zebrafish were subjected to a model of benzodiazepine withdrawal syndrome. After chronic administration of the benzodiazepine diazepam, drug treatment was halted for 3 days before novel tank testing and subsequent cortisol assessment. While behavioral data signified a strong anxiety-like phenotype, cortisol levels also tended to rise in these fish.
Conclusions: Our experiments substantiate zebrafish as dependable and consistent subjects in anxiety research, as well as in studies focusing on drug dependency and withdrawal. Based on the strong correlation of behavioral data and cortisol analysis, zebrafish prove to be an excellent model organism for experimental stress research.

FC-08-002
PTSD symptom severity and co-morbid psychiatric disorders

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Objectives: This study aimed to examine the associations between PTSD symptom severity and psychiatric disorders in persons diagnosed with PTSD.
Methods: A purposive sample of 30 PTSD male patients was studied. Data was collected using The Mississippi PTSD scale, the MMPI and a semi-structured schedule. Pearson correlations and chi-square analyses were used to analyze the data.
Results: High comorbidity has been found between PTSD and other psychiatric disorders, particularly depressive disorders (77%), anxiety disorders (60%), somatization (46.6%), psycasthenia (36.6%) and substance use (13.3%). PTSD symptoms were found to be more severe in patients who had other psychiatric symptoms and comorbid major depression. Aggressive tendencies and impulsivity were found in a majority of the patients. Patients with moderate PTSD symptoms reported more anxiety while those with more severe symptoms reported more depression. The comorbidity between PTSD and depression may be due to the overlapping symptoms shared by the two disorders.
Conclusions: Distinguishing between cause and effect in this connection may be difficult, as psychiatric illnesses may predispose people to being exposed to traumatic events, and traumatic events may in turn increase psychiatric symptoms. The generalizability of the results of the study is limited by the region of the data collection and by the number of participants.

FC-08-003
Balneotherapy in the treatment of generalized anxiety disorder

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Objectives: Balneotherapy emerged from preliminary studies as an effective and well tolerated treatment of generalized anxiety disorder and psychotropic medication withdrawal syndrome. We carried a study to assess efficacy of balneotherapy in acute generalized anxiety disorder.
Methods: We compared the efficacy and safety of balneotherapy to Paroxetine in a randomized muticentric study during 8 weeks. 237 patients meeting the diagnosis criteria of generalized anxiety disorder (DSM-IV) were recruited. Data analysis was performed by a trained medical investigator under the control of the research unit of methodology from Bordeaux University. Assessments were conducted medical inspector. The primary outcome measure was the change in the total score of the HAM-A between baseline and week 8.
Results: A total of 237 outpatients were enrolled in the four centers, 117 were assigned randomly to the balneotherapy and 120 to Paroxetine. There was significant difference in any of demography characteristics and in the number of drop out as well between the two groups. The mean change in HAM-A scores showed an improvement across the two groups with a significant advantage of balneotherapy compared with Paroxetine (-12,0 versus - 8,8 ; $p<0.0001$). Remission and sustained improvement rates were also significantly higher in the balneotherapy group (22 % versus 8 % and 56 % versus 28 %).
Conclusions: Balneotherapy is an interesting way of treatment of generalized anxiety disorder. Because of its safety profile it could also be tested in resistant forms and patients who are reluctant to pharmacotherapy. This study showed the interest of balneotherapy fort the cure of GAD. She can be proposed an alternative in case of failure or in pharmacotherapy resistant form. In the future it might be tested in BZD withdrawal syndrome

FC-08-004
Interleukin-18 initiates goblet cell-dependent mucosal barrier dysfunction of the mouse rectum in response to psychosocial stress

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Objectives: Psychosocial factors are important determinants of disease manifestations, treatment efficacy, and prognosis of functional and inflammatory bowel disorders. This study was designed to identify molecule(s) responsible for the vulnerability of the rectum to psychosocial stress.
Methods: C57BL/6J or interleukin-18 knockout (IL-18-/-) mice were isolated from its 4 brothers grown in the same cage. ACTH and corticosterone levels during isolation were measured by ELISA. Colorectal mucosas were subjected to histological examinations and gene expression analysis using a whole mouse genome microarray. The Ingenuity Pathway Analysis Application (IPA) was used to organize differentially expressed genes into functionally annotated networks and pathways. Cytokine mRNA levels were validated by real-time PCR. MUC2, IL-18, caspase-1, and notch1 levels were measured by immunoblotting.
Results: Isolation reduced food intake by about 20% and caused body weight loss (about 1.2%) during the initial 16 days without significant increases in plasma ACTH and corticosterone levels. Isolation reduced goblet cells and MUC2 expression in the rectum with a peak on day 8, but not in the colon. The stress changed expression of 722 genes in the rectum, which were organized into stress-responsive pathways, while only 72 mRNA levels were modified in the colon. Cytokine networks constructed with IPA showed selective up-regulation of IL-18 mRNA expression among proinflammatory cytokines. In fact, the stress increased expression of IL-18 and produced active forms of caspase 1, IL-18, and a negative regulator for goblet cells, Notch 1, only in the wild-type mouse rectum. Goblet cells and MUC2 mucin were significantly increased in the IL-18-/- mouse rectum, and the absence of IL-18 completely blocked the stress-induced changes in gene expression and the goblet cell responses in the rectum.

Conclusions: IL-18 may be a crucial determinant for the vulnerability of the rectum to psychosocial stress and be one of the potential therapeutic targets for stress-related intestinal disorders.

FC-08-005
Effects of the dorsal hippocampal opioidergic system in the modulation of anxiety

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Objectives: Recent studies have revealed the participation of the endogenous opioid system in modulation of several behavioral responses. The dorsal hippocampus is one brain region that plays an important role in anxiety
Methods: In present study we investigated the effects of μ and δ opioid receptors of dorsal hippocampus in the modulation of anxiety in rats, using the elevated plus maze test of anxiety
Results: Bilateral administration of morphine (0.5, 1 and 2 μg/rat; 1 μl/rat;0.5 μl/in each side) into dorsal hippocampus (CA1) decreases the percentage of open arm time (OAT%) and percentage of open arm entries (OAE%) indicating anxiogenic-like effect. Intra-CA1 injection of naloxone, an opioid receptor antagonist (4, 6 and 8 μg/rat) produced significant anxiolytic-like behaviour. The intra-CA1 injection of δ opioid receptor agonist, [D-Pen 2,5]-Enkephalin acetate hydrate (0. 5, 1 and 2 μg/rat) and δ opioid receptor antagonist, naltrindole hydrochloride (1, 2 and 5 μg/rat) has no effects on OAT% and OAE.
Conclusions: These result may demonstrate that the dorsal hippocampal μ-opioid system is involved in the modulation of anxiety behaviors.

FC-09
Neurodegenerative Disorders

FC-09-001
Effects of Chinese herb Danshen-Dahuang on learning, memory ability and hippocampal gene expression of APP, PS1, BACE in rats with Alzheimer disease

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Objectives: To investigate the effect of Chinese herb Danshen-Dahuang on learning and memory ability in rats with Alzheimer disease (AD) induced by D-galactose and AlCl3 and its possible mechanisms.
Methods: Wistar strain rats were given D-galactose 60 mg·kg- 1·d-1,ip,and AlCl3 5 mg·kg- 1·d- 1,ig,once daily for 90 d. Since the 20th day of D-galactose and AlCl3 intraperitoneal injection, the rats in Danshen-Dahuang group had been treated with Danshen-Dahuang extraction by intragastric administration 10 g·kg-1·d-1 for 70 days. Subsequently, learning and memory ability of the mice was evaluated by Morris water maze, biochemical methods to assay acetylcholine(ACh)and acetylcholinesterase(AChE)contents in whole brain,RT-PCR to determine the expression of amyloidβ-protein precursor(APP),presenilin-1(PS1)andβ-site APP-cleaving enzyme(BACE)genes and Aβ1-40 immunohistochemical staining to observe morphological changes in hippocampus.
Results: Rats intragastric administration with Danshen-Dahuang, mice had shorter latency (P< 0.05) and less error times (P<0.05) in water maze test compared with those in AD model group. At the same time, Danshen-Dahuang down regulated the expression of APP, PS1, ACE mRNA (P<0.05) and Ach content reinforcement,AChE activity decline in hippocampus, which emerged Alzheimer-like pathological changes.
Conclusions: The combined use of D-galactose and AlCl3 may well make an animal model whose pathological changes are very similar to those of Alzheimer's disease. Danshen-Dahuang improves the learning and memory ability of AD rats, its mechanism may be related to the downregulated expression of APP, PS1, BACE mRNA.

FC-09-002
Relations of regional cerebral perfusion, atrophy and functional genetic variants in mild cognitive impairment (MCI) and Alzheimer's disease (AD)

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Objectives: In incipient and early AD hypoperfusional changes have been identified in medial temporal lobe structures, which are also sites of volume loss in the disease course. However, stage-specific relations of regional cerebral perfusion and atrophy and respective genetic associations are not yet understood. We studied regional and global cerebral blood flow (rCBF; gCBF) with perfusion-weighted MRI in patients with MCI and mild AD in relation to MR-morphometrical hippocampal and amygdalar volumes and to functional genetic variants.
Methods: 30 MCI subjects and 15 AD patients were examined using perfusion weighted MRI co-registered to high-resolution 3-D anatomical images at 1.5 Tesla. Hippocampal and amygalar volumes were measured by manual volumetry. DNA samples were genotyped for functional variants of APOE, Endothelin 1, IL1ß, PP2A activator, NFkappaB subunit B, KCNN3, NOS 3.
Results: RCBF was reduced in the posterior cingulum and regional brain volumes of both amygdale and the right hippocampus were reduced in mild AD vs. MCI. rCBF values and brain volumes of amygale and hippocampi were uncorrelated in MCI or AD. Reduced hippocampal but not amygdalar volumes were associated with the presence of one or two APOE epsilon 4 alleles in MCI and AD, while no APOE allele association was found with rCBF or gCBF. In contrast, gCBF was significantly associated with two functional variants of the NOS3 gene.
Conclusions: According to our data, rCBF and brain volume changes are at least partly dissociated in incipient and early AD. This finding may be explained by the diachisis hypothesis of early AD: Localised neuronal atrophy can elicit functional effects, such as hypoperfusion, at distant sites of the CNS via changes of connectivity. Another relevant factor may be divergent genetic effects on brain atrophy and perfusion: We find the APOE epsilon 4 allele associated with hippocampal atrophy but not with rCBF or gCBF, while two functional NOS3 variants appear to be associated with gCBF.

FC-09-003
Centers of interest in Alzheimer patients, focus on apathy

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Objectives: The evaluation of this domain is important in Alzheimer Disease considering the fact that the persistence of the interest is recognized as a potential protective factor against the development of a dementia. The interest test has been developed to allow the evaluation of centers of interest and of activities carried out in old people, with or without degenerative pathology.
Methods: The test is composed of pictures that illustrate daily activities or of leisure. The normative data have been carried out on the selected 50 pictures. In a second stage, 38 subjets (average age =76,6 ; DS=7,3) WITH Alzheimer Disease (AD) ; 10 subjets (average age =77,5 ; DS=8) A minimum cognitive impairment (MCI), and their caregivers. The number of centers of interest has been evaluated by each patient and its caregiver. The data have been compared with a population of 39 control subject (average age=76,2 ; DS +4,4). Also, the Apathy Inventory has also been used in these subjets that presented of AD or a MCI.
Results: Starting from caregiver evaluation, the number of interest is significantly smaller for AD subjects and MCI comparatively with controls (F = 9,01 ; p <0,0001). on the contrary, they are not differences concerning the number of the interest between subject AD and MCI. A significant correlation exists (r = 0,65 ; p <0,001) among the evaluation among caregivers values and for the patient. On the contrary, a significant correlation doesn't exist (r = 0,255) among the evaluation of the loss of interest for the control and the companion with the Inventory Apathy.
Conclusions: The test of interest allows to evaluate in a more precise way that would make it a simple questionnaire the interests of the subjets that suffer AD. These characteristics transform it in a tool adapted to the non pharmacological evaluation of clinical elements of intervention in neurodegeneratives pathologies in old people.

FC-09-004
Brain iron accumulation as a risk factor for neurodegenerative disorders

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Objectives: Assess brain iron in healthy aging and prevalent degenerative diseases. Examine the relationship of brain iron to gender, age at onset, and the pattern of amyloid deposition. Brain iron promotes oxidative damage and protein oligomerization. Increased levels may predispose to proteinopathies that occur in highly prevalent age-related degenerative disorders such as Alzheimer's and Parkinson's diseases (AD, PD).
Methods: The amount of iron in ferritin molecules (ferritin iron) was measured in vivo with MRI by utilizing the Field Dependent Relaxation Rate Increase (FDRI) method. Ferritin iron was measured in four subcortical nuclei [caudate (C), putamen (P), globus pallidus (G), thalamus (T)], three white matter regions [frontal lobe (Fwm), genu and splenium of the corpus callosum (Gwm, Swm)] and hippocampus (Hipp) in 165 healthy adults and AD and PD subjects.

Results: There was a high correlation (r > .99) between published post-mortem brain iron levels and FDRI. There were significant age-related changes in ferritin iron (increases in Hipp, C, P, G, and decreases in Fwm). Men had significantly higher ferritin iron than women in five regions (C, T, Fwm, Gwm, Swm). AD and PD subjects had elevated iron in several brain regions that were especially marked in males with earlier-onset disease. In AD, the pattern of beta amyloid (Ab) distribution (assessed with PIB) matches late-myelinating regions suggesting that iron released from the breakdown of this vulnerable myelin may contribute to Ab aggregation.
Conclusions: Higher brain ferritin iron levels in men may lower age of onset and influence the distribution of protein deposits in degenerative diseases. It is possible that brain iron accumulation is a risk factor that can be modified. MRI provides the opportunity to assess brain iron levels in vivo and may be useful in targeting individuals or groups for preventive therapeutic interventions.

FC-09-005
The clinical and neurobiological overlap between the major psychoses and frontotemporal dementia: More than a frontotemporal coincidence?

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Objectives: Despite Kraepelin's prediction that schizophrenia was a neurodegenerative disorder disorder of frrontal and temporal regions, the relationship between the major psychoses (schizophrenia and bipolar disorder) and frontotemporal dementia (FTD) has not been previously examined. We have undertaken a series of studies to examine this relationship, including a literature review, clinicopathological case series and a neuropathological examination of TDP-43 in the major psychoses.
Methods: 1. A Medline based literature review examined 751 cases of FTD with the aim of identifying those cases in which psychosis was the presenting syndrome. 2. We examined clinicopathological correlations in 17 subjects with young onset FTD (onset before the age of 60). 3. A neuropathology study included 23 subjects (9 schizophrenia, 3 bipolar disorder, 11 control) examined for hippocampal dentate gyrus distribution of TDP-43 and ubiquitin.
Results: 1. Lit review: Young patients with FTD frequently present with a schizophrenia-like psychosis. One third of patients with onset of FTD before the age of 30 and one quarter with onset before the age of 40 presented with a schizophrenia-like psychosis. Clinicopathological case series: Patients with FTD who had presented with and were treated as having schizophrenia / bipolar disorder exhibited neuropathological changes of FTD associated with motor neurone disease type (ubiquitin and TDP-43 positive neuronal cytoplasmic inclusions) 3. Neuropathology study: Three patients (2 schizophrenia and 1 bipolar disorder) with onset of psychosis after the age of 50 and with a family history exhibited abnormalities of TDP-43 in the dentate gyrus.
Conclusions: While the shared clinical and neurobiological features of the major psychoses and FTD may constitute a 'frontotemporal coincidence', our findings identify a subgroup of patients previously diagnosed with major psychosis who have clinical and neuropathological features which overlap with those identified in FTD.

FC-09-006
Subthalamic neuronal activity in patients with obsessive-compulsive disorders or parkinson's disease

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Objectives: Dysfunction in the basal ganglia circuitry has been implicated in obsessive and compulsive disorder (OCD). In a recent clinical research program, stimulation of the subthalamic nucleus (STN) has proved to be efficient in alleviating obsessions and compulsions in OCD patients and permitted to study neuronal activity in this disorder (Mallet, 2008).
Methods: Unit neuronal activity of STN neurons were recorded in awake OCD patients at rest and compared to data obtained in patients with Parkinson's Disease (PD). The mean firing rate and interspike intervals were calculated for each cell. The firing pattern was classified as regular, irregular or bursting. Neuronal activity was also sampled for each period and epochs of elevated discharge rate were classified as burst using a Poisson surprise analysis with S≥3. Percentages of action potentials and duration with S≥3 and mean S value were calculated for each cell. The precise localization of neuronal activity recordings was performed using a 3-D deformable basal ganglia atlas with a particular reference to motor, associative, and limbic STN subterritories.
Results: 156 STN neurons were isolated in 11 OCD patients and 113 neurons in 10 PD patients. In comparison to PD, the mean discharge frequency of STN neurons was lower in OCD patients (24.1 ± 14.1 Hz vs 32.1 ±17.7 Hz, P<10-3) with a higher burst type activity (p<0.03). The mean S value was higher in OCD patients (7.0±3.5 vs 5.9±1.9, P<10-2) with a higher mean percentage of action potentials (39.0±13.5 vs 32.8±14.4 %, P<10-3) and duration with S≥3 (17.7±4.7 vs 14.9±5.6 %, P<10-4).
Conclusions: In OCD patients, the subthalamic neuronal activity seems abnormal with an increase in the bursting type activity. This is in line with the hypothesis of the role of basal ganglia, and the subthalamic nucleus, in the physiopathology of this disorder.

FC-10
Psychotic Disorders IV

FC-10-001
D2/3-Receptor availability in schizophrenia decreases with progression of psychosis: An [18F] Fallypride Study

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Objectives: The presence of possible disturbances of the D2/3-receptor distribution in schizophrenia is still a matter of debate. Some PET studies using low-affinity ligands found no change or slight elevations in the striatum. Molecular imaging studies using high affinity ligands are rare and suffered from small group sizes. Some of these studies suggest a decrease of D2/3-receptor availability in extrastriatal regions. Thus, we use PET and the high-affinity D2/3-receptor ligand [18F]fallypride for determination of D2/3-receptor availability in drug-free patients.
Methods: 20 patients suffering from schizophrenia (31.6±11.7 years; eight subjects at first episode) and 18 healthy control subjects (32.9±9.7 years) were included. All subjects were drug-free for at least six months. Subjects underwent an 180 minute PET-scan after bolus injection of 213±24.6 MBq [18F]fallypride. After movement-correction and normalization, TACs were derived for putamen (PUT), caudate nucleus (NC), inferior temporal lobe (GTi), the thalamus (THAL), and the Cerebellum. BPND-values were calculated using the SRTM.
Results: Both in striatal and in extrastriatal brain regions BPND-values of patients were significantly higher than in control subjects (PUT: +19%, p=0.015; NC: +18%, p=0.013; THAL: +19%, p=0.017; GTi: +20%, p=0.039). The age-corrected excess of patient-BPND was negatively correlated with the duration of psychosis in NC and THAL (NC: r=-0.51, p=0.023; THAL: r=-0.48, p=0.033; PUT, r=-0.41, p=0.072).
Conclusions: This study is the first investigation showing an increased D2/3-receptor-availability in extrastriatal regions of patients suffering from schizophrenia. Furthermore, we could confirm a very early observation that patients with schizophrenia apparently show this excess predominantly at the time of onset of psychotic symptoms; afterwards, their age-related decline appears to be more rapid compared to healthy subjects. This time-course may explain the conflicting results of several previous investigations.

FC-10-002
Increased EEG sources (LORETA) in the left hemisphere of sinistral male schizophrenics and in the right hemisphere of dextral male schizophrenics

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Objectives: To investigate possible differences in patterns of cerebral disorganization in dextral and sinistral male schizophrenics.
Methods: 17 male schizophrenic, ambilateral and sinistral (or 24.6% of the 65 male schizophrenic group) were compared to 52 dextral male schizophrenics and 29 ambilateral and sinistral healthy male controls. These schizophrenics were all unmedicated. The LORETA sources were derived from a multi-channel EEG system of 48 electrodes (5 of these for artefact monitoring). The source analysis was carried out after factor analysis of the cross spectral matrix (30 factors accounting for over 99% of the variance) on the two factors with maximum variance on one group and minimum variance on the other and vice-versa.
Results: Compared to controls the sinistral schizophrenics have increased sources lateralized to the left hemisphere. When the sinistral schizophrenics however are compared to dextrals then the dextral schizophrenics have increased sources in the right hemisphere. When the dextral schizophrenics (n=49) are compared to dextral controls (n=65) the sources are increased in the right hemisphere either in the right frontal or right temporo-parietal region in all bands and conditions. The implications of these somewhat unexpected findings will be discussed.
Conclusions: The increased left hemispheric sources in sinistral schizophrenics is consistent with this group being pathological left handers. Considering the dextral schizophrenics the unexpected findings of increased right hemispheric sources may be the result of transcallosal disinhibition, given, the large body of evidence relating the schizophrenic syndrome to predominantly, dominant hemispheric dysfunction.

FC-10-003
Erythrocyte membrane fatty acids and transition to psychosis in ultra-high risk individuals: Basic research findings from a RCT

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Objectives: Reduced levels of erythrocyte arachidonic acid (AA) and docosahexaenoic acid (DHA) have been described in schizophrenia. No study has yet examined the fatty acid composition in the prodromal phase of psychosis, or the relationship between fatty acids and transition to psychosis.
Methods: The study sample comprised 81 ultra-high-risk individuals (according to criteria of Yung et al., 1998) (mean age=16.4, SD=2.1 years) who participated in a 12-week RCT of 1.2 g/day omega-3 fatty acids vs. placebo (ClinicalTrials.gov number, NCT00396643). The intervention period was followed by a 40-week monitoring period. Measures included PANSS, MADRS, and GAF. Fatty acids were determined at baseline using gas chromatography. Primary outcome of interest was conversion to psychotic disorder.
Results: Low DHA ($p<0.05$) and high n-6:n-3 ration ($p<0.01$) correlated with more severe negative symptoms at baseline. Low trans-vaccenic acid ($p<0.01$) correlated with more severe PANSS global symptoms at baseline. 93.8% participants (76/81) completed the intervention. By study end (12 months), 4.9% (2/41) individuals in the omega-3 group and 27.5% (11/40) in the placebo group made a transition to psychosis ($p=0.004$). Cox regression analysis controlling for effects of treatment revealed low baseline trans-vaccenic acid as a significant predictor of transition to psychosis in ultra-high-risk individuals ($p<0.05$), while both DHA and AA did not predict transition.
Conclusions: Membrane phospholipid abnormalities may be associated with both psychopathology and the onset of psychotic disorder in ultra-high-risk individuals. The most important finding of the RCT, however, is that a 12-week intervention with omega-3 fatty acids was found significantly superior to placebo in preventing the onset of psychotic disorder over the entire study period of 12 months.

FC-10-004
Impaired predictive component of smooth pursuit in schizophrenia

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Objectives: Eye tracking dysfunction is an electrophysiological endophenotype usually studied in schizophrenia. Smooth pursuit eye movements use prediction based on internal representation of target movement. This component has been studied by comparing the gain, i.e. the ratio of eye velocity to target velocity, during predictable (pure sinusoid) and unpredictable (pseudo-random stimuli composed of a mixture of sinusoids of different frequencies) target motions. The aim of this experiment was to study the predictive component and the pursuit performances in schizophrenics as compared with controls.
Methods: Fifty-one schizophrenics and twenty-one controls were studied. During a predictable task, subjects were asked to track a target which moved in horizontal sinusoidal waveform at 0.4 Hz. The smooth pursuit gain was computed as the ratio of the amplitude of eye velocity to target velocity. For unpredictable task, the target motion was composed of five sinusoidal waveforms: 0.1, 0.2, 0.4, 0.6 and 0.8 Hz. The pseudo-random pursuit gain was calculated for each subject and each frequency.

Results: The mean sinusoidal smooth pursuit gain was significantly decreased in schizophrenics as compared to healthy controls with no significant differences between patient's groups. During pseudo-random task at 0.4 Hz, all groups were similar for gain. The gain was higher during predictable target as compared to pseudorandom stimulus at 0.4 Hz. However the difference between the means of the gain at the two paradigms was significantly lower in schizophrenics as compared to controls. No correlation was found between the gain and any of the clinical variables.
Conclusions: The predictive component was assessed by calculating the difference of gain between sinusoidal and pseudo random smooth eye velocity. This difference was lower in schizophrenics. The predictive mechanisms involved in smooth pursuit were impaired in schizophrenic patients.

FC-10-005
Neurocognitive impairments among first-epidode psychotic patients without drug consumption

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Objectives: To study potential neurocognitive impairments among stabilized patients with a first psychotic episode without drug consumption compared to healthy people.
Methods: 21 patients (mean age: 23,8 years old ± 5,1 sd) and 7 volunteers (mean age: 22,42 years old ± 3,6 sd) performed a neurocognitive battery assessing orbitofrontal (OFC) functions (Iowa Gambling Task -IGT-), dorsolateral prefontal (DLPC) functions (WCST, STROOP test, Trail Making Test A-B), and also memory (WMS, WAIS information and vocabulary, Rey-Osterrieth Complex Figure Test) and attention (Toulouse-Pierron test). We also included MMSE as a global measure of mental functioning. Inclusion criteria were: 1) first psychotic episode 2) less than 6 months of psychopharmacological treatment, 3) steady phase of their psychotic illness. For statistical analysis we used the Mann-Whitney test ($p<0.05$).
Results: No statistical significance was found on the global scores on the IGT between first-episode patients and healthy subjects. Our findings suggested a dissociation between the tasks sensitive to DLPC [WCST errors (0,010), WCST categories (0,055)] and tasks sensitive to OFC. Furthermore, we found significant impairments in terms of memory and learning [WMS logical memory (0,002), WMS digit span (0,017), WMS visual reproduction (0,031), WMS verbal paired associates (0,031), WAIS vocabulary (0,017)] and attention [STROOP words (0,008), STROOP colors (0,027)]. MMSE score was also statistically significant (0,023).
Conclusions: The present findings suggested that DLPC functions are impaired at the onset of the illness while orbitofrontal functions might have a subsequent deterioration related to the progression of the illness itself, as previous studies showed.

FC-10-006
State and trait aspects of auditory oddball event-related potentials in schizophrenia

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Objectives: The pattern of auditory oddball event-related (ERP) abnormalities in schizophrenia is well established, however, the data on its trait and state aspects are rather controversial.
Methods: The present study comprised the family studies in 116 parents and 35 siblings of patients with schizophrenia. The dynamics of ERP parameters during the in-patient period, the neurophysiological abnormalities in the patients in remission (examined at least 6 months after the discharge from the clinic), as well as the correlations between the PANSS scores and neurophysiological characteristics were also studied (on the whole, 45 patients with schizophrenia were examined). The control group included 65 mentally healthy subjects without family loading of mental illnesses. Auditory ERPs were recorded in the standard auditory oddball paradigm (tones, 60 dB, 80% non-targets (1000 Hz) and 20% targets (2000 Hz)).
Results: Main findings comprised P300 reduction and prolongation and non-target N100 reduction in the parents of patients with schizophrenia. Against the background of marked reduction of psychopathological symptoms, the significant difference by P300 amplitude between the patients and the controls was found only in the single leads (however, the correlations between PANSS scores and P300 amplitude didn't reach the level of significance). P300 prolongation and non-target N100 reduction persisted both in the in- and out-patient groups, while N200 prolongation and P200 reduction were mostly pronounced during in-patient period.
Conclusions: Thus, P300 reduction, P300 prolongation, non-target N100 reduction merit attention as the possible endophenotypes of the disease, however the former phenomenon is also markedly modulated by the state of a patient. It was assumed that P300 decrease reflects the abnormalities in a wide circuit of cortical and subcortical structures part of which can be restored to almost "normal" functioning. On the other hand, non-target N100 reduction is due to the activity of a fewer and probably more consistently impaired generators.

FC-10-007

The clinical correlate of neurological soft signs in an epidemiolo gically representative sample of first episode psychosis patients. Evidence from the Picos Veneto study

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Objectives: Neurological Soft Signs (NSSs) are minor neurological abnormalities in sensory and motor performance identified by clinical examination. NSSs are located to three neurological domains: integrative sensory function, motor coordination and motor sequencing. Several authors found an association between NSSs and negative symptoms. The present study aims to test whether 1) there is a diagnostic specificity of NSSs and 2) patients with more NSSs have a higher level of negative symptoms.

Methods: This study was conducted in the context of the Psychosis Incident Cohort Outcome Study (PICOS), a large multisite research taking place in the Veneto Region (Italy), aiming to characterise patients experiencing their first episode of psychosis and to develop a comprehensive predictive model of outcome, by integrating clinical, social, genetic and MRI data. Patients were assessed by using a set of standardised measures such the Neurological Examination Scale (NES) and the Positive and Negative Syndrome Scale (PANSS).

Results: At baseline 351 patients were recruited. Sixty-two patients had the NES assessment, 65% were males with mean age of 31. Twenty-two percent had an ICD-10 diagnosis of schizophrenia, 56% of non affective and 22% of affective psychosis. This sample is representative of the whole cohort with respect to socio-demographic and clinical characteristics. It was found that schizophrenic patients tend to have more severe NSSs in primary neurological subscale, even if the signs depending by antipsychotic side effects were removed. There is a correlation between NES and PANSS, showing that patients with greater negative and/or total symptom score in the PANSS have higher NSSs, particularly in the sensory and sequencing subscales.

Conclusions: Identifying whether NSSs are associated with a specific symptom profile would be informative of the neurobiological substrate of psychosis: the present data suggest that psychotic patients having higher sensory and sequencing NSS could have parietal and frontal neurological dysfunctions.

FC-11
Affective Disorders (Bipolar)

FC-11-001
How often bipolar disorder merges after a diagnosis of unipolar depression?

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Objectives: Follow a cohort of patients that have been diagnosed with Major Depression and measure the occurrence of a subsequent Bipolar Disorder diagnosis.
Methods: IMS LifelinkTM is an integrated employer claims database. It represents the health care experience of roughly 1.8 million employees, dependents, and retirees. The databse contains inpatient and outpatient encounters, as well as prescriptions. In a cohort study design, a group of 11,517 patients initially diagnosed with unipolar depression were followed for 7 years.
Results: The incidence of bipolar disorders in this unipolar cohort was 1.7% (n= 1,013). Significant differences emerged in age at with an incidence of 5.7 % in younger patients (18-34 years) compared with 3.8% in 35-54 y.o patients and 2.5% in >= 55 y.o. Unipolar depressed patients were significantly more likely than bipolar patients to present more diabetes, cardiovascular diseases and neoplams. Those with histories of substance abuse showed a significantly higher rate of switching to bipolar illness (incidence 5.0% vs. 1.7%). Patients with initially bipolar disorder (n=2,057) were more likely to have psychiatric hospitalisations, ER visits and use of more than 2 psychiatric medications.
Conclusions: Young patients with diagnosis of unipolar depression and history of substance abuse may be at especially high risk for eventually developing bipolar disorder. Greater attention to recognising those at highest risk for switch and the need for a longitudinally based diagnostic process in the study of bipolar disorder.

FC-11-002
Women with bipolar disorder: Clinical challenges

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Objectives: The management of bipolar disorders across the female reproductive life cycle (menarche to menopause) imposes a challenge to clinicians. The critical review of the management of bipolar disorders in a large community practice across the female reproductive life cycle (from menarche to menopause and beyond). to assess the safety of psychotropic medication.
Methods: Female-specific reproductive events and hormonal fluctuations appear to impact the course of bipolar disorder over a lifetime.The management of this disorder is an ongoing challenge. This presentation examines data based on a literature review of treatment options and a retrospective chart review. The charts of 20 pregnant women with bipolar disorder in an outpatient urban community setting will review the treatment practices and focus on safety of psychotropic medications in women with bipolar disorder.
Results: Monitoring the bipolar patient during pregnancy and the postpartum period is critical. Patients and family members should be involved in the treatment decision process, and informed of the risks associated with treatment discontinuation, safety of psychotropic agents and substance abuse. Prophylaxis with mood stabilizers reduces the burden of illness and decreases rates of relapse. Pregnancy outcomes in a community setting were similar to those presented in published results.
Conclusions: Treating women with bipolar disorder remains a significant challenge for physicians. Reproductive events and hormone fluctuations during a woman's lifecycle requires ongoing monitoring. Treatment during pregnancy/lactation must balance the benefits against the risks. Monitoring the patient through the postpartum period is critical to the health of the newborn and mother. Clinical experience demonstrated no major congenital malformations and reflected the results published in literature.

FC-11-003
Do psychotic symptoms in mania predict later course of bipolar disorder?

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Objectives: Although psychotic symptoms are typically reported as present in about half of patients with a manic or mixed episode, their influence on the course of bipolar disorder are unclear. Using data from the EMBLEM (European Mania in Bipolar Longitudinal Evaluation of Medication) study, a 2-year prospective observational study of patients with an acute mania/mixed episode in 14 European countries, we determined the presence and severity of psychotic symptoms, the persistence of such symptoms over a 2-year follow-up period, and their influence on time to recovery and remission.
Methods: Symptom severity was assessed using the CGI-BP, which gave overall, mania and depression scores on a scale of 1-7. Hallucinations/delusions were rated using a similar scale: score 0-3 = no/mild psychosis, score 4-5 = moderate psychosis, score 6-7 = severe psychosis.
Results: Of the 2416 patients eligible for 2-year follow-up, 960 (39.7%) had at least moderate psychotic symptoms at baseline. Of these 960 patients, 22.1% had severe psychosis. Compared to patients with moderate and severe psychosis, more of those with no/mild psychosis were older, female, outpatients, in a relationship and living together, in an independent residence, had less alcohol and cannabis use problems, and had lower mania scores (total YMRS, CGI-BP overall and mania) but higher CGI-BP depression scores at baseline. Kaplan-Meier survival analysis showed that moderate psychosis resolved faster than severe psychosis. Cox regression modelling showed that severe psychotic symptoms were significantly associated with a longer time to remission versus no psychotic symptoms (relative risk 0.71, 95% confidence limits 0.51-0.99, p=0.041). There were no differences between moderate psychosis and no psychosis.
Conclusions: Bipolar patients with severe psychotic symptoms present during a manic or mixed episode may have more enduring psychosis which may have a negative effect on long-term outcomes.

FC-11-004
Cognitive Behavior Therapy (CBT) versus Psychoeducation (PE) in bipolar disorder: A randomized controlled study

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Objectives: The purpose of this randomized controlled group therapy study is the investigation of the effects of CBT (Cognitive Behavior Therapy) versus PE (Psychoeducation) additional to ongoing prophylactic medication treatment on relapse prevention, quality of life, illness concepts, coping-behavior, compliance and attitudes to medication in patients with bipolar disorder.
Methods: 100 patients with bipolar disorder were treated either with CBT (treatment manual of Schaub et al, 14 weekly sessions) or with PE (3 sessions with bibliotherapy also within 14 weeks) togehter with ongoing pharmacotherapy. Booster sessions after 6 and 9 months.Diagnostic interviews were carried through with MINI, evaluations with CGI, scales for depression and mania, quality of life, illness-concepts, attitudes to medication,compliance, coping-behavior, number of episodes and number and duration of inpatient episodes 1 and 2 years before and after the intervention.
Results: 100 patients (age 40+/-11 years, 59% female sex, illness duration 183+/-131 months were treated with CBT (n= 52) or PE (n=48). Results after 14 weeks of treatment demonstrate a significant improvement for both groups for quality of life, illness concepts and compliance for medication.
Conclusions: 3 sessions PE with bibliotherapy have similar improvements to 14 sessions CBT after 14 weeks of treatment on compliance, illness concepts and quality of life. The longterm-effects also on relapse prevention will be investigated further at 12 and 24 months follow-up.

FC-11-005
Cross-prevalence of migraine and bipolar disorder

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Objectives: We explored the prevalence and clinical characteristics of bipolar disorder (BD) patients according to their migraine status. We also examined the psychiatric comorbidity in migraine sufferers.
Methods: 323 BD I/II subjects were studied, using the Schedule for Affective Disorders and Schizophrenia, Lifetime version (SADS-L) format; and the Structured Clinical Interview for DSM-IV disorders (SCID) as diagnostic interviews, as well as a structured questionnaire to assess the presence of migraine. Statistical analyses were conducted using parametric analysis and log-linear models. Additionally, 102 migraine patients were interviewed using SADS-L, and the current and lifetime psychiatric morbidity was analyzed.
Results: 24.5% BD patients had co-morbid migraine; those with BD II had a higher prevalence (34.8%) when compared to BD I (19.1%) ($p<0.005$). Compared with the BD group without migraine, those BD patients with co-morbid migraine had significantly higher rates of suicidal behaviour, social phobia, panic disorder, generalized anxiety disorder, and obsessive compulsive disorder. In the second study, 41.2% of the sample had a current psychiatric diagnosis; the most frequent diagnosis was major depressive disorder (16.6%); and 73.5% had a lifetime psychiatric diagnosis, with major depressive disorder (30.4%) and BD II (7.8%) being the most prevalent.
Conclusions: Migraine has a higher prevalence within the BD population, particularly among BD II subjects, and it is associated with suicidal behaviour and comorbid anxiety disorders. Moreover, migraine sufferers have high rates of current and lifetime psychopathology. A greater understanding of this co-morbidity may contribute to our knowledge of the underlying mechanisms associated with bipolar disorder.

FC-11-006
Cognitive emotion regulation and inhibitory mechanisms in bipolar disorder and schizophrenia

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Objectives: Impaired inhibition of emotional material may contribute to maladaptive emotion regulation in bipolar disorder and schizophrenia, with potential negative implications both clinically and in terms of interpersonal and social functioning. We examined associations between emotional inhibition and the conscious employment of cognitive emotion regulation strategies in bipolar disorder and schizophrenia.
Methods: Preliminary data are reported for nine bipolar disorder (Mean age = 41.89yrs, SD = 10.87) and fourteen schizophrenia patients (Mean age = 47.5yrs, SD = 8.52). All participants completed the Affective Go/No-Go test of emotion inhibition from the Cambridge Neuropsychological Test Automated Battery (CANTAB), and the Cognitive Emotion Regulation Questionnaire to assess the tendency to employ particular cognitive strategies to regulate emotional responses to negative life events.
Results: There were no significant differences between bipolar disorder and schizophrenia participants in the pattern of errors or latencies on the emotional inhibition task. However, there were group differences in the employment of cognitive strategies for regulating emotions: bipolar patients demonstrated reduced tendency to engage in 'positive reappraisal', 'other blame', 'positive refocusing', and 'refocus on planning' compared to schizophrenia patients. Furthermore, group tendencies toward employment of these particular cognitive regulation strategies were differentially associated with inhibitory deficits for emotional material, reflecting divergence in the significance of emotion processing biases in bipolar disorder and schizophrenia.
Conclusions: These preliminary data suggest that impaired emotional inhibition and emotion processing biases may have differential effects upon the employment of conscious, cognitive emotion regulation strategies in bipolar disorder and schizophrenia.

FC-12
Genetics I

FC-12-001
Finger ratio differences and psychological traits: A case for epigenetics?

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Objectives: Prenatal testosterone plays important roles for sexually dimorphic phenotype development. High prenatal testosterone makes human being more masculine. Low finger length ratio (2nd digit/ 4th digit: 2D/4D, masculine), especially on right hand, is thought to be influenced by high prenatal exposure to testosterone. There's possibility that epigenetic changes caused by testosterone do some role for the sexual differences and finger length ratio. We examined the relationship between some psychological traits (trait anxiety, depression, internet addiction and empathy) and finger length ratio for college students to investigate the relationship among prenatal testosterone, 2D/4D and psychological traits. The relationship between 2D/4D and internet addiction was examined for the first time in the world.
Methods: A total of 187 colleague students(male:67, female: 120) completed self-report measures of Spielberg Trait Anxiety Inventory (STAI), Beck Depression Inventory (BDI), Young's internet addiction test and empathy scale (Mehrabian and Epstein's scale, 1972). After photocopying right palm of participant's hand, the length of second and fourth finger was measured from basal crease to tip using vernier caliper. Statistical analysis using correlation and t-test were performed to examine the relationship between psychological traits and 2D/4D.
Results: Significant sex differences were observed on the average ratio of 2D/4D. Men had a lower 2D:4D ratio than women, confirming the typical sex difference in digit proportions. Men with high 2D/4D showed higher trait anxiety scores($r=.390$, $p<.003$) and higher BDI score($r=.273$, $p<.05$). There were no statistical differences between Young's internet addiction test score and 2D/4D. Women with high 2D/4D showed higher empathy scale score($r=0.270$, $p<.01$).
Conclusions: Men with high 2D/4D(feminine type) showed higher score in feminine phenotypes such as anxiety and depression. Women with feminine 2D/4D showed higher score in empathy scale (a feminine phenotype). We discussed the epigenetics of prenatal sex hormone in the development of human mind's sexual differences.

FC-12-002
mRNA expression of candidate genes are blood biomarkers for major depression

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Objectives: An increasing number of mRNAs have been associated to psychiatric disorders. Despite the importance of the nervous system function in the pathophysiology, some studies showed that relevant variations of mRNA expression is also observed in peripheral blood samples. Our aim was to test this paradigm in major depression by analyzing the level of expression of selected mRNAs.
Methods: We collected blood samples from a very homogeneous population of 10 patients suffering from recurrent major depressive disorder with melancholic major depressive episode (MDE) and a HDRS-17 items score > 25 at inclusion, as well as 10 age- and sex-matched controls. The molecular evolution of MDE was also assessed by collecting blood samples from the same patients 8 weeks later. After an extensive review of the biological data related to mood disorders, we retained 83 candidate for mRNA level of expression analysis. We then determined the mRNA level of expression in peripheral blood mononuclear cells (PBMCs) by quantitative real-time RT-PCR.
Results: Patients exhibited a global clinical improvement during the follow-up. Among 83 gene candidates, 32 were excluded from the final analysis due to a poor expression in PBMCs. By contrast, we found 14 differentially expressed mRNAs between patients and controls during MDE and/or 8 weeks later. Noteworthily, PPM1K, CREB, HTR1B, IL2RG and TPH1 may constitute MDE biomarkers.
Conclusions: Overall, our results indicate that PBMCs obtained at different time intervals during MDE progression represent a promising avenue to discover predictive markers of this disease.

FC-12-003
Dopamine and Cannabinoid receptors gene alterations and high impulsivity between two strains of mice

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Objectives: Impulsivity is a multifactorial attribute characterized by hyperactivity, attention impairment, novelty-seeking, anxiety-like behavior and delay discounting. The purpose of this study was to identify gene expression alterations in the brain of two strains of mice displaying a behavioral endophenotype with low or high impulsivity trait.
Methods: Behavioral tests were conducted to characterize the differences in motor activity, anxiety-like behavior, attention, memory, and impulsivity between DBA/2J and A/J strains of mice. Relative gene expression (dopamine D2 receptor (DrD2), cannabinoid CB1 and CB2 receptors) was measured by real time reverse transcriptase-PCR from total RNA isolated from microdissected selected brain regions.
Results: Behavioral analyses revealed that DBA/2J mice presented hyperactivity compared to A/J mice. DBA/2J displayed high level of anxiety (light/dark box), showed impaired preattentional level (prepulse inhibition test) and short- and long-term memory (step down inhibitory avoidance test). DBA/2J were more prone to novelty seeking behavior (head-dipping) and earned significantly less delayed rewards (delayed reinforcement task) than A/J mice. The increased impulsivity behavior found in DBA/2J mice was associated to reduced DrD2 receptor gene expression in the caudate-putamen (CPu), increased CB1 gene expression in the CPu and hippocampus (Hipp) and decreased in the amygdala (Amy), and enhanced CB2 gene expression in the Amy.
Conclusions: These results revealed that high impulsivity trait could be associated with profound alterations in the expression of the DrD2, CB1 and CB2 genes in specific brain regions. In addition, these data suggest that the functional manipulation of these receptors may result beneficial to control the impulsivity in a variety of neuropsychiatric disorders.

FC-12-004
Association study of tryptophan hydroxylase 2 gene in bipolar patients with panic disorder comorbidity

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Objectives: Panic disorder (PD) is a common and potentially disabling condition characterized by unexpected panic attacks, fear of their recurrence or harmful consequences. Frequent comorbidity between PD and mood disorders has been widely reported in clinical and epidemiological studies and, recently, an increasing attention has been paid to the co-occurrence of PD and bipolar disorder. Several studies have shown that 5HT level is important in the modulation of panic symptoms, therefore, serotonin-related genes are good candidates for the study of PD like tryptophan hydroxylase 2 gene might be a good candidate gene since TPH2 is a rate limiting enzyme in the serotonin biosynthetic pathway and plays an important role in the regulation of serotonergic function. In this study we aimed at investigating the PD comorbidity in Bipolar Patients and associations with TPH2 polymorphisms.
Methods: Our sample consisted in 285 individuals with bipolar disorder (47 with panic disorder comorbidity) which were genotyped for eight Tag-SNPs covering the whole gene of human THP2. Statistical analyses were performed by UNPHASED version 3.0.12 and Haploview.

Results: In allelic analyses, we found an association between minor allele frequency and the presence of the panic comorbidity in rs11179000 (allele T/ p=0.04), rs1487275 (allele C/ p=0.02) and rs10879357 (allele A/ p=0.02). In genotypic analyses, we observed that the homozygotes TT (rs4448731), TT (rs4565946), GG (rs4760820) were more frequent in patients with panic comorbidity suggesting the genetic high risk factor localized on these genotypes (p=0.0004, p=0.005, p=0.006, respectively). The haplotype T-C (rs4448731, rs4565946) was significantly more frequent in BD patients with panic disorder comorbidity (p=0.005, padjusted=0.02). We should emphasized that these results survived after permutation tests.
Conclusions: Our results showed that bipolar patients with panic disorder comorbidity can have a different genetic liability as compared with patients withou this comorbidity. Further studies are needed to replicate the positive association that we observed.

FC-12-005
Genetic disease and mental health

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Objectives: This paper concerns genetic illnesses with a fatal prognosis Familial Amyloid Polyneuropathy (FAP) and the implications it has in the family system, or in the family's mental health.
Methods: We will present a study case: A family with a FAP member (the father), two daughters (in risk) and the wife. The wife is very depressed and the daughters are very anxious about the possibility of being carriers. We will present the interviews, ant the session's therapy. FAP is an inherited disorder in which the liver produces a mutation of transthyretin, (TTR-Met 30) a transport protein. Deposits of this abnormal protein results in progressive loss of sensation and motor function, organ failure, pain and weakness. It is a multisystemic disease, which attacks several organs, causing death in a few years (Average: 14 years). PAF is a degenerative disease, chromosomal dominant, with almost total penetration, which is transmitted from parents to offspring with equal distribution between the sexes. The primary cause of FAP is a variant of transthyretin (TTR), gene on chromosome 18. The transmission is from one generation to the next, never missing a generation, and the possibility of an individual with one carrier-parent developing the disease is 50%. The only way of knowing if one has the disease or not (when at risk) is to be tested by the genetics test or instead to wait for the symptoms (it is a hard wait).
Results: When a family has an inherent and fatal disease, everybody is affected, because they suffer or they see others suffering or they live in the anxiety for the future, so, all family and all their members needs support and help
Conclusions: At the end we conclude that genetics diseases need an interdisciplinary approach, as they affect all members, even those who are not carriers.

FC-12-006
The role of cGMP-nitric oxide pathway on learning and memory in rats

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Objectives: Nitric oxide (NO), a cell messenger for activating cGMP is produced by the activation of the enzyme nitric oxide synthase (NOS) in a wide varity of tissues including the brain (Cechova and Pajewski 2004). In recent studies NO had been shown to improve cognitive functions (Plech et al. 2003) which is supported by the fact that NOS inhibitors impaired learning and memory (Baratti and Kopf 1996). [1H-[1,2,4]Oxadiazole[4,3a] quinoxaline-1-one] (ODQ) is a highly selective, irreversible, heme-site inhibitor of soluble guanylyl cyclase and 3-bromo-7-nitroindazol (3-Br-7-NI) is a selective neuronal NOS inhibitor. The aim of this study was to investigate the effect of these compounds on learning and memory in passive avoidance and three panel runway paradigm in rats.
Methods: ODQ (5, 10 and 20 mg/kg), 3-Br-7-NI (5,10 and 20 mg/kg) were dissolved in DMSO and administered intraperitoneally 20 and 30 min. prior to tests respectively.The data were analysed by using ANOVA post hoc Tukey test.
Results: ODQ and 3-Br-7-NI both decreased the latency significantly in passive avoidance test in a dose dependent manner. Both drugs significantly and dose dependently increased the number of errors and latency in the three-panel runway test. The effect of 3-Br-7-NI was reversed by pretreatment with L-arginine (250 mg/kg). ODQ and 3-Br-7-NI had no effect on locomotor activity in any of the doses used.
Conclusions: Our results confirm that ODQ and 3-Br-7-NI impaired learning and memory and the effect of 3-Br-7-NI was found to be NO dependent. These findings suggest that the cGMP-nitric oxide pathway may play an important role in learning and memory.

FC-13
Brain Function I

FC-13-001
Allelic variation in the serotonin transporter promoter modulates cortical excitability

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Objectives: Neurotransmitter pathways such as the serotonergic system are supposed to be involved in the regulation of cortex excitability, thereby affecting neuropsychological functioning. This study investigated the impact of a functional polymorphism in the promoter region of the 5-hydroxytryptamine transporter gene (5-HTTLPR) on measures of motor cortex excitability
Methods: 120 healthy subjects with distinct 5-HTTLPR allele pattern underwent transcranial magnetic stimulation (TMS) as a non-invasive procedure that may be used for studying individual differences in motor cortex excitability.
Results: 60 subjects carrying one or two copies of the short 5-HTTLPR allele (s/s and s/l) showed a significant reduction in short intracortical inhibition (SICI, p = .012) and an increased cortical silent period (CSP, p = .042) as compared to 60 age- and gender-matched individuals homozygous for the long allele (l/l). In contrast, motor threshold (MT) and intracortical facilitation (ICF) did not differ significantly between groups.
Conclusions: The present results provide further evidence of a role for serotonergic transmission in the modulation of cortical excitability. Differential effects on the measures under study suggest a differential modulatory role of serotonin on distinct forms of cortical inhibition.

FC-13-002
Lipopolysaccharide-induced free radical formation in the striatum of mice

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Objectives: Encephalopathy associated with septic shock, but also psychiatric disorders might be caused by the central nervous formation of reactive oxygen species (ROS) associated with inflammation. Systemic application of lipopolysaccharide (LPS, 100 µg/kg i.p.), which serves also as a model for major depression, results in enhanced inflammatory processes characterized by stimulation of microglia, or macrophages, which then impair normal brain function. The aim of this study was to analyze the effect of peripherally applied LPS on the central nervous formation of ROS and IL-6 in wild-type and mice lacking the NADPH oxidase Nox2 subunit gp91phox.
Methods: Microdialysis was performed in the striatum of mice. Central nervous ROS were detected by Electron Spin Resonance spectroscopy using 1-hydroxy-3-methoxycarbonyl-2,2,5,5-tetramethylpyrrolidine (CMH) as reactant, infused via a microdialysis probe. IL-6 was measured in microdialysis samples by immunoassay. At the end of the experiments, blood was obtained by heart puncture for the detection of IL-6 in plasma.
Results: LPS significantly increased ROS formation in the striatum of wild-type mice and resulted in a significantly enhanced IL-6 production. LPS showed no enhanced ROS formation in gp91phox deficient mice, while central IL-6 was significantly increased. IL-6 plasma values were enhanced in both types of mice.
Conclusions: In conclusion, a gp91phox-containing NADPH oxidase complex is involved in the central nervous ROS formation after peripheral LPS stimulation and might be a pharmacological target in patients with septic shock.

FC-13-003
Optimise ECT techniques: The effects of pulse width manipulation on the amnesic side-effects of ECT treatment in depression

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Harm-Pieter Spaans

Objectives: Although electroconvulsive therapy (ECT) techniques have progressed in the past decades, retrograde amnesia remains an important adverse effect of ECT (Lisanby et al 2000), which prevents the more widespread use of this most efficacious treatment of depression. Studies suggest that clinicians can to a certain degree manipulate the efficacy and amnesic effects of ECT. Unfortunately more efficacious forms of ECT seem to induce more amnesia. ECT with bilateral electrode placement has been shown to be more efficacious than unilateral electrode placement but also carries an increased risk of memory problems (Sackeim et al., 1993). These authors showed that the relative strength of electrical stimulation above the seizure threshold was a major determinant for the efficacy of ECT. Unilateral ECT was more efficacious if the seizure was generated by an electrical stimulus with charges (mC) of at least two and a half times above the seizure threshold compared to an electrical stimulus just above seizure threshold. Higher electrical stimulations resulted in significantly more adverse cognitive effects. ECT studies have used electrical stimulation with brief pulse devices delivering pulse widths of 1 msec. Newer ECT devices can deliver pulse widths of 0.3 msec. or less, the so called ultrabrief pulse stimulation. Few studies are available thus far on the use of ultrabrief pulse devices, but the results are promising (Pisvejc et al., 1998; Lisanby & Sackeim 2001). In this study we aim to compare treatment with brief-pulse (1 msec.) versus ultrabrief pulse (0.3 msec.) stimulation. The amnesic effects and the antidepressive efficacy of both treatments are compared. We hypothesize that treatment with ultrabrief pulse stimulation has less adverse amnesic effects compared to treatment with brief pulse stimulation. This poster or free communication presents the preliminary results of this prospective single blind controlled study into cognitive effects in a clinical setting.

FC-13-004
Decreased BDNF serum levels in drug naïve non-depressed obsessive compulsive patients

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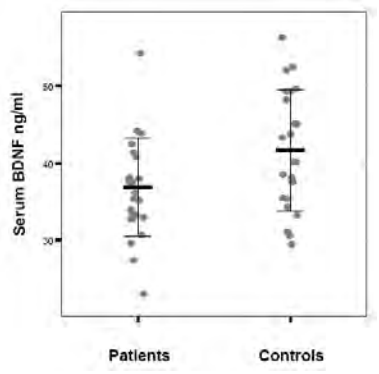
Objectives: There is lack of data regarding BDNF serum levels in patients with obsessive-compulsive disorder (OCD). The aims of the present study were: 1) to assess the serum BDNF content in a sample of drug naive patients with OCD without concomitant depression and without any recent severe psychological distress; 2) to assess whether changes in circulating BDNF may be associated to particular OCD clinical characteristics.
Methods: The affected subjects (N=24) were recruited from all drug naive patients with a principal diagnosis of OCD and consecutively referred to the Mood and Anxiety Disorders Unit, Department of Neurosciences, University of Turin. In parallel a control group of 24 unrelated volunteers matched for gender, age and body mass index with the patient group was enrolled. Venous blood samples for patients and controls were collected in the morning after an overnight fast. BDNF levels were measured by the ELISA method.
Results: Serum BDNF levels differed between OCD patients (36.90 +/- 6.42 ng/ml) and controls (41.59 +/- 7.82 ng/ml) and the difference was statistically significant (p=.028) (see Figure 1). Patients with higher levels of serum BDNF showed more severe OCD symptoms (r=.434; p=.034). Moreover, in patients with a lifetime history of depressive disorders the serum BDNF levels were significantly lower (33.25 +/-6.02 ng/ml) than in those without (38.72 +/- 59.63 ng/ml) a lifetime history of depressive disorders (p = .046).

Conclusions: In conclusion, our findings reveal for the first time that serum BDNF levels are decreased in drug naïve patients with OCD and without concomitant depression. There is also evidence suggesting that these levels are lower in patients with lifetime history of unipolar depression and that a higher degree of obsessive-compulsive symptomatology is associated with higher serum BDNF levels. Future studies are required to determine whether the antiobsessional treatments can induce any change of serum BDNF levels.



FC-13-005
Verbal fluency and BDNF Val66Met polymorphism in schizophrenia

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Objectives: The two types of tests, semantic and phonological, seem to have different neuronal substrates. Our objective was to investigate whether performances in phonological and semantic verbal fluency were selectively associated with genotype of BDNFVal66Met polymorphism in patients with schizophrenia.
Methods: Association study (123 outpatients with schizophrenia: 86 men and 37 women; 130 unrelated healthy controls: 63 men and 67 women)
Results: No difference in BDNF genotype distribution was observed between the patients and controls. When patients were classified on the basis of BDNF genotype (carriers of 1 or 2 copies of the MET alleles vs. homozygous VAL carriers), no differences between groups were observed on age, educational level (years of study), duration of the disease, and gender composition. Regarding verbal fluency, scores related to semantic fluency were associated to genotype, but not those of phonological fluency. Patients homozygous for the VAL allele produced significantly more words in the semantic categories of «animals» and «fruits». Effect size of these differences was medium (d = 0.43 for «fruits», d = 0.52 for «animals»). BDNF genotype accounted for 3.9% of the variance of both scores of semantic verbal fluency.
Conclusions: Findings of this study mirrored the neuropsychological dissociation between semantic and phonological VF by showing unique association of the semantic VF performance in schizophrenia to the BDNF Val66Met polymorphism.

FC-14
Other II

FC-14-001
Suicide risk in relation to various psychiatric disorders

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Objectives: Persons with history of hospitalized psychiatric illness are at high risk for suicide, however, variation of the risk by sex, age and psychiatric diagnosis needs to be explored in a more detail.
Methods: This large study is based data from Danish national population registers and includes all 13,681 male and 7488 female suicides and 273,371 male and 149,757 female population controls matched for sex, age and calendar time. Risk of suicide is estimated by conditional logistic regression and adjusted for socio-economic factors.
Results: The study shows that suicide risk was significantly elevated for patients with a history of hospitalized psychiatric illness and the estimated risk varies significantly by sex and across diagnosis. Further adjustment for personal socioeconomic status eliminated these estimates only to a limited extends. The elevated risk was substantially greater for male patients diagnosed with depression, borderline personality disorders or adjustment disorders and for female patients diagnosed with borderline personality disorders, bipolar disorders, depression, or substance abuse disorders. Dementia increased the risk at the lowest level for both sexes. At the same time, the increased risk associated with various disorders declines with increasing age although the pattern of estimated risks across diagnosis differed slightly by age group. For young people, the disorder increasing suicide risk the most was depression in men while it was schizophrenia in women. For middle age adults, depression raised suicide risk strongest in men whereas borderline personality disorders increased the risk strongest in women. For people above 60 years old, reaction to stress and adjustment disorders elevated the risk the most.
Conclusions: Psychiatric disorder is strongly associated with suicide but the risks and therefore the approaches to prevention differ between different groups of patients.

FC-14-002
Insights into the suicidal mind

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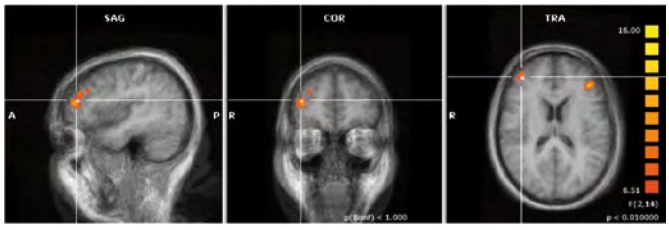
Objectives: To investigate the neural activation associated with the recall of attempted suicide.
Methods: Patients who recently had attempted suicide were asked to participate in a narrative interview. Interview sequences with descriptions of (1) mental pain, of (2) suicide action, and of (3) neutral activity were used for script-driven recall during fMRI scanning.
Results: Areas of frontal deactivation were found during both, recall of mental pain and suicide action. Mental pain was associated with a deactivation in the left medial prefrontal cortex and the anterior cingulate cortex, while no such pattern was found in the suicide action condition.
Conclusions: The results imply a two-phase model of suicidal behavior: (1) an experience of mental pain, followed by (2) a suicide action as a solution to mental pain, which is deemed unbearable by the individual. The pattern of neural activation in the mental pain condition suggests that the experience of mental pain is characteristic of a traumatic experience, in which problem-solving capacities are seriously impaired. A two-phase model of suicidal behavior may help the development of specific treatments focusing on coping with mental pain.



FC-14-003
Thyroid axis activity and suicidal behavior in depressed patients

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Objectives: The aim of this study was to investigate the relationship between suicidal behavior and hypothalamic-pituitary thyroid (HPT) axis activity in depressed patients.
Methods: The serum levels of thyrotropin (TSH), free thyroxine (FT4), and free triiodothyronine (FT3) were evaluated before and after 8 AM and 11 PM TRH challenges, on the same day, in 95 medication-free DSM-IV euthyroid major depressed inpatients and 44 healthy hospitalized controls
Results: Compared to controls: 1) patients with a positive suicide history (PSH; n=53) showed lower basal FT4 (at 8AM: $p<0.005$; at 11PM: $p<0.03$), but normal FT3 levels, while patients with a negative suicide history (NSH; n=42) showed normal FT4 and FT3 levels; 2) TSH responses to TRH (delta TSH) were blunted in NSHs (at 8 AM: $p<0.03$; at 11PM: $p<0.00001$), but not in PSHs. Compared to NSHs, basal FT4 levels were reduced in PSHs (at 8AM: $p<0.002$; at 11PM: $p<0.006$). HPT parameters were not significantly different between recent suicide attempters (RSA; n=32) and past suicide attempters (PSA; n=21). However, compared to controls, RSAs showed lower 11PM-delta TSH ($p<0.04$) and lower basal FT4 values (at 8AM: $p<0.002$; at 11PM: $p<0.008$).
Conclusions: Our results, obtained in a large sample of depressed inpatients, indicate that various degrees of HPT axis dysregulation are associated with the history of suicide. In patients without a suicide attempt history, one may hypothesize that hypersecretion of hypothalamic TRH (as reflected by decreased TRH receptor responsiveness) represents a compensatory mechanism to maintain normal thyroid hormone secretion. In suicide attempters this mechanism is ineffective, but it is suggested that enhanced conversion of T4 to T3 would maintain normal T3 concentration. In recent suicide attempters this latter phenomenon could be associated with lower TSH reserves.

FC-14-004
HPT axis and personality traits in attempted suicide

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Objectives: Studies relating thyroid hormones to personality traits are few and mainly focused on forensic psychiatric populations. In delinquent male participants, the association between thyroid hormones and psychopathy- and aggression-related personality traits has been found. The aim of the study was to investigate personality traits, using the Karolinska Scales of Personality (KSP) in 100 euthyreoid suicide attempters.
Methods: Standard multiple regression analyses were conducted with TSH, T3, T4 and T3/T4 ratio respectively, as the dependent variable and KSP factors (Anxiety Proneness, Aggressiveness, and Impulsivity) and subscales (Detachment, Social Desirability, and Socialization) as independent variables.
Results: In men, but not in women, high scores on Aggressiveness and low on Detachment were associated with low T3/T4 ratio.
Conclusions: Suicide attempters exhibit greater lifetime aggression and detachment. Our finding is partly in line with earlier studies of male forensic psychiatric populations. HPT axis may be related via personality trait Aggressiveness to suicidal behaviour in men.

OTHER - Free Communications

FC-14-005
The effect of restricting access to a suicide jumping site

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Peter Herbison

Objectives: The road to a headland that had become a suicide jumping hotspot was temporarily closed because of construction work. This created an opportunity to assess whether loss of vehicular access would lead to a reduction in suicides and emergency police callouts for threatened suicide at the site.
Methods: Deaths at the headland were ascertained for a 10 year period before road closure and for two years following closure using records from the local police inquest officer, the coroner's pathologist and Marine Search and Rescue. Police provided a list of police callouts for threatened suicide at the site for a four year period before closure and for two years following closure. Simple rates were compared and incident rate ratios were calculated where possible.
Results: There were 13 deaths at the headland involving suicide or open verdicts in the 10 years before access was restricted, and none in the two years following road closure. This difference was statistically significant (incident rate difference of 1.3 deaths per year, 95% Confidence Interval (CI) 0.6 to 2.0). No jumping suicides occurred elsewhere in the police district following the road closure. Police callouts for threatened suicide also fell significantly, from 19.3 per year in the 4 years prior to road closure to 9.5 per year for the following two years (incident rate ratio 2.0: 95% CI 1.2 to 3.5).
Conclusions: This study provides evidence that preventing vehicular access to a suicide jumping hotspot was an effective means of suicide prevention at the site. There was no evidence of substitution to other jumping sites.

FC-14-006
Psychiatric manifestations of Hashimoto's disease / encephalopathy

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Objectives: The existence of hashimoto encephalopathy (HE) in patients with hashimoto thyroidits (HT) has been discussed with controversy, as well as its possible pathophysiology. Two retrospective studies from neurology have pointed to the relevance of HE. There are no equivalent studies from psychiatry. Therefore, we set out to investigate the occurrence of a potential HE, its clinical manifestations and the possible role of thyroid and brain functioning.
Methods: A retrospective analysis of all cases treated over the last 10 years at the Department of Psychiatry and Psychotherapy of the University Clinic in Ulm, Germany, was performed. All cases were investigated by means of a standardised assessment with these items: reliability of the diagnosis HT and HE according to a new rating scale, evaluation of symptoms at admission, laboratory parameters, pathologies in MRI, EEG and CSF, therapy and outcome.
Results: A total of N=37 cases of possible HT were found. Among these, about 2/3 had a secure diagnosis of HT. As expected, middle-aged women were most frequently concerned. On admission the clinical manifestations were: depression (41%), atypical depression (22%) psychotic disorders (19%), and others. As for laboratory tests, no typical pattern of thyroid hormones, TSH and anti-TPO/-TG antibodies was observed. These parameters did not correlate with psychopathology and even were contrary to intuition (N=4 depression in hyperthyroidism, N=1 mania in hypothyroidism). N=9 cases had proven brain pathologies (MRI, EEG or CSF) which excluded a psychiatric disorder in the narrow sense.
Conclusions: Our pilot study indicates that HT and HE may be a disorder to look for in patients with psychiatric syndromes. The exact mechanism of brain affection and the specific role of both thyroid hormones and antibodies is still poorly understood. Specific testing of thyroid status, antibodies and brain integrity is recommended for a patient subgroup (atypical depression, middle-aged female, history of thyroid disorder).

FC-15
Affective Disorders (Unipolar) II

FC-15-001
Inter-individual differences in positive affect and vulnerability to chronic stress in the rat: A model for male depression?

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Tanel Mällo, Denis Matrov, Kadri Kõiv

Objectives: Because negative and positive emotionality do not form a continuum but rather are orthogonal, the trait of experiencing positive affect could make a unique contribution to the pathogenesis of affective disorders. Animal models for positive emotionality are scarce but 50-kHz ultrasonic vocalizations (USVs) in rats have been associated with positive and rewarding experience. We have previously reported that stable inter-individual differences in the level of these USVs (chirps) are associated with differences in anxiety-related behaviours.
Methods: Effect of four weeks of chronic variable stress were measured on depression- and anxiety-related behaviours, and on cerebral oxidative metabolism by cytochrome oxidase histochemistry, in both male and female high (HC) - and low (LC) -chirping rats.
Results: Significant differences in brain oxidative metabolic activity were found between male and female rats, with lower metabolic activity in females in several brainstem and reward-related regions and higher metabolic activity in amygdala and related limbic regions. Stress almost exclusively affected male LC-rats and female HC-rats, increasing metabolic activity in all affected regions in male LC-s and decreasing it female HC-s. No systematic behavioural effect of stress was evident in females, suggesting that the changes in regional activity in the brain contributed to adaptation with stress. In LC-males, stress elicited increased levels of 22-kHz USVs, earlier and more stable reduction of weight gain, lower sucrose intake and preference, and higher levels of immobility in the forced swimming test.
Conclusions: Regional activity patterns of oxidative metabolism differ between male and female rats. Stress-induced behavioural changes, accompanied by increased metabolic activity in limbic brain regions, are indicative of greater vulnerability to chronic variable stress in male rats with low positive affectivity. Thus, these findings support the notion that low inherent positive affectivity predisposes to anxiety and affective disorders, but this is particularly characteristic to males.

FC-15-002
Depression is associated with decreased blood pressure but antidepressant use increases the risk for hypertension

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Eco de Geus, Richard van Dyck, Brenda Penninx

Objectives: It has been hypothesized that psychopathology is associated with increased blood pressure. This may play an important role in the increased risk of cardiovascular disease among individuals with psychopathology. The present study compared blood pressure levels between subjects with anxiety and depression and healthy controls. The effects of antidepressants were taken into account, since antidepressant use is associated with low cardiac vagal control and high heart rate (HR), which are known to influence blood pressure regulation.
Methods: Blood pressure data were obtained in a large cohort study, the Netherlands Study of Depression and Anxiety (NESDA, N=2981). Based on the DSM-IV based CIDI interview, 590 participants were classified as controls, 2028 participants had a depressive and/or anxiety disorder; 1384 were not taking antidepressants and 644 used tricyclic antidepressants (TCAs), selective serotonin reuptake inhibitors (SSRIs) or serotonergic and noradrenergic(SN)-working antidepressants. Multiple regression analysis was used to establish the independent contribution of anxiety and depression as well as antidepressant use to diastolic and systolic blood pressure, after controlling for covariates. HR and HR variability measures were added to the equation to test whether effects of anxiety/depression or medication were mediated by vagal control over the heart.
Results: Depressive subjects had significantly lower systolic blood pressure and were less likely to have hypertension (OR=0.60, 95% CI=0.44-0.82) than controls. Significantly higher blood pressure, however, was found among users of TCAs and they were more likely to have hypertension (OR=3.19; 95%CI=1.35-7.59). These findings were partly mediated by the TCA effects on cardiac vagal control and HR. Also users of SN-working antidepressants had higher systolic and diastolic blood pressure and were more likely to have hypertension, which was fully explained by the effects on cardiac vagal control and HR.
Conclusions: This study shows that depressive disorder is associated with low systolic blood pressure and the use of certain antidepressants associates with high blood pressure and hypertension.

FC-15-003
Association between lifetime hormonal factors and hormone therapy, with late-life depression in women

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Joanne Ryan, Jacqueline Scali, Isabelle Carriere, Karen Ritchie

Objectives: The potential benefits of hormone therapy in treating depressed postmenopausal women remains controversial and the influence of lifetime hormonal markers is unknown. This study aimed to determine whether hormonal factors across the lifetime, in addition to hormone therapy, are associated with late-life depressive symptoms in elderly women.
Methods: The Centre for Epidemiology Studies Depression Scale was used to assess current depressive symptomatology in 4069 community-dwelling women aged 65 years and over, who were recruited as part of the 3C-Study in France. All women responded to questionnaires concerning their use of hormone therapy and a subset of 1013 women also provided detailed reproductive histories. Multivariate logistic regression models were generated to determine whether there was an association between hormonal factors and late-life depression at baseline. The association between incident depression and hormone therapy over a 4-year follow-up period was also examined.
Results: The prevalence of depressive symptoms was 20%. Age at menopause was associated with depressive symptoms, but only among women with a lower education level. For these women, an earlier age at menopause increased their risk of late-life depression (linear effect, OR=0.95, 95%CI: 0.91-0.99). On the other hand, long-term oral contraceptive use (≥10 years) was protective against depression (OR=0.3, 95%CI: 0.1-0.9). Over the 4-year follow-up, there was no association between depression and continuous hormone therapy use, however women who stopped treatment early after inclusion, had a significantly higher risk of depression.
Conclusions: Lifetime hormonal factors that are significantly associated with depression symptoms in later life have been identified. Hormone therapy was not associated with improved psychiatric symptomatology in elderly women; however discontinuing treatment could increase depression risk.

FC-15-004
Anti-stress and anti-oxidative effects of St. John´s wort extract (STW 3-VI) in a model of chronic stress

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Objectives: The antidepressive efficacy of St. John´s wort extract STW 3-VI in mild to moderate depression is comparable to that of SSRIs, as clinical studies have shown. As there exist interdependencies between depression, parameters of inflammation and a reduced antoxidative capacity, all these three should be studied in a pharmacological model of chronic stress.

Methods: Male Sprague Dawley rats were treated once daily orally with STW 3-VI (125, 250, 500 or 750 mg/kg b.w.), fluoxetine (10 mg/kg b.w.) or placebo for 21 days. Half of the animals (n=12) of each group were exposed to restraint stress (1 h per day), the other half remained unstressed. At the end of the study, motility in the open field, body and organ weights as well as relevant plasma, organ and genomics parameters were determined.
Results: Chronic stress reduced motility and growth rate of the animals, reduced the organ weights of spleen and thyme, increased the weight of the adrenals, plasma parameters of stress and inflammation (IL-6, CRP, ACTH and corticosterone) and reduced parameters of antioxidative capacity (SOD, Catalase, Glutathione peroxidase) in the hippocampus. Fluoxetine and STW 3-VI significantly antagonized these changes, fluoxetine having effects partly also in unstressed animals, while STW 3-VI effects beeing almost specific to stressed animals.
Conclusions: Both St. John´s wort extract and fluoxetine antagonized the stress induced enhancements of plasma parameters of inflammation and stress and the decrease of antioxidative capacity, which are known to occur also in depressive diseases. The specifity of the effects of St. John´s wort was remarkably higher than that of fluoxetine, which underlines its usefulness in therapy.

FC-15-005
Depersonalization and depressive phenomenology in unipolar depression

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Objectives: Our study was aimed at finding if the presence of depersonalization was related to a specific phenomenological expression of depressive symptomatology.
Methods: The study included 84 subjects suffering from unipolar depression without psychotic feature. Based on the Cambridge Depersonalization Scale (CDS) score, the subjects were divided into two groups – a group with associated depersonalization (CDS≥70) (40 subjects) and a group with subsyndromal depersonalization (CDS<70) (44 subjects), the later one being treated as a control group. The groups were compared in regard to the intensity of depressive symptomatology, depressive symptoms frequency and the depressive symptoms duration. General Socio-Demographic Questionnaire, the Cambridge Depersonalization Scale and The Patient Health Questionnaire – 9 were used.
Results: The depressive patients with depersonalization had dominantly severe episodes, almost all patients had the feeling of sadness, insomnia, and decrease of energetic potentials. The biggest difference between the groups, in terms of greater number of manifest symptoms in the patients with depersonalization, was for psychomotor disturbances (agitation or retardation), insomnia, decrease of energetic potentials and concentration. In the same time, 75% of the subjects with associated depersonalization had continuously present anhedonia, sadness/disphoria, insomnia and decrease of energetic potentials. Unlike this group, the control group subjects experienced sadness, appetite problems, concentration and motor behaviour changes almost half less frequently. Particularly significant were the differences regarding suicidal thoughts. It was shown that in the group with depersonalization there was quite higher percentage of patients with suicidal thoughts, mostly continuously present, that representing a significant suicidal risk factor.
Conclusions: Unipolar depression, associated with depersonalization is more severe in its intensity, it has a bigger number of manifest symptoms and they tending to continuous duration.

FC-15-006
HPA-axis activity in a large cohort of depressed and anxious subjects

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Objectives: Depression and (to a lesser extent) anxiety have been associated with hyperactivity of the hypothalamic-pituitary adrenal axis, which may explain some of their somatic consequences. However, results are inconsistent. Our purpose is to examine the association between anxiety and depressive disorders with various cortisol indicators in a large cohort study.
Methods: Data are from 1,843 participants of the Netherlands Study of Depression and Anxiety (NESDA), recruited from community, general practice and specialized mental health care. Four groups were compared: 308 controls without psychiatric disorders, 255 persons with an anxiety disorder (no history of MDD), 450 persons with a MDD diagnosis (no history of anxiety), and 830 persons with both anxiety and MDD diagnosis, as assessed using the DSM-based CIDI interview. Cortisol levels were measured in seven saliva samples, determining the 1-hour cortisol awakening response (CAR), evening cortisol levels and cortisol suppression after a 0.5 mg dexamethasone suppression test. Analyses were adjusted for sociodemographics, somatic health and awakening time.
Results: Persons with a MDD disorder and those with comorbid disorders showed a significantly higher CAR compared to controls (effect sizes (Cohen's d) between 0.18-0.29), with the highest levels for the comorbid group. The comorbid group also had significantly higher evening cortisol at 22h00 (d=0.15) compared to controls. Anxiety disorder was not significantly associated with cortisol. Post-dexamethasone cortisol level did not differentiate between groups. The use of psycho-active medication was generally associated with lower cortisol levels and less cortisol suppression after dexamethasone ingestion, but additional adjustment for psychoactive medication did not essentially change results for the association between psychopathology and cortisol levels.
Conclusions: In conclusion, this large cohort study shows a significantly higher cortisol awakening curve among persons with depressive disorder, especially those with comorbid anxiety, which suggests a modest hyperactivity of the HPA-axis among the depressed.

FC-16
Neuroimaging I

FC-16-001
The neural correlates of grief due to unrequited love

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Objectives: The aim of this study was to investigate the neural substrates of romantic love and grief. Brain activity in romantic love compared to recent grief was studied and it was hypothesized that subjects actively grieving compared to those currently in love would have decreased brain activity in regions specific to emotional and reward circuits such as frontal brain areas, anterior cingulate, bilateral insula, posterior cingulate.
Methods: Twelve volunteers intensely in love and twelve volunteers recently separated from their romantic partners were scanned performing 3 runs of fMRI imaging acquisition. Subjects viewed partner photos vs. sex photos during the first run, autobiographical pictures vs. neutral pictures during the second run and autobiographical texts vs. neutral texts during the third run. A fourth run was acquired for the visual control task (checker board). Rating scales including the Passionate Love Scale (PLS) and the Beck Depression Inventory (BDI) were additionally recorded. Post-processing and statistical analysis of the fMRI data were performed using BrainVoyager® QX v1.8.6.
Results: Brain activation specific to the partner occurred in the group of romantic love mainly in frontal areas, anterior and posterior cingulate cortex, bilateral insula and left caudate nucleus. Subjects grieving showed significantly diminished activation in these regions during all runs. Furthermore, grieving subjects revealed clinical symptoms of depression in the BDI.
Conclusions: During acute grief compared to romantic love, subjects exhibited clinical symptoms of depression and decreased brain activity in a brain network which has been described to be involved in major depression. This might be a cue for the close relationship between grief and depression.

FC-16-002
Investigation of orbitofrontal sulcogyral pattern: Is it possible to distinguish individuals with schizophrenia from those with bipolar disorder?

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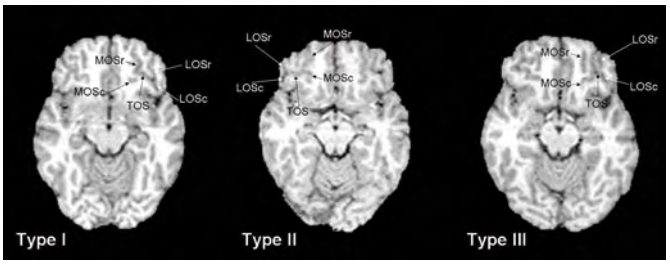
Objectives: Orbitofrontal sulcogyral patterns have been previously classified in healthy volunteers (Chiavaras and Petrides, 2000) and investigated in a group of patients with schizophrenia (Nakamura et al., 2007). The purpose of the present study was to evaluate orbitofrontal cortical folding patterns in patients with bipolar disorder and to compare the findings to healthy controls and to a group of individuals with schizophrenia.
Methods: Forty five subjects (mean age 40.38 years) with bipolar disorder, 26 age-matched patients with schizophrenia and 49 healthy controls with no family history of mental illnesses had a high-spatial resolution structural MRI scan of the brain (McIntosh et al., 2005). For each hemisphere, sulcogyral patterns were classified into three types (Type I–III), using the methodology of Chiavaras (2000), blinded to the group membership. Chi-squared analysis was performed to evaluate the distribution of the sulcogyral patterns.
Results: Type III was more frequently present in the right hemisphere of patients with schizophrenia comparing to the healthy volunteers. The prevalence of Type III in the left hemisphere was greater in patients with bipolar disorder than in healthy controls or schizophrenia subjects.
Conclusions: We are the first to report alterations in orbitofrontal sulcogyral pattern in a group of patients with bipolar disorder. Our results for the healthy control and schizophrenia groups are in keeping with the previous reports of Chiavaras (2000) and Nakamura (2007). In addition, the Type III pattern may be able to distinguish patients with bipolar disorder from those with schizophrenia, suggesting that neurodevelopmental influences on orbitofrontal patterning could impact on the presentation of psychotic illnesses.



FC-16-003
Reproducibility of functional Magnetic Resonance Imaging activations in schizophrenic patients during story comprehension: Impact of task performance

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Objectives: Longitudinal functional Magnetic Resonance Imaging (fMRI) studies of schizophrenic patients might be of great interest in evaluating brain response to therapeutic interventions. However, it is crucial to assess the reliability of fMRI paradigms. Indeed, it has been suggested that schizophrenic patients present unreliable activations (Manoach et al., 2001). Our aim was to assess the test-retest reliability of Blood Oxygen Level Dependant response in schizophrenic patients (N=10) in comparison with healthy subjects (N=10) with a paradigm of story comprehension.
Methods: Participants were scanned twice, 21 months apart, while performing each time two story comprehension experimental conditions of different complexity (French narrative versus Rest; French narrative versus Tamil). The former story was easier to understand while the second needed more integrated language processes. Their grasp of the stories was assessed with a questionnaire. For each condition and group, global reproducibility was evaluated with the percentage of spatial overlap between the 5,000 most activated voxels at each session, while local reproducibility was assessed using maps of relative standard deviation (RSD) of activations between the sessions.
Results: In both conditions, patients had lower comprehension scores than controls. For the low-complexity condition, reproducibility did not differ between patients and controls whereas, for the high-complexity condition, patients were less reproducible than controls. Differences in reproducibility were located in high-order language integrative areas (left inferior frontal, left posterior middle temporal, left medial superior frontal gyri; Figure). However, most of these differences were removed when comprehension scores were included as a covariate. Moreover, in these areas, RSD were significantly negatively correlated with comprehension scores for the high-complexity condition.

Conclusions: These results indicate that reproducibility of activation patterns for speech comprehension in schizophrenic patients does not differ from that of healthy controls once task performance is taken into account.

					Cluster level		Voxel level
Anatomical localization	*N*voxels	*x*	*y*	*z*	*P*corrected	*Z* value	*P*corrected
L MTG/Angular	434	-40	-64	18	<0.001	4.28	0.046
L medial F1	61	-12	64	30	0.003	3.97	0.129
L IFG tri	13	-58	26	10	0.178	3.54	0.423
After controlling for scores at the 1st session							
L MTG	30	-32	-70	20	0.03	3.62	0.328

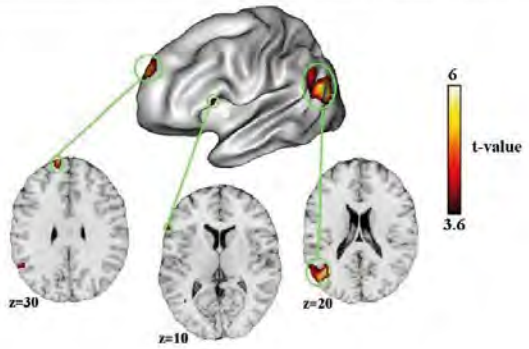

Figure **Top:** Cortical activation clusters showing higher reproducibility among controls (N = 10) than among patients (N = 10) for the Story *versus* Tamil condition. Bottom line: Results when including a task performance score at the first session as a covariate. L: Left; MTG: Middle temporal gyrus; Angular: Angular gyrus; F1: superior frontal gyrus; IFG tri: *pars triangularis* of the inferior frontal gyrus.
Bottom: Cortical areas exhibiting higher activation reproducibility in controls than in patients for the Story *versus* Tamil condition. SPM *t*-map (top) and selected axial slices (bottom) of the two-sample *t*-test comparing average RSD maps of controls and patients, superimposed onto the MNI template.

FC-16-004
Emotional modulation of working memory and the influence of the COMT polymorphism

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Objectives: The knowledge concerning the functional organisation of the frontal cortex is still limited and therefore subject to intensive examination. Numerous imaging studies have linked the prefrontal cortex to a variety of different functions, including task-switiching processes, working memory and emotional self-regulation. The n-back paradigm has been used extensively to gather evidence for the neuroanatomical correlates of working memory. In this task subjects are presented with a stream of stimuli and have to determine, whether a currently displayed stimulus matches the one presented n trials previously. Previous studies have shown that the COMT Val108/158Met polymorphism, which influences prefrontal dopamine, has been associated with lower processing efficiency in Val homozygotes. On the other hand, Met homzygotes display hyperreactivity of the amygdala to emotional stimuli.
Methods: We investigated the influence of the COMT Val/Met polymorphism on the interaction of emotion and working memory, we used an emotional n-back task here. We implemented an fMRI-paradigm with a 0-back condition and a 2-back condition and 32 gray-scaled pictures of real faces in neutral and negative emotional version.
Results: Performance of the 2-back versus 0-back condition was associated with increased activation of a prefrontal-parietal network, while the presentation of emotional versus neutral faces elicited activation of the right amygdala. In the neutral condition, Val homozygotes showed an increased fronto-parietal network activation when compared to Met homozygotes, possibly as a sign of lower processing efficiency. Notably, this pattern reversed in the emotional condition. Here, fronto-parietal activation was stronger for Met homozygotes relative to Val homozygotes.
Conclusions: Our results suggest that increased prefrontal processing efficiency in Val homozygotes might be disrupted when emotional salience of stimuli interferes with cognitive processing of stimuli. Further research might be directed at the systematic investigation of cognitive processing under stress situations in relation to the COMT genotype.

FC-16-005
Prefrontal transcranial Direct Current Stimulation (tDCS) modulates resting-state functional connectivity in healthy subjects: A functional magnetic resonance imaging (fMRI) study

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Objectives: Dorsolateral prefrontal cortex (DLPFC) tDCS has been associated with improvement in cognitive domains as well as improvement of mood. Anodal tDCS of the left DLPFC has been successfully applied to treat chronic pain, major depression and addiction. However, little is known about the influence of tDCS on large-scale brain networks revealed by spontaneous fMRI signals. Our goal was to examine resting-state functional connectivity after left DLPFC tDCS in healthy subjects.
Methods: 13 healthy right-handed male subjects (mean age: 27.4 years) underwent two stimulation conditions (active tDCS and placebo tDCS) in random order on two separate days. Before and after each tDCS a fMRI scan was carried out, which consisted in resting quietly in the scanner, eyes-closed. For stimulation, we used an Eldith DC stimulator: the anode was placed over the left DLPFC and the cathode over the right supraorbital region. Each tDCS was applied at 2 mA, 20 min. Independent Component Analysis (ICA) was applied to fMRI data sets using Brain Voyager QX. Co-activation networks were identified, grouped with a self-organizing group ICA and compared using ANOVA.
Results: Individual analysis of fMRI signal revealed the few networks usually showed in resting state paradigms but new networks were discovered closed to the site of stimulation, in the active condition. The group analysis revealed connectivity clusters which were not found in the placebo condition, namely in the left middle frontal gyrus, parahippocampal gyrus, inferior parietal lobule and an inverse connectivity cluster in the right anterior cingulate.
Conclusions: To the best of our knowledge our study is the first to show that tDCS applied over the left DLPFC is able to modify functional connectivity during a resting state task, not only close to the stimulation site but also in remote brain structures.

FC-16-006

Structural brain differences between first-episode schizophrenia and first-episode affective psychosis: A population-based magnetic resonance imaging study

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Objectives: The extent to which psychotic disorders represent distinct biological entities or can be regarded as a continuum is controversial. This study aimed to compare the lateral ventricular volumes between first-episode psychosis (FEP) patients and healthy controls and also between specific diagnostic subgroups.

Methods: Subjects were 122 FEP patients and 94 healthy controls, participants in an epidemiological study and recruited from a defined catchment area in São Paulo, Brazil. The region of interest method was employed on magnetic resonance images to examine the lateral ventricular volumes. T-tests and the Mann-Whitney test were employed for analysis of FEP versus controls, while analysis of variance (ANOVA) was used for comparisons between schizophrenia/schizophreniform disorder (n= 62), affective psychosis (n= 46) and healthy controls.

Results: Right and left lateral ventricular volumes were larger in FEP subjects than controls (z= -2.545, p= 0.011 and z= -2.824, p= 0,005, respectively). The ANOVA showed that patients with schizophrenia/schizophreniform disorder had larger right lateral ventricles (p: 0.041), and larger right (p= 0.008) and left (p= 0.02) temporal horns than controls, while there was no difference between affective psychosis patients and controls. Moreover, patients with schizophrenia/schizophreniform disorder showed larger left temporal horns (p= 0.042) than the affective psychotic subjects. None of the findings were attributable to effects of antipsychotic medication.

Conclusions: Neuroanatomical differences between schizophrenia and affective psychosis disorders are evident at the first episode of illness. These data are consistent with a model of psychosis in which schizophrenia but not affective psychosis is neurodevelopmental in origin.

FC-17
Psychotic Disorders V

FC-17-001
A functional MRI study of face perception in patients with schizophrenia

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Objectives: Deficits in emotion processing are a hallmark of schizophrenia, with consequences for social functioning and subjective well-being. The authors evaluated cerebral blood flow response in schizophrenia patients during face perception to test the hypothesis of diminished limbic activation related to emotional relevance of facial stimuli.
Methods: Thirteen patients with schizophrenia (male, n=7; female, n=6) and 17 comparison subjects (male, n=8; female, n=9) viewed facial displays of happiness, sadness, surprise, anger, fear, and disgust as well as neutral faces using the Japanese and Caucasian Facial Expressions of Emotion and Neutral Faces (JACFEE and JACNeuF) (Matsumoto and Ekman, 1988). Functional magnetic resonance imaging was used to measure blood-oxygen-level-dependent signal changes as the subjects alternated between tasks of discriminating sex (sex-judgement tasks; man versus woman) with an interleaved reference condition.
Results: The groups did not differ in performance on the task. Healthy participants showed activation in the bilateral fusiform gyrus, medial temporal structures, occipital lobe, and inferior frontal cortex relative to the baseline condition. The increase was greater these regions in the right hemisphere than those in the left hemisphere. In the patients with schizophrenia, minimal focal response in the right fusiform gyrus, medial temporal structures, and occipital lobe was observed for the facial perception task relative to the baseline condition. Contrasting patients and comparison subjects revealed voxels in the left medial temporal structures, occipital lobe in which the healthy comparison subjects had significantly greater activation.
Conclusions: When the sex-judgement task was used, impaired activation was seen in patients with schizophrenia for detection of facial attributes such as sex. Impairment in the medial temporal structure such as amygdale may lead to misunderstanding of social communication and may underlie difficulties in social adjustment experienced by people with schizophrenia.

FC-17-002
Arousal-cognition decoupling in Schizophrenia: An EEG-fMRI study

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Objectives: Cognition appears as a major determinant of social and occupational status in schizophrenia and has become a target to therapeutic interventions. Among the latter, procognitive drugs have been proposed which target arousal systems. This study attempts to test for the rational of arousal targeted intervention to improve cognition. Are most hypoactive regions sensitive to arousal? If it is the case, then are hypoactive regions also merely hypo-aroused or is it that cortical arousal is no more properly converted in cognitive activity, i.e. not correctly coupled?
Methods: Seventeen right-handed patients and the same number of controls took part in the study. Patients were stabilized or remitted and selected from a group to which a cognitive remediation was proposed. Participants performed a working memory paradigm during the EEG-fMRI acquisition. As low EEG frequencies are well correlated with arousal, they allow to map regions sensitive to it. The overlap between the hypoactive and arousal sensitive maps was evaluated by their mutual information (MI). Arousal was evaluated by self evaluation, EEG low frequency power and EEG-fMRI using both SnPM and ROI methods. The arousal-cognitive coupling was evaluated by the slope of the regression line between arousal and task effect.
Results: Quite all the voxels that were hypoactive in the patient group were sensitive to arousal ($p<10^{-5}$). But patients were not hypo-aroused whatever the measurement method perhaps because they already optimized their arousal using nicotine and caffeine. Conversely, the patient's arousal-cognition coupling index was decreased in the hypoactive regions ($p = 0.005$).
Conclusions: Arousal targeted procognitive drugs might well help in reducing patients cognitive deficit since all task-related hypoactive regions are arousal sensitive. However, it might well be that patients already optimized their arousal using nicotine and caffeine. Alternatively patients may fail to convert arousal in a coherent cognitive activity.

FC-17-003
Global abnormalities in white and gray matter of chronic schizophrenia: A diffusion tensor imaging study

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Objectives: This study is aimed to investigate global alterations in white matter (WM) and gray matter (GM) of schizophrenia using Diffusion Tensor Imaging (DTI).
Methods: Thirty male patients with chronic schizophrenia and 30 aged matched male controls were scanned using DTI. Within whole brain WM/GM and cerebral WM/GM, Fractional Anisotropy (FA) and Trace (Tr) were used to quantify water diffusion and Mode was calculated to estimate tensor shape (i.e., cylindrical or disc-like tensor). WM/GM regions of interest were derived from automatic tissue segmentation of structural MR images, which were coregistered into DTI space.
Results: Reduced FA ($t_{58}=2.40$, $P=0.020$) and increased Tr ($t_{58}=2.57$, $P=0.013$) were found in whole brain WM of schizophrenic subjects, as well as in cerebral WM (FA, $F_{1,58}=6.34$, $P=0.015$; Tr, $F_{1,58}=3.94$, $P=0.05$), although WM ROI volumes did not differ between the study groups. Only in cerebral WM, reduced Mode was found in the patient group ($F_{1,58}=4.46$, $P=0.039$), suggesting a more disc-like shape of the diffusion tensor. In whole brain GM, Tr was quite significantly high ($t_{58}=3.96$, $P=0.0002$) and whole brain GM ROI volume was significantly small ($t_{58}=2.78$, $P=0.007$) in the patient group, with a negative correlation ($r=-0.638$, $P=0.0001$) between them. Reduced FA in cerebral WM and increased Tr in cerebral GM observed in the schizophrenia group showed hemisphere×group interactions which were more lateralized to left hemisphere. However any group difference in DTI variables did not show any lobar-based regional specificity.
Conclusions: These findings suggest that global DTI abnormalities in schizophrenia are present in both WM and GM. In WM, the patient group is characterized by reduced FA, increased Tr, and reduced Mode, possibly reflecting more incoherent fiber orientations. In GM, the patient group is characterized by increased Tr and decreased ROI volume, possibly supporting 'neuropil reduction' hypothesis in GM region.

FC-17-004
Detection of 6p25 region in male schizophrenia via fluorescence in SITU hybridization (FISH) techniques

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Objectives: A number of applied molecular cytogenetic studies require the quantitative assessment of fluorescence in situ hybridization (FISH) signals. Here we detected quantification of FISH signals and also used for analysis of somatic pairing of homologous chromosomes in nuclei of peripheral blood lymphocytes using FISH with "classical" satellite DNA probes for chromosomes 1, and 6, in male schizophrenia. The breakpoint is near a possible locus for schizophrenia also identified.

Methods: 65 male patients have been described with cytogenetically visible deletion of the short arm of chromosome 6. We report patients with terminal 6p deletion detected by subtelomeric screening using FISH. Detailed FISH analyses with probes covering the distal 6p25 region estimated the size of the terminal deletions to approximately 5.5 Mb and approximately 4.8 Mb. Array-based comparative genomic hybridization (array CGH) was used to confirm the cryptic deletions.
Results: Most patients with subtelomeric defects lack a characteristic phenotype. However, some of the subtelomeric deletions result in a specific phenotype. Submicroscopic 6p deletion appears to be a recognizable clinical phenotype, and this region should be thoroughly investigated with FISH probes, including at least a subtelomeric 6p probe and a probe covering FOXC1, some patients presenting with a characteristic facial appearance, ocular abnormalities, predominantly anterior-chamber eye defects, hearing loss, and mental retardation.
Conclusions: This approach has shown a relatively high efficiency for the quantitative registration of chromosomal heteromorphism due to variations of centromeric alphoid DNA in homologous parental chromosomes in male schizophrenia. We propose this approach to be efficient and to be considered as a useful tool in addition to visual FISH signal analysis for applied molecular cytogenetic studies.

FC-17-005
Metabolic derangement in schizophrenia: Relation to antipsychotic treatment

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Objectives: first, find out the risk for metabolic disturbances among a group of drug naïve schizophrenics. Second,to compare the metabolic effects of first, second generation and combined first and second generation antipsychotics.
Methods: The study included 122 Egyptian schizophrenics from the Institute of Psychiatry, Egypt. They were divided into 4 groups (36 patients on 1st generation antipsychotics (gp 1), 40 patients on 2nd generation antipsychotics (gp 2), 16 patients on both(gp 3), 30 neuroleptic naive patients(gp 4)). Thirty healthy subjects as control group (gp 5). Anthropometric measures, fasting glucose, insulin and adiponectin, total cholesterol, TG, HDL, LDL and insulin resistance index (HOMA IR) and quantitative insulin sensitivity check index (QUICKI) were evaluated.
Results: The prevalence of insulin resistance and atherogenic lipid profile are higher in gp 4 (86.7% and 60%) compared to gp 5 (0% and 6.7%, p value <0.01). Gp 3 show the highest prevalence of insulin resistance (100%, p value <0.01) and atherogenic lipids (87.5%, p value <0.01). Fasting insulin is highest among gp 2 (41.78±23.46 µIU/ml, p value <0.01) and there is a positive significant correlation between fasting insulin and duration of treatment among gp 2 (r=0.38, p value <0.05). There is a significant negative correlation between QUICKI and duration of treatment (r= -0.276, p value <0.05)among patients on atypical antipsychotics (gp2 + gp3). Fasting adiponectin was highly significant lower in gp 1,2,3 and 4 compared to gp 5 (p value<0.01), gp 2 show the lowest level (1.73±0.58ng/ml). There is a highly significant negative correlation between BMI and fasting serum adiponectin (r=0.48, p value <0.01) among gp 2 patients.
Conclusions: Schizophrenia puts the patient at a higher risk for insulin resistance prior to antipsychotics. Combined typical and atypical antipsychotics showed the highest prevalence

FC-17-006
Influence of antypsychotic treatment on cognitive functions in schizophrenia with comorbid addiction to substances

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Objectives: Objectives: Data from literature show that there is a beneficial impact of second generation antipsychotics on cognitive functioning in schizophrenia. The purpose of this study was a to find out if there are differences in cognitive functioning in schizophrenic patients with and without a comorbid addiction, treated with typical and atypical neuroleptics.
Methods: Methods: 80 subjects with a diagnose of schizophrenia according to ICD-10 were examined. In the first group of 40 patients they were additionally addicted to psychoactive substances including: opiates, amphetamines, hallucinogens and cannabis. In the other 40-patients group no addiction was found. In each of the groups 20 patients were treated with typical neuroleptics and 20 with atypical neuroleptics. The neuropsychological battery used to assess the cognitive functions included: trail making test, part A and B, Stroop test, part RCNb and NCWd and verbal fluency test. The addicted patients were examined six weeks after the withdrawal of the psychoactive substance to avoid their direct influence.
Results: Results: In the whole examined population of 80 patients results of all applied test were better in the group treated with atypical neuroleptics, though the observed differences turned out not to be statistically significant. Statistically significant differences in cognitive functioning between patients treated with typical and atypical neuropleptics were found only in the group of patients without a comorbid addiction. In this group the performance of the tests was better in the group treated with atypical neuroleptics. The type of antypsychotic treatment had no impact on results of applied tests in patients suffering from schizophrenia additionally addicted to psychoactive substances.
Conclusions: Conclusions: The analysis of the above results may implicate the fact that there can be a higher complexity in the action of both atypical and typical neuroleptics on cognitive functions in schizophrenia with a comorbid addiction.

FC-18
Anxiety II

FC-18-001
Transgenerational transmission of trauma – case of Albania

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Objectives: To identify the degree of traumatization of former political persecuted individuals (imprisoned and/or internally displaced at labor camps) during the dictatorship of the second part of last century and their psychological symptoms; To identify if there is any relationship between the degree of parental traumatization and the emotional difficulties of their offspring derived by the symptoms of their parents.
Methods: 149 torture survivors (and 149 their offspring) randomly selected from a list of 1236 survivors drawn by the official list of 43006 former political persecuted using the criteria: being under 30 at the imprisonment moment, condemned not earlier than 1970, having actually a child between 6 and 18. Instruments: (a) Parents – General data Questionnaire, PTSD Diagnostic Scale, Family Environmental Scale, WHO QoL Bref; (b) Children – STAI, UCLA-PTSD Reaction Index, Family Environment Scale. Statistical significance defined at 95% level ($p<0.05$). Frequency of the main variables (from questionnaires) reported in conformity of the different item's response, as well as a number of correlations and predictive factors. Statistical analyses – using SPSS 11.0
Results: 28.85% of parents diagnosed as full PTSD (74.41% males and 25.59 females). Significant correlation between dissociative symptoms and full/partial PTSD. 9.375% of offspring presented full PTSD, while 64.8% - partial
Conclusions: Children of parents who survived torture experiences presents high level of anxiety, stress related complains and high risk in developing post-traumatic stress disorder. There is a clear need of focused work on this group in assisting to overcome the emotional and behavioral difficulties

FC-18-002
Reduced resting state connectivity between amygdala and orbitofrontal cortex in social phobia

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Objectives: In social phobia, exposure to unfamiliar faces and public performance leads to a heightened, uncontrolled emotional and physiological arousal that is usually associated with a hyperreactivity of the amygdalar region. Here, we investigated whether the functional connectivity between the amygdala and regions involved in emotional control reflects a suspected fronto-limbic dysregulation in social phobic patients.
Methods: We compared the functional connectivity of the amygdala in 10 unmedicated patients with social phobia and 28 healthy controls. The volunteers were measured during 5 minutes of resting state using a 3 Tesla Medspec S300 (Bruker Biospin, Germany) scan and single-shot EPI (TE=40ms, TR=1000ms, MA=96x64). The left and right amygdala were defined as seed regions based on the AAL template. By pixel-wise correlation with the signal time course in left and right amygdala, functional connectivity maps were obtained from frequency filtered data ($0.007< f <0.08$Hz) after correction for physiological signal fluctuations. A voxel-wise comparison between the connectivity maps of patients and healthy controls was done by independent samples t-tests.
Results: Patients with anxiety disorder showed significantly less functional connectivity between the left amygdala and left orbitofrontal cortex (MNI: -10, 42, -16; $t>3.33$; $p<0.001$ uncorr.), as well as left amygdala and left precuneus/posterior cingulate cortex (MNI: -10, -56, 46; $t>3.33$; $p<0.001$ uncorr.). No alterations in the functional connectivity of the right hemisphere were observed.
Conclusions: In the present study, we observed a negative functional connectivity between left orbitofrontal cortex and left amygdala in patients relative to healthy controls. This result suggests a constitutively reduced prefrontal control over threat perception and fear reaction in social phobia. Furthermore, reduced functional connectivity between amygdala and components of the posterior default-mode network may be indicative of an altered episodic memory processing, possibly contributing to the fearful anticipation of negative performance that is characteristic for social anxiety.

FC-18-003
Examining changes in resistant anxiety symptoms of ADHD with co-morbid generalized anxiety disorder in adult patients treated with mixed amphetamine salts (adderall XR)

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Objectives: Substantial proportion of patients with ADHD may suffer from comorbid anxiety. The main objective is to examine the effectiveness of the mixed amphetamine salt adderall XR, in the treatment of ADHD, with comorbid refractory anxiety symptoms.
Methods: Consenting adult patients (n=32) with confirmed diagnosis of generalized anxiety and comorbid ADHD participated in this study. All patients had significant comorbid anxiety symptoms (HAM-A >10), and failed to respond to 8 week trials of serotonin reuptake inhibitors. All patients were treated with the mixed amphetamine salt, adderall XR, as adjunctive to serotonin reuptake inhibitors and were followed for at least 12 weeks. The primary effectiveness measure was the adult ADHD self report scale (ASRS-v1.1) symptom checklist. Other scales included the Clinical Global Impression severity subscale (CGI-S), Hamilton anxiety scale (HAM-A), and the Sheehan's disability scale. Baseline measures prior to the treatment with adderall XR, were compared to those at 4, 8, and at 12 weeks of treatment. Monitoring for pulse, blood pressure and weight changes was carried out at baseline and at endpoint.
Results: All patients completed this open label trial. There was significant and robust resolution of symptoms of all effectiveness measures, including the symptoms of anxiety, as shown by changes from baseline in ASRS-v1.1, HAM-A, and CGI at 8 weeks. Also there was significant reduction in disability score at 12 weeks. Patients tolerated the treatment and there were no significant cardiovascular changes or weight changes at 12 weeks. Detailed analysis of the relationship between ADHD, and anxiety symptoms will be presented.
Conclusions: Mixed amphetamine salts adderall XR, can be used safely in adult patients with ADHD, and co-morbid anxiety symptoms. Larger controlled studies are needed to support the effectiveness of mixed amphetamine salts in patients with co-morbid anxiety symptoms. Treatments need to include the targeting of the ADHD symptoms effectively in order to achieve better resolution of anxiety symptoms.

FC-18-004
GSK3ß as a biological marker of stress in the prefrontal cortex

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Objectives: GSK3ß is at the convergence of several intracellular signalling pathways that are directly linked to synaptic plasticity. We have recently shown that exposure to acute and chronic stress impairs synaptic plasticity in the prefrontal cortex by reducing long-term potentiation in the hippocampal–prefrontal connection. The purpose of the present study was to investigate the potential role of GSK3ß in this process. GSK3ß is a serine/threonine (ser/thr) kinase with a high basal activity, primarily determined by the phosphorylation status of ser9. The dephosphorylation of this residue leads to further activation of GSK3ß. Conversely, phosphorylation of ser9 by several kinases results in inhibition of its activity. β-catenin, a substrate of GSK3ß is phosphorylated by this enzyme on ser33/37, thr41 and by Akt on ser552.

Methods: Two protocols of stress (acute and chronic) were used and rats sacrificed. Brains were rapidly removed and prefrontal cortex (lateral and medial) dissected. Immunoblotting was carried out with phosphorylation-state-specific antibodies and antibodies against total GSK3β and β-catenin. We monitored the phosphorylation of GSK3ß at ser9 and β-catenin at ser33/37, thr41 and ser552 in prefrontal homogenates. Data were analyzed with Student´s T-test to evaluate statistical differences.
Results: A reduction in the phosphorylation state of ser9-GSK3ß was found in the medial prefrontal cortex of chronic stressed rats and in the phosphorylation of ser9-GSK3β and of ser552-β-catenin in the lateral prefrontal cortex. No significant changes in the phosphorylation states of GSK3ß and β-catenin was detected in acute stressed animals.
Conclusions: This work suggests that different cellular mechanisms are involved in acute and chronic stress. GSK3ß would contribute to the effects of chronic stress on plasticity through the PI3K/Akt signalling pathway while the MEK/MAPK signalling cascade shown to be downregulated in prefrontal cortex would play a key role in the effects of acute stress (Qi et al., 2008).

FC-18-005
Personality and clinical correlates of response to a laboratory stressor in patients with social anxiety disorder

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Objectives: Patients with social anxiety disorder (SAD) report intense anxiety when exposed to performance and social interaction situations. However, few studies have evaluated factors that predict response to social stressors. In the present study, we determined whether personality traits, measured by the NEO-PI-R and Anxiety Sensitivity Inventory (ASI), and severity of social anxiety symptoms,measured by the Liebowitz Social Phobia Scale, Social Phobia Scale, and Social Interaction Scale, influenced reactivity to a speech task in patients with generalized SAD.
Methods: Participants were 37 drug-free patients with DSM-IV SAD who participated in a treatment outcome study. Prior to starting treatment patients delivered a 10 minute impromptu speech. Visual analogue ratings of subjective anxiety, fear of embarrassment and fear of being judged, and measures of respiratory exertion (Borg Scale) and heart rate variability (HRV) were obtained at baseline and during the 10 minute speech task. Change scores (speech task minus baseline values) were calculated for these measures. The relationship between personality and clinical measures and change scores in fear and anxiety, respiration, and HRV were analyzed with Pearson's correlation analysis.
Results: The laboratory stressor induced robust changes in subjective and physiological indices of anxiety. A significant negative correlation was found between Neuroticism and change from baseline in respiratory exertion ($r= -0.33$, $p<0.05$) and between Extraversion and change from baseline in self-rated anxiety ($r= -41$, $p<0.05$). A significant positive correlation was also found between the ASI and fear of embarrassment ($r=0.34$, $p<0.05$). None of the baseline measures of social anxiety severity correlated significantly with subjective or physiological response to the stressor.
Conclusions: These findings suggest that personality traits but not severity of social anxiety influence response to a laboratory stressor involving psychological threat and harm in patients with SAD. Interestingly, none of the measures correlated with HRV, a measure of cardiac autonomic reactivity. These results are preliminary and require replication in a larger sample.

FC-18-006
Long term consequences on mental health of traumatic exposure in an elderly general population and impact of genetic vulnerability

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Objectives: Our study aimed to evaluate in a community-based study the associations between the experience of a life-time traumatic event, current mental health and the impact of genetic vulnerability related to genes coding for serotonin transporter (5-HTT), tryptophan hydroxylase 1 (TPH1), catechol-O-methyl transferase (COMT) and monoamine oxidase A (MAOA).
Methods: 1697 non-institutionalised persons aged 65 years and over, randomly recruited from the Montpellier district electoral rolls, completed the Watson's PTSD Inventory to evaluate post-traumatic stress disorder (PTSD) and the Mini International Neuropsychiatric interview to assess life-time symptoms of psychiatric disorders. DNA was collected for a subset of 1513 subjects.
Results: 55.6% of the study sample (58.5% of men and 53.6% of women) had experienced a traumatic event according to DSM-IV criteria. Thirty per cent of these traumatized subjects had developed re-experiencing symptoms, 18.1% avoidance/numbing symptoms, and 2.2% PTSD (0.5% of men and 3.4% of women). Logistic regression adjusted for age, sex, and education indicated that past traumatic events were associated with a significantly higher risk of life-time major depression, the risk of current major depression being notably increased by more than 3-fold ($p=0.004$). The re-experiencing symptoms were significantly associated with a higher risk of current psychiatric co-morbidity (for at least two disorders $OR=2.85$, $p=0.002$). The presence of the high-expression MAOA variant was associated with traumatic experience in men ($OR=1.58$, $p=0.008$), whereas for both sexes TPH1 CC genotype was associated with more avoidance/numbing symptoms ($OR=3.94$, $p=0.018$).
Conclusions: Our findings indicate that 1) lifetime experience of traumatic events is frequent in the elderly and have long-term consequences on mental illness and that 2) traumatic exposure as well as severity of life-time post-traumatic symptoms could be modulated by genes coding for aminergic neurotransmission.

FC-19
Psychopharmacology II

FC-19-001
Characteristic of clozapine responders & non-responders in a naturalistic tertiary setting in India

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Objectives: Clozapine is a gold standard treatment for treatment resistant schizophrenia, is known to improve cognition, social functioning & decrease suicidality. Unfortunately intolerability and side effects of clozapine causes exclusion of a significant number of patients, and they have to be switched back to other antipsychotics. One possible way to deal with this problem is to identify both responders as well as non-responders of clozapine. There is now some genetic basis for tolerability, side effects and efficacy, however it is still inconclusive. Clinical indicators with high reliability and validity are much more helpful. The present study attempts to explore such possibility.
Methods: One hundred patients with treatment-resistant schizophrenia referred for Clozapine therapy were studied over the period of one year of treatment to determine the Clozapine tolerance, response & side effects Assessment was done on day one, on day 90 and again on the last day of the one-year treatment. Initial assessment included diagnostic confirmation as per DSM 1V, assessment using PANSS, CGIS, Clinical parameters, blood parameters &, serum prolactin, Blood monitoring was done frequently and side effects were recorded using a checklist for Clozapine-related side effects.
Results: The end point analysis showed that 55% of the patients had significant response, 15% poor response, and 30% no response to the drug. The mean dose of Clozapine was 450 mg in the responders. Overall tolerability was 40% Mixed positive and negative symptoms, presence of depression, age > 40 years, lack of prolactin elevation, lack of side effects in first four weeks, & switching from olanzapine were significantly correlated to excellent efficacy of CGIS
Conclusions: Significant number of patient either does not tolerate clozapine or do not show good response. Switching back from Clozapine is significant. Clinical markers of response may add value to therapeutics of clozapine in schizophrenia

FC-19-002
Effects of Olanzapine and Risperidone on glucose metabolism and Insulin sensitivity in chronic schizophrenic patients with long-term antipsychotic treatment: A randomized five month study

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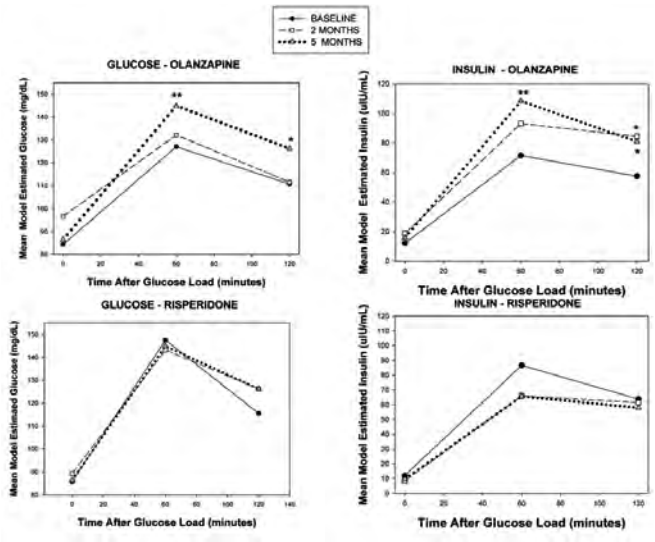
Objectives: Comparisons of diabetic potential, glucose related metabolic levels, and insulin resistance between olanzapine and risperidone have produced variable results in cross-sectional and epidemiological studies. Randomized prospective studies of metabolic effects during treatment with these drugs may provide results that are more informative. We present a randomized controlled study of glucose and insulin dynamics of schizophrenics treated with olanzapine or risperidone.
Methods: Hospitalized patients with chronic schizophrenia, most of whom had been treated with multiple antipsychotics in the past, were randomly assigned to treatment with a single antipsychotic, olanzapine or risperidone, for a period of 5 months. Glucose, insulin, weight and related metabolic parameters were assessed monthly over a 5 month periods and a glucose toelrance test was perfomed on 3 occassions during this study.
Results: There were no overall drug treatment differences in fasting glucose or glycohemoglobin or 2 hr glucose levels in OGTT, and no differences between the two drug groups at the 5 month time point There were no consistent drug treatment differences in the number of patients who developed borderline or diabetic glucose levels. Olanzapine treated patients showed a significantly greater increase than risperidone treated patients in a fasting measure of insulin resistance (P=.041), and olanzapine patients showed greater decreases in insulin sensitivity during OGTT (P=.023) compared to risperidone treated patients. Olanzapine treated patients had a significantly greater increase in 1 hour glucose and insulin levels during OGTT in subsequent months compared to baseline, and greater increase in glucose and insulin area under the curve over time than the risperidone treated patients.
Conclusions: The increase in insulin levels during olanzapine treatment may compensate for the increase in insulin resistance, and serve to reduce fasting and postprandial glucose levels. This may contribute to the lack of differences between olanzapine and risperidone in indices of diabetic or pre-diabetic glucose levels or glycohemoglobin. How many years this compensatory mechanism will persist needs further investigation.



FC-19-003
Antipsychotic polypharmacy and use of sedatives and hypnotics in outpatients at Birch Hill Hospital – incidence and adherence to guidelines

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Objectives: To determine prescribing rates and adherence to guidelines in respect of antipsychotic polypharmacy, high dose antipsychotic prescribing, and sedative use in a general hospital outpatient population.
Methods: Prospective casenote audit involving 250 consecutive attenders of an outpatient clinic serving five consultant psychiatrists. All patients who were on at least one antipsychotic medication were included in the audit. Patients were divided into a monopharmacy and a polypharmacy group. Information was obtained regarding medication type, dose, percentage of maximum British National Formulary recommended dose, duration of treatment, and whether an ECG was recorded or not. Data was analysed using descriptive statistical methods. Differences between the groups were estimated using t-test and chi square where applicable.

Results: 196 case notes were included in the final analysis. Results showed that polypharmacy was present in 17.35% of cases. Reasons for polypharmacy were documented in 52.95% of cases (61% of documented reasons were not in accordance with recommended guidelines). High dose antipsychotics were used in 2.47% of the monotherapy and in 38% of the polypharmacy group (P<0.01). An ECG was done in 35% of the total number of patients on high dose antipsychotic therapy. In the monotherapy group 6.17% versus 26.47% in the polypharmacy group of patients were on at least 1 sedative or hypnotic (P<0.001). 42% of patients prescribed sedatives had schizophrenia spectrum disorders and none of them had anxiety disorders.
Conclusions: The current study confirms that despite repeated recommendations against the practice, polypharmacy rates remain consistent at the 20% level. The association of polypharmacy with high dose antipsychotic prescribing increases the cardiovascular risk, however an ECG was not obtained in the majority of cases in contravention of national guidelines. Antipsychotic polypharmacy and its association with long-term sedative use may reflect efforts to manage treatment resistance, or control behavioural disturbance. Nevertheless, thorough documentation, calculating the total antipsychotic dose, and obtaining an ECG would constitute good practice.

FC-19-004
Patterns of Risperidone long acting prescription: A utilization study in Saudi Arabia

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Objectives: Objectives: To describe the patterns of prescriptions associated with risperidone long acting in the clinical practice in Saudi Arabia.
Methods: Methods: In this study, 500 prescription forms of Risperdon long acting were collected and analyzed from the outpatient and inpatient database in Al Amal Psychiatric Hospital through 3 years.
Results: RESULTS: The prevalence of co-prescription was 45.5% for anticholinergic, 31% for oral risperdone, 24% for mood stabilizers, 16% for antidepressant and 14% for other neuroleptics. The most prescribed dose was 25 mg every two weeks (51%). 30% of patient discontinued Risperdone long acting and the main reason for discontinuation was lack of response.
Conclusions: Conclusions: The high level of concomitant drug prescription in patients treated with risperidone long acting illustrates the gap between clinical trials and utilization in naturalistic settings. The high association of co prescription with risperidone long acting has been insufficiently studied for efficacy or safety, and has to be explored further from both a pharmacological and clinical point of view.

FC-19-005
Antioxidant neuroprotection by neuroleptics revisited

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Objectives: Tricyclic neuroleptics have received considerable interest for their potential antioxidant and neuroprotective properties in different models of neurodegenerative disease. However, results have been highly variable, and a clear structure-activity relationship has not been achieved. We have performed a systematic investigation of diverse phenothiazine-based neuroleptics and related structures lacking modulatory activity on dopamine receptors for their protective potential in an in vivo model of Parkinson's disease potentially amenable to large-scale neuroprotective drug screening.
Methods: Caenorhabditis elegans nematodes were genetically engineered to express variants of GFP in either all neurons or in all dopaminergic neurons, respectively. The animals were challenged with two mitochondrial toxins known to specifically affect dopaminergic cells (rotenone and 1-methyl-4-phenyl-pyridine (MPP)). Individual protection of the 8 dopaminergic neurons of the nematodes by different phenothiazine-based compounds was analyzed.
Results: Phenothiazine-based neuroleptics with antagonist activity on dopamine receptors were found to exacerbate neurotoxicity of both rotenone and MPP in Caenorhabditis elegans. However, unsubstituted phenothiazines with a free NH-group in the tricyclic structure were observed to be exceptionally potent antioxidants and fully protected the animals from neurodegeneration and developmental arrest. Unsubstituted phenothiazines are known to lack antagonist activity on dopamine receptors, as receptor binding fully depends on the N-substitution.
Conclusions: The same chemical moiety that is essential for dopamine receptor binding prevents antioxidant activity in phenothiazines. Hence, these properties are not only uncoupled, but even mutually exclusive. Unsubstituted phenothiazines may be promising candidate structures for antioxidant neuroprotection in Parkinson's disease and other neurodegenerative conditions accompanied by oxidative stress. Contamination of commercial phenothiazine neuroleptics with unsubstituted precursors or degradation products may explain occasional reports of neuroprotection by tricyclic neuroleptics.

FC-19-006
Fitness to drive under escitalopram or mirtazapine

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Objectives: Driving is a daily activity for most people in developed countries and is important in maintaining independence. Depressed patients may have impaired driving behavior because of the pathology itself, with psychomotor and cognitive disturbances. Additionally, adverse effects of antidepressant treatment, such as sedation, agitation, sleep disturbances, and central anticholinergic effects, may be detrimental.
Methods: 24 depressive inpatients diagnosed according to ICD 10 criteria were randomly assigned to either a group treated with escitalopram (n=12) or mirtazapine (n=12). Participants were tested before pharmacologic treatment (t0), and on days 7 (t1) and 28 (t2) with computerized tests related to car driving skills. Data were collected with the Act and React Testsystem (ART 90) and the Wiener Testsystem (WTS) measuring visual perception, reactivity, stress tolerance, concentration and vigilance. In addition patients went through various risk simulations on a static driving simulator (FT-SR 200).
Results: Before onset of antidepressive treatment about 54% of patients did not pass the threshold criterion according to the German guidelines for road and traffic safety. After 28 days of pharmacologic treatment both groups showed a significant reduction of psychopathologic symptoms as well as distinct improvements in driving skills. About 67% of our sample could be classified as fit to drive after four weeks of treatment. Especially in visual perception, selective attention and stress tolerance significant improvements could be shown. Furthermore we found a significant decline in accident rates in the risk simulations on the driving simulator. Statistically significant differences between treatment groups could not be shown.
Conclusions: Analysis of our data point to an advantage of partly remitted depressive patients under escitalopram or mirtazapine in contrast to non-treated patients with regard to driving skills.

FC-20
Genetics II

FC-20-001
Moderate caloric restriction reduces anxiety-like behavior and changes gene expression in the mouse amygdala

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Objectives: This study was designed to reveal the molecular basis of the beneficial consequence of moderate caloric restriction and initial weight loss on behavioral changes by examining the gene expression in the brain of 80% calorie-restricted mice with two different regimens.
Methods: Three groups of male C57BL/6J mice (8-9 weeks of age, n = 90) were used: mice fed *ad libitum* (AD), feeding every other day (ACR), or given daily half the amount of food consumed by ACR mice on which ACR mice were fed (CR, caloric restriction). They were subjected to behavioral tests (open field, elevated plus maze, light-dark transition, and forced swimming test) and gene expression profiling in the prefrontal cortex, amygdala, and hypothalamus with whole genome microarray and biofunctional pathway analysis of differentially expressed genes.
Results: The behavioral tests showed that CR mice, which received moderate CR (80%), displayed reduced anxiety- and depression-like behaviors with a peak on day 8, compared with AD mice, while these behavioral changes were absent in ACR mice. The gene expression was changed in the three brain regions. Among the brain regions examined, the most profound changes in gene expression were observed in the amygdala of CR mice: a total of 884 genes were specifically up-regulated. The ingenuity pathway analysis showed that these 884 genes significantly modified 32 canonical pathways, particularly α-adrenergic and dopaminergic receptor signalings. Quantitative RT-PCR confirmed the specific up-regulation of 6 genes (*Adcy2*, *Adcy5*, *Gys1*, *Mras*, *Ppp1r1b*, and *Ppp1r10*) encoding key molecules in the two signals.
Conclusions: This study demonstrated that the regular intake of CR reduced anxiety- and depressive-like behaviors. The specific up-regulation of α-adrenergic and dopaminergic receptor signals in this region may be associated with the beneficial consequence of psychological state.

FC-20-002
Impact of schizophrenia candidate genes on smooth eye pursuit in a population of young men

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Objectives: Smooth eye pursuit dysfunction has been proposed as potential endophenotypes for schizophrenia. It is unknown whether the expression of these endophenotypes at the population level is modulated by the genetic variability of candidate susceptibility genes for schizophrenia.
Methods: We examined in a population of 2130 young military conscripts the impact of 28 single nucleotide polymorphisms (SNPs) within the RGS4, NRG1, DTNBP1, COMT, MDAAO, BDNF, DAOA/G32, HT2A and DRD4 genes on the following smooth eye pursuit indices of performance: root mean square error, gain and saccade frequency. Parametric regression analysis was used to assess the effects of each SNP on each of the smooth eye pursuit parameters. In case of a significant effect (P<0.05) the effect was confirmed using non-parametric analysis namely bootstrap and permutation techniques.
Results: Only the NRG1, the NRG3 and the DRD4 SNPs exhibited associations with the smooth eye pursuit indices of performance. The SNPs NRG221533, NRG241930 and NRG243177 SNPs of the NRG1 gene were associated with differences in root mean square error, whereas the SNP NRG433E1006 of the same gene was associated with differences in saccade frequency. The SNP-521 of the DRD4 gene was significantly associated with pursuit root mean square error. For the other SNPs examined no associations with pursuit performance parameters reached significance.
Conclusions: The NRG1and DRD4 individual polymorphisms might exert gene-specific modulating effects on smooth eye pursuit performance, a potential schizophrenia endophenotype, at the population level.

FC-20-003
Catechol-O-Methyltransferase (COMT) gene and response to cognitive remediation in schizophrenia: Preliminary findings

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Objectives: Genetic variation in the Catechol-O-Methyltransferase (COMT) gene may influence neurocognitive functioning. The authors aimed to evaluate the effect of the association of COMT Val108/158 Met genotype with the response to a computerized neurocognitive rehabilitation treatment (CRT) in chronic schizophrenia.
Methods: Inpatients with DSM-IV schizophrenia, who underwent CRT for 3 hours per week for 12 weeks, were genotyped for COMT alleles. Baseline and endpoint battery of neuropsychological assessments, on functional skills, and PANSS were assessed. CRT response definition was >= 20% improvement on the Trail Making tests and WCST test for Responders vs. Non-responders. Because of the small sample size of Met homozygous patients, Met carriers (Met/Val = 17) and Met homozygotes (Met/Met = 2) were combined and compared to Val homozygotes (Val/Val n = 19). We analyzed Responder versus Non-Responder outcomes by using an interaction between conditions and having a normal performance (i.e. no change in score) at follow-up.
Results: We present results on 38 subjects of a total planned enrollment of 142. The RM ANOVA Mixed Models showed significantly greater improvement of the global cognitive index score (p = 0.050), Trail Making Test scores (p = 0.011) and working memory tasks (p = 0.049) for the (Met/Val + Met/Met) group who were Responders to CRT in comparison to Val/Val group who were Non-Responders. There was a significant association between higher PANSS scores and genotypes Val/Val (p = 0.044) for rs4680. Correlation of changes in overall global cognitive score and PANSS total score, between effect sizes of improvement (higher global cognitive index score and lower PANSS scores) was significant (p = .038).
Conclusions: Presence of Met allele was associated with significantly greater improvements in overall neurocognitive functioning after 12-weeks of CRT supporting the hypothesis that COMT polymorphism influences cognitive functioning through CRT, with the caveat that because of the small sample size.

FC-20-004
Association between dopaminergic pathway gene polymorphisms and schizophrenia (SCHZ) in Malaysian individuals

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Objectives: Molecular components of the dopaminergic system may play an important role in the pathophysiology of schizophrenia. Dopamine D3 receptors (DRD3) concentrated in limbic regions of the brain (important for cognitive, emotional and endocrine function) may be particularly relevant to schizophrenia (SCHZ). The enzyme catechol-O-methyltransferase (COMT) is crucial for the inactivation of prefrontal dopamine. Most association studies have investigated an exonic Met158Val polymorphism, which appears to influence COMT activity in vitro. Interest in the Met158Val polymorphism has continued because it may be correlated with working memory and cognitive functions in SCHZ
Methods: In this study, we investigated the relationship of the single nucleotide polymorphisms (SNPs) of Ser9Gly DRD3 and Met158Val COMT with Malaysia cases-control. A total of 110 patients with SCHZ and 110 healthy controls were investigated. PCR-RFLP was performed to genotype these two SNPs.
Results: Allele and genotype distributions of Ser9Gly polymorphism did not differ statistically between cases and controls. However, there was a significant difference for Met158Val.
Conclusions: No associations were found between the Ser9Gly DRD3 with SCHZ while Met158Val COMT could be a susceptible gene for SCHZ based our preliminary results. We believe that further studied are required to examine the relationship between other dopamine-related genes and the behavioral phenotypes of SCHZ in the Malaysia population.

FC-20-005

Conditional CRH overexpressing mouse mutants: Dissecting CRH-sensitive pathways in vivo

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Objectives: Corticotropin-releasing hormone (CRH) plays a prominent role in coordinating the neuroendocrine, autonomic, behavioral and immunological responses to various stressful stimuli. Dysregulation of the CRH system and accompanying chronically elevated levels of CRH are implicated in the pathogenesis and maintenance of psychopathology of human stress-related and affective disorders, including anxiety disorders and major depression. To study the effects of central CRH hyperdrive we created a highly flexible genetic mouse model that allows the overexpression of different dosages of CRH in a spatio-temporally controlled fashion.

Methods: A genetic mouse model was generated by combining the properties of the ubiquitously expressed ROSA26 (R26) locus with the Cre/loxP system. A single copy of the murine Crh cDNA, which is preceded by a Cre-recombinase-sensitive transcriptional terminator was introduced into the R26 locus. Breeding to different lines of Cre mice, enabled full spatio-temporal control of exogenous CRH expression, which is driven by the R26 promoter.

Results: CRH overexpression in the entire central nervous system resulted in stress-induced hypersecretion of stress-hormones and increased active stress-coping behavior reflected by reduced immobility in the forced swim test and tail suspension test. These changes were related to acute effects of overexpressed CRH as they were normalized by CRH-R1 antagonist treatment and recapitulated the effect of stress-induced activation of the endogenous CRH system. Genetic, pharmacological and molecular dissection identified an enhanced activation of the noradrenergic system as molecular mechanism underlying the observed phenotype.

Conclusions: We have created a new, highly flexible transgenic mouse model, which can help in dissecting the contribution of CRH-sensitive pathways involved in the transition from physiological to pathological stress responses, which are thought to underlie the etiology of affective and anxiety disorders. This animal model is also suited for validating drug candidates targeting the central CRH system.

FC-20-006

GAB2, GSTP1, SORL1, BDNF, GAPDH and APOE, polymorphisms associated with late onset Alzheimer disease

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Objectives: We investigated genes with relevant neurological function such as oxidative stress, neuronal apoptosis, and neuronal differentiation in patients with late onset Alzheimer's Disease (AD). At the present study, we searched for associations of late onset AD and 8 single nucleotide polymorphisms (SNPs) on 5 different genes (GAB2, GSTP1, BDNF, GAPDH, and APOE).

Methods: DNA was extracted from AD patients and elderly controls, We performed genotypic analysis by using allelic discrimination on real-rime PCR. At this time were analyzed more than 400 subjects.

Results: It was found a strong association at the studied population between the APOE*E2 allele in controls and also between the APOE*E4 allele in AD patients (P = 0,00127), confirming data already published. For GAB2 rs2373115 polymorphism, our results suggest that the TT genotype offers a higher susceptibility for developing AD, with a strong association (P = 0,005). The other genes studied did not show any significant association between its genotypes and AD. Combining APOE*4 allele with all studied polymorphisms we detected a strong association for some genotypes.

Conclusions: We have analyzed genes involved with relevant roles in neuronal homeostasis, such as oxidative stress, neuronal apoptosis and neuronal differentiation. We have confirmed the APOE*E4 allele and GAB2 rs2373115 'TT' genotype as important targets for development of Alzheimer's disease. Our findings confirmed previous data that GAB2 modifies late onset AD risk in APOE*E4 carriers and influences Alzheimer's neuropathology. Although any of the other genes analyzed has shown a direct association with AD when compared between patients and controls, it was possible to observe an association to AD in APOE*E4 carriers, suggesting a modifying effect of this allele. If those associations prove to be consistent in larger samples, the biological roles of these genes on AD will require further clarification.

FC-21
Other III

FC-21-001
Neural substrates of Anorexia Nervosa: A review of structural and functional neuroimaging studies

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Objectives: Anorexia nervosa is characterized by abnormal behaviours involving eating, weight and body image perception, that are resistant to change, leading to a high rate of relapse after initial treatment. This study aim to identify structural and functional cerebral alterations correlated with these behaviours in anorexia nervosa patients and to investigate their reversibility after weight recovery.
Methods: Published reports from refereed journals of the last ten years are collected, analyzed and synthesized into a summary of the most significant neuroimaging findings. We used as keywords "neuroimaging", "anorexia", "body image distortion", "hunger and satiation", "cerebral blood flow", differently matched together.
Results: Computed tomography and magnetic resonance imaging have demonstrated brain gray and white matter volume loss, cerebral spinal fluid increase and enlargement of ventricular spaces and of cortical sulci. This shrinkage of brain tissue, known as "pseudoatrophy", is associated with starvation and generally reverses with weight restoration as a function of re-feeding. Functional neuroimaging techniques have revealed greater activation in the orbitofrontal and anterior cingulate cortices and less activation in the lateral prefrontal cortex in response to food stimuli; moreover they have shown decreased activation in the lateral fusiform gyrus, in the temporal lobes and in the inferior parietal cortex in response to body shape stimuli. The abnormalities in these regions partially persist after weight gain.
Conclusions: Although these results are still under debate, the previously reported regions could reflect specialized neural systems for regulation of hunger and satiation and for processing of body image respectively. These findings suggest that, once nutritional health has been restored, targeted treatment is necessary to improve patients' enteroceptive awareness of hunger and satiation and their own body experience.

FC-21-002
Influence of parental rearing attitudes on gene expressions of glucocorticoid signaling in peripheral blood cells of healthy young adults

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Objectives: It has been suggested that adverse parenting increases a risk for mood disorders in young adults. In this study, we aimed to examine associations between parental rearing attitudes, mental state, and gene expression of peripheral blood cells in young healthy adulthood.
Methods: We recruited 164 university freshmen (100 male and 64 female; mean age, 19.7 with SD of ± 2.3 years) and collected saliva for measurement of cortisol and peripheral blood for RNA extraction. The extracted RNA were subjected to our original microarray carrying oligonucleotide probes for 1,811 stress-responsive genes. Concomitantly we asked them to answer several questionnares regarding to mental health, parental attitudes and life style. For statistical analysis, Welch t-test and Principal component analyses (PCA) were used. $p < 0.05$ was considered significant.
Results: We extracted 8 students who perceived low care combined with overprotection (LOW) and 9 students who grew up with optimal parenting (OPT; high care and low protection) by PCA. LOW students had significantly higher scores of Zung self-rating depression scale and hospitality anxiety and depression scale, compared with OPT students. Microarray analysis identified 16 differentially expressed genes in peripheral blood cells between LOW and OPT students. The Ingenuity Pathways Analysis revealed that 15 out of the 16 genes were associated with the hypothalamus-pituitary-adrenal axis-related network. In such genes, real-time reverse transcriptase PCR validated significant down-regulation of *TGFBR3*, *ATP8A1*, and *SLC35A3*, and up-regulation of *SLC31A2* and *glucocorticoid receptor* (*GR*). Further analysis of downstream in GR signal revealed that *IL1R2* and *IκBα* significantly upregulated their expressions in LOW. Of the 7 confirmed genes, 6 genes except for *SLC35A3* are GR signal-related genes.
Conclusions: Our results suggest that adverse parenting may significantly modify the glucocorticoid signal in healthy young adults as well as their depressive mood.

FC-21-003
Iatrogenic Hypothermia – a case report

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Objectives: The authors present a case of a 39-year-old mentally retarded man who developed hypothermia (30ºC), several days after starting olanzapine and levomepromazine.
Methods: Worldwide literature presents the description of four cases of hypothermia associated with olanzapine, however this is more frequent to occur with the first generation of antipsychotics agents.
Results: In this particularly case, the association of a first and a second generation antipsychotic agent, seems to have a cumulative effect leading to hypothalamic dysregulation and hypothermia, a fact that highlights the complexity of the temperature regulation system.
Conclusions: Temperature dysregulation, a known side effect of antipsychotic medications, is thought to be mediated by the effects of these on hypothalamic neurotransmission. Most commonly, they can cause hyperthermia which can be associated to the neuroleptic malignant syndrome, a life-threatening emergency. Hypothermia, traditionally defined as a drop in core body temperature below 35ºC (95ºF), is also a known side effect of both first and second generation antipsychotic agents.

FC-21-004
Shared neurobiological markers in autism and fragile x syndrome with autistic features, however….

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Objectives: The aim of the present study was to examine the extent to which autism and FXS with autistic features (FXS + Aut) show brain/phenotypic similarities and differences. À priori we predicted that the neurobehavioral resemblances to autism in the FXS + Aut may be reflected in neuroanatomical similarities.
Methods: Ten children with autism and seven with FXS + Autistic features underwent morphological (T1) 1.5T philips Intera magnetic resonance imaging in Egypt. Neuroimaging data was then transferred and analyzed through the fully automated CIVET pipeline at the Montreal Neurological Institute (MNI), McGill University Canada. All subjects were diagnosed and underwent medical, clinical and neuropsychological assessments at the National Research Centre (Egypt): Childhood Autism Rating Scale (CARS), Wechsler Intelligence Scale for Children-Revised, social IQ, Raven's Progressive Matrices and DNA for FXS mutation were done.
Results: We found no significant difference between autism and FXS with autistic features regarding whole brain volumes, regional volumes, gyrification index and cerebral cortical thickness. However, children with autism showed significant decrease in the medial prefrontal (MFC) bilaterally and the anterior cingulate (ACC) cortices. The left MFC correlated negatively with mother's age and the CARS.

Conclusions: Given the fact that autism and FXS + Aut share behavioral phenotypes, they may bear a great deal of similarity in terms of brain neuroendophenotypes. Autism and autistic symptoms in FXS may reflect a common etiological or pathophysiological pathway between the two conditions. We postulate that the difference between the two groups in the MFC and ACC cortices thickness suggests an altered social cognitive style. Functional magnetic resonance imaging studies directly differentiating between social indifference (autism) and social avoidance (FXS + Aut) are needed in order to further characterize the spectrum of social abnormalities between these two groups.

FC-21-005

Hypothalamic-Pituitary-Adrenal (HPA) hypoactivity in circa 200 Fibromyalgia or Chronic fatigue (CFS) patients. Cortisol rhythm, Dexamethasone Supression Test (DST) and Free urinary cortisol (CLU.)

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delia ostera, pablo beretta, tomas maresca, juan jose romanella, gloria alcira pizzuto, mariela calvo

Objectives: To determine alterations in the HPA axis in Fibromyalgia patients, in order to corroborate if it is only a "stress related" disorder.
Methods: The sites of the study are the Center for Family Medicine (CEMIF), the Clinical Biochemical Institute and the Institute of Biological Psychiatry (ipbi) in Argentina in an interdisciplinary setting with psychiatrists, family doctors, biochemistry specialists, and medical residents. intervening in this work. 189 patients diagnosed as of fibromyalgia or CFS according to Ferrand-Barcelona Institute Inventory and with strict exclusion criteria (primary psychiatric, endocrinological, immunological or neurological pathologies and no treatment with drugs with immune, endocrinological or Central Nervous System action authorized since one month prior to testing) underwent biochemical measurements of ACTH, morning and dawn Cortisol, DST and 24 hs-CLU
Results: ACTH showed high in 14 cases and low in 8. Morning cortisol was altered in 2 cases, and evening cortisol was altered in 28. Cortisol rhythm secretion was altered in 108 subject's cases (more than 50%). Both cortisol determinations presented abnormalities in 79 patients. Circadian cortisol rhythm remained unaltered in 81 patients. DST revealed no suppression in 31 patients (less than 25%). DST no suppressive response plus rhythm alteration was observed in 20 cases (10%). CLU was altered in 50% dissociated as CLU with low excretion in 46.6% and only 5% correlating with both low CLU and high ACTH. Less than 5% revealed high CLU. Statistical Measures and ANOVAs T distribution was performed
Conclusions: Most of all fibromyalgia patients showed a hypofuctionality of HPA axis. It is note worthy that this dysfunction does not resemble that expected in major depressive disorders but remembers us all of that described in post-traumatic stress disorders (PTSD) One of us has published, ten years ago, the similarity in cortisol alterations between PTSD and CFS

FC-21-006

Long term outcome in prepubertal anorexia nervosa: A retrospective study of young adult subjects

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Objectives: This study is a retrospective evaluation of the outcome of early onset anorexia nervosa. The objective was to explore the psychosocial and somatic outcome in fifteen young adult subjects previously treated for prepubertal anorexia nervosa. In the literature, it is sometimes hypothesized that early onset anorexia nervosa is associated with a worse prognosis than later onset anorexia nervosa.
Methods: Subjects were interviewed an average of 11 years after their hospital discharge, through face to face and telephone interviews. Upon initial admission, all patients suffered from prepubertal anorexia nervosa (mean age 10 years) and were treated on an inpatient unit. The outcome criteria are based on the assessment of current eating disorder symptoms, psychiatric comorbidity and its direct impact on subjects' physical health, quality of life and psychosocial outcome. Assessment instruments were: Mini International Neuropsychiatric Interview (MINI), Morgan-Russell Outcome Assessment Schedule, Eating Disorder Inventory (EDI-2), MOS SF-36 questionnaire and a socio-demographic anamnestic questionnaire. BMI computations were based on self-reported weight/height.
Results: A preliminary qualitative analysis showed that six (40%) subjects had eating disorders: two (13.3%) had anorexia nervosa, four (26.6 %) bulimia. Eight (53.3%) had eating restrictive behaviour and eight (53.3%) were worried about physical appearance and weight. Twelve (80%) had one or more axis-1 DSM-IV diagnosis. Mean BMI score at admission was 14.45 (- 2 SD) and 20,7 (+ 0.5 SD) at follow-up.
Conclusions: To conclude, despite the methodological bias due to the small size of our sample, our results emphasize the chronic nature of psychiatric symptoms in early onset anorexia nervosa even when the subjects' somatic condition is improved.

FC-22
Brain Function II

FC-22-001
Mental fatigue and impaired information processing after brain injury

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Objectives: Fatigue is a common symptom and may impair working capacity and social activities during many years after a mild or moderate brain injury. Mechanisms of origin of mental fatigue are not fully understood and no clear treatment guidelines have been developed. Therefore, it is important to develop appropriate assessment methods and increase our knowledge about mental fatigue.
To put cognitive tests in relation to a self assessment questionnaire about mental fatigue.
Methods: Persons with mild traumatic brain injury (MTBI) working full time (14) and on sick-leave (32) were included, and persons with more severe traumatic brain injury (STBI, 12). Control participants (40) of similar age (mean 42 years), education and gender, were recruited from general community. A new self assessment scale including items of importance for mental fatigue was used. Digit coding (WAIS-III), reading speed (DLS), digit span (WAIS-III) and spatial span (WMS-III) were included. Verbal fluency (D-KEFS) and Trail Making Test A and B and two extensions of TMT with higher load on divided attention were also used. Persons with brain injury were assessed for depression and anxiety by CPRS-A.
Results: Persons with MTBI and STBI reported significantly more mental fatigability, mental recovery and stress sensitivity than controls. Cognitive tests showed a significantly attenuated information processing speed for persons with MTBI and STBI on sick-leave, but not for those working full-time, compared to controls. Divided attention was affected but to a lower extent. A significant correlation appeared for subjective mental fatigability and tests measuring information processing speed. Very low scores for depression were assessed for persons with brain injury in this study.
Conclusions: Persons with MTBI and co-occurring mental fatigue performed with slower information processing speed. It is suggested that mental fatigue should be assessed separately from depression.

FC-22-002
A meta-analysis comparing the placebo response of a non-pharmacological vs. a pharmacological intervention in major depressive disorder

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Objectives: To investigate the placebo response in a pharmacological and a non-pharmacological intervention in Major Depressive Disorder (MDD).
Methods: Systematic review and meta-analysis for MDD trials whose intervention was escitalopram or repetitive transcranial magnetic stimulation (rTMS). We searched for articles in MEDLINE and other databases from April/2002 to April/2008. We then calculated the pooled effect size for the placebo group in the escitalopram and rTMS arms, using Cohen's d (random-effects model) as the measure of effect size.
Results: Forty-one studies were included. We found a large placebo response for both escitalopram (1.48; 95% C.I. 1.26 to 1.6) and rTMS studies (0.82; 95% C.I. 0.63 to 1). Exploratory analyses show that sham response is negatively associated with refractoriness and positively associated with add-on rTMS studies, but not with age, gender and sham method utilized.
Conclusions: We confirmed that placebo response in MDD is large regardless of the intervention and is associated with depression refractoriness and treatment combination (add-on rTMS studies). Our exploratory findings of lower placebo responses in rTMS trials when compared to escitalopram trials might be explained by cultural and methodological factors.

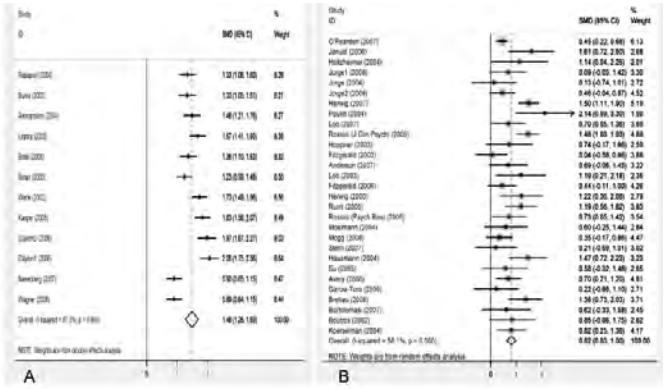

Fig 2 - Forest plot showing effect sizes (standardized mean difference of mood scores from baseline to after treatment in the control group of each study) from the random effects model of escitalopram (A) and rTMS (B) studies. Effect sizes are Cohen's d, and error bars represent the 95% confidence interval.

FC-22-003
Impaired cognition, sensorimotor gating, and hippocampal long-term depression in mice lacking the prostaglandin E2 EP2 receptor

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Objectives: Cyclooxygenase-2 (COX-2) is a neuronal immediate early gene that is regulated by N-methyl D aspartate (NMDA) receptor activity. COX-2 enzymatic activity catalyzes the first committed step in prostaglandin synthesis. Recent studies demonstrate an emerging role for the downstream PGE2 EP2 receptor in diverse models of activity-dependent synaptic plasticity and a significant function in models of neurological disease including cerebral ischemia, Familial Alzheimer's disease, and Familial amyotrophic lateral sclerosis. Little is known, however, about the function of the EP2 receptor in behavior and cognition.
Methods: EP2-/- mice (ages 3-12 months) were tested in standard tests of fear and social memory while spatial memory was analyzed in multiple water maze tasks that assess reference and episodic-like/working memories. In addition, prepulse inhibition of acustic startle response and anxiety lelvels were tested. Electrophysiological studies of the Schaffer collateral-CA1 pathway were conducted EP2-/- mice and their littermates.
Results: Here we report that deletion of the EP2 receptor leads to significant cognitive deficits in standard tests of fear and social memory. EP2 -/- mice also demonstrated impaired prepulse inhibition (PPI) and heightened anxiety, but normal startle reactivity, exploratory behavior, and spatial reference memory. This complex behavioral phenotype of EP2-/- mice was associated with a deficit in LTD in the Schaffer Collateral-CA1 pathway of the hippocampus.
Conclusions: Our findings suggest that PGE2 signaling via the EP2 receptors plays an important role in cognitive and emotional behaviors that recapitulate some aspects of human psychopathology related to schizophrenia. This study may be relevant to the older literature from the 1970s and 1980s in which a number of studies suggest a role for prostaglandin signaling in schizophrenia and the more recent interest in the role of COX-2 in this disease.

FC-22-004

Increased vulnerability of the mesencephalic dopaminergic systems of the human neonate to perinatal hypoxia: Implications in psychiatry

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Objectives: Hypoxia during the last trimester or during the intrapartum period could cause long-term damage to the central nervous system leading to behavioral and/or neurological deficits later in development. Epidemiological studies implicated perinatal insults as etiological risk factors for schizophrenia, attention deficit hyperactivity disorder and developmental forms of parkinsonism. Experimental models of perinatal hypoxia showed selective long-standing changes not only in the hippocampus but also in mesencephalic dopaminergic systems. Purpose of our study was to investigate the effect of perinatal hypoxia on brainstem catecholamine systems of the human neonate.

Methods: We studied immunohistochemically the expression of tyrosine hydroxylase (TH, the first and limited enzyme for catecholamine synthesis) in locus coeruleus (LC), substantia nigra (SN) and ventral tegmental area (VTA) of 16 full term neonates died with signs of perinatal hypoxic-ischemic encephalopathy. Autopsies were performed following written consent of their parents. The evaluation of the severity and duration of the perinatal hypoxic insult was based on clinical data and severity of neuropathological lesions.

Results: Our results showed that hypoxia does not affect equally all the catecholaminergic neurons. Compared to LC, neurons of SN and VTA appeared especially vulnerable to perinatal hypoxia. In the majority of the neonates who suffered prolonged perinatal hypoxia, we observed dramatic reduction or absence of TH-immunoreactivity in SN and VTA. In neonates that died after short hypoxic insult, we observed normal development, morphology and TH-immunoreactivity of mesencephalic dopaminergic systems.

Conclusions: Given that, according to Verney (1999), the development of human catecholamine systems is completed after the 22nd week of gestation, we suggest that the reduction or absence of TH-immunoreactivity in SN and VTA of the full term neonate is due to prolonged perinatal hypoxia. Since SN and VTA innervate basal ganglia and prefrontal cortex respectively, our results provide the anatomical basis of both the extrapyramidal and/or congnitive disturbances in children survived after prolonged perinatal hypoxia.

FC-22-005

Autonomic nervous system and its association with brain function in major depressive disorder

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Objectives: We recently demonstrated elevated brain serotonin turnover in untreated MDD, with over a 2-fold increase in turnover being associated with carriage of the s allele of the serotonin transporter (5-HTT) gene. Further, sympathetic nervous activity (SNA) followed a bimodal distribution, with some extraordinarily high values and some marginally lower than in healthy subjects. Therefore, we hypothesized that the bimodal distribution of SNA may be related to the 5-HTT genotype and hence, the degree of SNA in MDD may be dependent upon the level of brain serotonin turnover.

Methods: Twenty-five unmedicated patients with moderate-severe MDD were studied at rest and following 10 minutes mental arithmetic, before and approximately 12 weeks after SSRI treatment. Using arterial blood sampling with norepinephrine isotope dilution methodology, SNA levels were assessed. In parallel, cardiac baroreflex function and heart rate variability were used as indexes of parasympathetic/vagal activity, and 5-HTT genotype determined. Statistical analyses comprised 2 way repeated measures ANOVA.

Results: Resting SNA was significantly higher in patients carrying the s allele (712±76 v 386±82ng/min). In response to mental stress, SNA and heart rate increased by a similar magnitude in the long and short genotype groups, whereas blood pressure was substantially increased in the s genotype group ($P<0.001$). Vagal activity decreased following stress but bore no association with the 5-HTT genotype. Therapy markedly decreased HamD and BDI-II, and resting heart rate and vagal activity ($P=0.03$ and 0.05, respectively). SNA was reduced ($P<0.01$) in the s genotype, 262±91ng/min (s allele) v 245±83ng/min (l allele). Interestingly, SSRI therapy was associated with dampening of the sympathetic, parasympathetic and associated hemodynamic responses to stress.

Conclusions: Elevated SNA is evident in MDD patients carrying the s allele of the 5-HTT gene. Given previous observations linking 5-HTT genotype and brain serotonin turnover, robust measures of SNA may provide an indirect marker of brain function in MDD.

FC-22-006

Striatum abnormalities in schizophrenia patients` families

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Objectives: Some data indicate that striatum abnormalities are related both with ongoing disease process and predisposition to schizophrenia. However these data need a clarification.

Methods: In order to investigate striatum parameters in schizophrenia patients` families 96 subjects (34 patients with schizophrenia, 32 their unaffected relatives, 34 controls) were investigated. 3 mm coronal T1-weighted 3D magnetic resonance images were acquired on a 0.5 Tesla magnet Tomikon S50, Bruker (Germany). Volumes of left and right caudate (VLC, VRC), left and right nucleus lentiformis (VLNL, VRNL) were calculated. The data analysis in patients was carried out taking into account both the group as a whole one and two its subgroups: 1 – patients with chronic paranoid symptoms (continuous paranoid schizophrenia) (10 subjects), 2 – patients with negative symptoms (remissions of episodic schizophrenia) (17 subjects).

Results: Results showed none-significant decreasing of caudate and nucleus lentiformis volumes in both hemispheres in patients as well as in their relatives compared with controls. Asymmetry of striatum parameters in all groups was demonstrated: in patients and relatives the VLC was less than the right one ($p<0.05$, tendency correspondingly), the VRNL was less than the left one (tendency, $p<0.05$ correspondingly), in controls mentioned ganglia parameters were reversed (tendency). The degree of reduction of studied striatum structures in patients was more prominent in 2-nd subgroup where negative symptoms were dominating.

Conclusions: The results confirm the role of striatum structures abnormalities in pathogenesis of schizophrenia. The differences in reduction degree of striatum ganglia in patients of 1-st and 2-nd subgroups may be hypothetically related with oedema of brain tissue more developed in cases with positive symptoms. True degree of structures reduction appears by fading of disease exacerbation and forming remission with negative symptoms. The data also support the significance of brain structures asymmetry as a factor of predisposition to disease and its development.

FC-23
Psychotic Disorders VI

FC-23-001
Outcome in first-episode schizophrenia: 4-year follow-up

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Objectives: Our department has been specializing, on a long-term basis, in the problems of first episode schizophrenia. Concerning psychopathology we found that on admission the occurrence of positive, negative and general symptoms was balanced, at discharge and after 1 year negative and general symptoms were the most frequently observed. Now, we present the data obtained at the 4-year follow-up.
Methods: Male patients consecutively hospitalized at the Department of Psychiatry were included if they were experiencing their first admission for first-episode schizophrenia (according to ICD 10), provided written informed consent and were reassessed at the 4-year follow-up. The psychic state was evaluated using PANSS. The study was designed as an open, naturalistic, follow-up study.
Results: Since 1996 we have recorded in our databases more than 160 patients, males, who have been observed longitudinally from the first index hospitalization. During the index hospitalization the average age was 23 years. The average duration of the index hospitalisation was 6 weeks. At the 4-year follow-up totally 97 patients should be reassessed; 73/97 (75%) of the patients came to a reassessment. 4 patients out of 24 who did not come committed suicide. 58% (42/73) of patients have fulfilled the criteria for remission according to Andreasen. No significant difference in baseline demographic values was found between remitters and nonremitters, although a trend to lower age at index hospitalization and longer duration of illness was observed (21 vs. 23 years and 9.4 vs. 5.7 months). No statistically significant difference in the total PANSS and PANSS subscales scores was found between remitters and nonremitters before or after the acute treatment. However, the relative decrease of the total PANSS and negative and general subscale scores, e.g. delta PANSS during the index hospitalization was significantly higher in remitters than in nonremitters.
Conclusions: The treatment responsivity and dynamics of some symptoms may be important for the outcome.

FC-23-002
New diagnostic and treatment approaches to schizophrenia with obsessive-compulsive symptoms

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Objectives: Obsessive-compulsive (OC) symptoms have been observed in a substantial proportion of schizophrenia patients. The complex nature of the treatment response of OC and schizophrenia symptoms is as yet unclear. Here we present our model of the clinical typology of schizophrenia with prominent OC symptomatology and some possible predictors of response of OC and schizophrenia symptoms on some atypical antipsychotic agents (AAAs).
Methods: This case series study describes our experience with clozapine, risperidone, olanzapine, quetiapine and ziprazidone and amisulpiride as a sole agents and in combination with serotonin reuptake inhibitors (SRIs): clomipramine, fluvoxamine, fluoxetine, paroxetine, citalopram, sertraline, in patients with OCD-schizophrenia (n=58) and schizo-obsessive disorder (n=69).
Results: In OCD-schizophrenia the better results were achieved in combination with SRIs, while the olanzapine showed the fastest overall improvement. In schizo-obsessive patients AAAs as monotherapy was the better therapeutic modality, and the risperidone showed the best results. Quetiapine, amisulpiride and ziprazidone were approximately equal in their antipsychotic and antiobsessive activity and overall safety.
Conclusions: The effects of different AAAs (with or without SRIs) on psychotic and OC symptoms are vary, probably due to different origin of OC symptoms. Based on our model of the clinical typology of OC symptoms in schizophrenia, we suggest that: 1) schizo-obsessive patients might be successfully treated with AAAs alone; 2) in OCD-schizophrenia AAAs monotherapy may be less efficient and in some cases even may worsen OC symptoms, so it should be treated concomitantly with SRIs. Further investigations are needed to substantiate our observations and to elaborate the most effective and safe therapeutic approaches to these difficult-to-treat group.

FC-23-003
Visual scanning of natural scenes in schizophrenia: Effect of a task-driven exploration and scene semantic consistency

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Objectives: Schizophrenia is known to be associated with impaired visual scanning of faces, landscapes, and meaningless stimuli, when scene exploration is not driven by a visual search task. Moreover, it has been showed that attentional capture by an irrelevant distractor has a different effect for patients with schizophrenia and healthy controls. In this study, we explore whether visual scanning of natural scenes in schizophrenia depends on task-driven exploration and scene semantic consistency.
Methods: In this study, observers (24 patients with schizophrenia and 24 healthy controls) were instructed to explore natural scenes (48 outdoor and indoor pictures) containing a semantically consistent or inconsistent object (for instance a dog versus a pig in a downtown street). Scenes were explored under two conditions: a visual search task in which observers determined whether scenes contained more than 5 targets, or free exploration. Eye movements were recorded in order to assess (1) whether patients with schizophrenia performed a visual search task comparable to healthy controls; and (2) whether semantically inconsistent items differentially capture attention of patient compared to healthy controls.
Results: Results indicated that patients' visual scanning closely approximated healthy controls in the number of fixations, mean fixation durations, mean number of entries in the region of interest, and mean fixation duration in the region of interest. Furthermore, patients showed no significant difference between observers with schizophrenia and healthy controls when they were required to performed a visual search task.
Conclusions: This result suggests that the visual scanning impairment observed in schizophrenia was eliminated when patients had to perform a visual search task. Finally, observers' eye movement patterns were compared to the prediction of a saliency model. Results indicated that salient parts of the scene seemed to attract early fixations of patients with schizophrenia more often than those of healthy controls, especially when the scenes contained semantically inconsistent objects.

FC-23-004
Heritability aspects of endocannabinoid functioning in schizophrenia

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Objectives: Epidemiological and experimental evidence suggests a role of the human endocannabinoid system in the pathophysiology of schizophrenia as cannabis use is associated with a twofold increase in the risk to suffer this disorder. In addition, the major psychoactive phytocannabinoid delta-9-tetrahydrocannabinol induces psychotic symptoms in healthy volunteers and schizophrenia patients. Over recent years, we were able to demonstrate that the endocannabinoid anandamide in cerebrospinal fluid is elevated in acute schizophrenia, inversely correlated to psychopathology. In addition, cerebrospinal anandamide is negatively affected by cannabis use in these patients. However, it remains conjectural if anandamide is also modified in relatives of schizophrenic patients.
Methods: Here we investigated levels of anandamide, 2-arachidonoylglycerol (2-AG), palmitoylethanolamide and oleoylethanolamide in plasma from 31 twin pairs discordant for schizophrenia as well as 8 concordant healthy pairs of twins by LC/MS as previously described.
Results: There was no significant difference of all investigated eicosanoids within the group of discordant "schizophrenia" twins. This was also the case for the healthy twin pairs. In contrast, "schizophrenia" twins showed significantly higher levels of anandamide and palmitoylethanolamide in plasma when compared to healthy twins ($p<0.001$).
Conclusions: As we supposed a model, were anandamide counterbalances other neurotransmitter imbalances in people at increased risk for schizophrenia, our data indicate, that anandamide and palmitoylethanolamide are modified in schizophrenia patients as well as in their non-affected monozygotic twins. This may further support a protective role for anandamide in schizophrenia.

FC-24
Neuroimaging II

FC-24-001
Microstructural alterations of an orbital and medial prefrontal network in detoxified alcoholics as detected by voxel-based Diffusion Tensor Imaging

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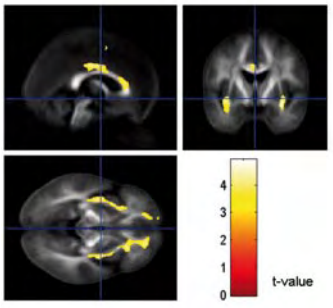
Objectives: To comprehensively assess the microstructural integrity of white matter pathways, we performed voxel-based Diffusion Tensor Imaging (DTI) in detoxified subjects with alcohol dependence. In contrast to a predefined region approach the whole brain was investigated in an exploratory fashion without a priori assumptions about the structures to be investigated.
Methods: 21 adult alcoholics (16 men) and 22 age-matched control subjects were enrolled in the study. DTI (25 directions) was performed on a 1.5T neuro-optimized GE-scanner at least one week after the detoxification had been started. Images were pre-processed and analyzed using a new approach by SPM2. Fractional anisotropy (FA) and apparent diffusion coefficient (ADC) were compared using t-tests ($p<0.05$, corrected).
Results: Compared with controls, alcoholics showed extensive decreases in FA in the white matter of the orbital and medial prefrontal cortex, the corpus callosum, the cingulate gyrus, the uncinate fasciculus, and the brainstem bilaterally compared with controls (see figure). Comparison of ADC maps revealed widespread increased diffusivity in gray matter of the frontal and parietal lobes bilaterally.
Conclusions: The findings of our DTI study identified disturbances of associational and commissural fibers in the orbital and medial prefrontal network of patients with alcohol-dependence. This network is thought to be involved in emotional and other self-referential processes. Linking neuropathological abnormalities with clinical characteristics in vivo, the results contribute to constraining the prevailing biological models of alcohol dependence extending the results of previous structural MRI studies with a region of interest approach.



FC-24-002
Associations between gray matter abnormalities and cognitive function in the at-risk mental state

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Objectives: While it is clear that psychosis and its prodromal state are associated with neuroanatomical abnormalities and cognitive deficits, the brain structure - cognition associations in this group are less clear. The aim of the study was to investigate brain structure – cognition relationships in individuals with an at-risk mental state (ARMS) relative to patients with first-episode psychosis and healthy volunteers.
Methods: The subjects were recruited within the Basel Early Detection of Psychosis Clinic (FEPSY), University Hospital Basel. We did two comparisons, cross-sectional and longitudinal. For the cross-sectional comparison magnetic resonance imaging data were acquired using a 1.5 T scanner from individuals at high risk of developing psychosis, similar to the PACE criteria (ARMS), patients with a first-episode psychosis (FE) and healthy volunteers (HC). For the longitudinal comparison, ARMS individuals were scanned again with MRI after at least 12 months. Images were processed and analysed using voxel based morphometry (VBM). For details see: Borgwardt SJ et al (2008) Reductions in frontal, temporal and parietal volume associated with the onset of psychsis. Schizophrenia Research, 106(2-3): 20-26. Borgwardt SJ et al (2007) Structural brain abnormlities in individuals with an At Risk Mental State who later develop psychosis. Full-length article. British Journal of Psychiatry, 191(Suppl 51): 69-75.
Results: Regional gray matter volume abnormalities in areas that are also altered in volume in schizophrenia were associated with specific cognitive deficits in people with an ARMS.
Conclusions: Some associations were specific to individuals with an ARMS and may be a correlate of their increased vulnerability to psychosis. Further structure – cognition associations within the ARMS group appear to be associated with the subsequent onset of psychosis.

FC-24-003
Metabotropic Glutamat receptor 5 Imagingin major depressive disorder

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Objectives: There is increasing evidence for a primary glutamatergic dysfunction in mood disorders: while monoaminergic antidepressants have a delayed onset of action, a single dose of the glutamatergic NMDA antagonist ketamine produced rapid and large antidepressive effects in patients with treatment-resistant depression. The metabotropic glutamate receptor 5 (mGluR5) is of special interest because it is tightly coupled with the NMDA receptor, it is expressed in brain regions that have been implicated in the pathophysiology of depression (prefrontal cortex, the anterior cingulate, the striatum, the ventromedial prefrontal cortex, the amygdala and the hippocampus), and mGluR5 antagonists including MPET and MTEP showed antidepressant-like and anxiolytic-like effects in various animal models of depression.. In a ongoing PET study we investigated mGluR5 binding in subjects with major depression and healthy controls.
Methods: We included 13 unmedicated subjects with major depression and 8 healthy controls. Images of mGluR5 receptor binding were acquired using PET and 11C-ABP688. ABP688 is a noncompetitive and highly selective antagonist, which binds to an allosteric site of the mGluR5; it showed high selectivity for mGluR5 and high uptake in receptor-rich brain regions.
Results: We found marked reductions of mGluR5 binding potential in the left dorsolateral prefrontal cortex (dlPFC) ($p=0.003$) and the right dlPFC ($p=0.007$).
Conclusions: This study provides evidence for an important role played by mGluR5 in the pathophysiology of depression. The assessment of a broad range of clinical variables including nicotine consumption and nicotine dependence will allow detection of correlations between mGlu5R binding and clinical characteristics with potentially high scientific and clinical impact.

FC-24-004
Depressive symptoms and risk of white matter lesions. The SMART-MR study

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Objectives: The vascular depression hypothesis proposes that vascular lesions in the brain increase the risk for late-life depression. Alternatively, depression may increase risk for cardiovascular disease and vascular lesions in the brain. We examined the association between depressive symptoms and white matter lesions (WML) on magnetic resonance imaging (MRI) in a large cohort of patients with arterial disease.
Methods: Within the SMART-MR study, an ongoing cohort study among patients with manifest arterial disease, cross-sectional analyses were performed in 852 patients (mean age 58 ± 10 years, 77% male). At baseline, depressive symptoms were assessed with the mental health index (MHI-5), a subscale of the SF-36. MRI was performed to quantify volumes of brain tissue and WML, using an automated brain segmentation program. WML volumes were expressed relative to intracranial volume. Location and number of infarcts were rated visually. Linear regression analyses were used to investigate the association between depressive symptoms as independent variable and log-transformed WML volume as dependent variable, adjusted for age, sex, smoking habits, alcohol intake, body mass index, hypertension, hyperlipidemia, diabetes mellitus, intima-media thickness and presence of infarcts on MRI.
Results: Median WML volume in the total study sample was 0.11% (10-90 percentile 0.04-0.52%), and median depressive symptom score was 76 (10-90 percentile 48-92). With more depressive symptoms, median WML volumes increased. Median WML was 0.12% for MHI-5 scores 1-68, indicating more depressive symptoms, 0.11% for MHI-5 scores 69–84 and 0.10% for MHI-5 scores 85-100. Regression analyses showed that more depressive symptoms were associated with more log-transformed WML, after adjusting for all covariates (β -0.004, 95% CI -0.007, -0.001, p=0.02).
Conclusions: Depressive symptoms increase risk for white matter lesions, independent of age, sex, vascular risk and presence of infarcts. Future studies should determine whether depression is a cause or a consequence of vascular risk.

FC-24-005
Resting state functional MRI and MR-spectroscopy in major depressive disorder: Preliminary results

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Objectives: Consistent resting state networks (RSN) across healthy subjects (Damoiseaux et al 2006) and differences in BOLD activation of several regions in Major Depressive Disorder (MDD) have been described (Greicius et al 2007). Recent studies support the involvement of glutamatergic mechanisms in MDD. Our goal was thus to test the correlation between fMRI activity at rest and glutamate concentration in several RSN's.
Methods: Functional MRI and MR-Spectroscopy on a Siemens 3T MRI System was applied on 20 healthy subjects and 20 depressed patients. We used a single voxel (PRESS) sequence (TE 80 ms) for Glu/Gln separation and functional MRI was recorded for ten minutes. The MRS Voxels of task positive regions such as dorsolateral prefrontal (dlPFC), anterior Insula/frontal Operculum (aIfO) and dorsal anterior cingulate cortex(dACC) and of task negative, default mode regions such as pregenual anterior cingulate cortex (pgACC) and posterior cingulate cortex (pCC) defined the regions of interest (ROI) used for the fMRI data analysis with AFNI. The activation within a region was defined as standard deviation of the mean BOLD fluctuation measured over 488 timepoints (TR 1.25 s).
Results: During the resting state condition we found different patterns of correlation between glutamate concentration and BOLD activity in our regions of interest. The comparison of depressive and healthy subjects showed significant differences in measures of functional activations and the glutamatergic system.
Conclusions: The observed group*region*metabolite interaction supported the specific involvement of previously described default mode regions in major depression. Our results support the important role of combined metabolic and functional studies in specific resting state networks. Alterations found in such approaches may guide future studies of generally altered conditions in key regions at rest and reveal their abnormal capacity to react upon stimulation in more specific task related protocols.

FC-24-006
An fMRI study investigating hippocampal volume, psychological stress and vulnerability for depression

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Objectives: Psychological stress significantly affects central nervous system regulation. Prolonged and chronic stress exposure has been suggested to contribute to several disorders, particularly depression. While several studies have investigated neural networks associated with the processing of psychological stress in normal populations, to our knowledge no study has directly investigated this in a population with an explicit vulnerability to depression, i.e. subclinically depressed individuals. In the present study, we examined the neural correlates of stress exposure in a group of healthy university students showing individual differences at the levels of subclinical depression. We also investigated hippocampal (HC) volume in this population.
Methods: We recruited 60 healthy college students (30 males) based on their scores on the Beck Depression Inventory (BDI). Two groups were formed: a control (BDI<10) and a subclinical group (9<BDI<19). Participants were further asked to complete several psychological questionnaires to assess personality profiles. Subjects underwent a high-resolution anatomical scan, followed by two functional runs of the Montreal Imaging Stress Task (MIST). Saliva samples were taken throughout the experiment to assess stress reactivity.
Results: Analysis of the results is in progress, and results will be presented at the meeting. We expect that there would be a negative correlation between HC volume and depression scores in this population. Further, we expect subclinical participants will show a higher stress response compared to the control group. We further expect a stronger deactivation in the limbic system in response to the MIST in the subclinical group when compared to the control group.
Conclusions: Investigating the neural correlates of psychosocial stress in a subclinical population is essential for better understanding the ways in which dysregulation of specific processes may represent a vulnerability in the illness proper. Furthermore, such research may offer some insight into potential targets for future prevention and treatment programs.

FC-25
Psychopharmacology III

FC-25-001
Impact of depression, anxiety comorbidity and antidepressant treatment on heart rate variability: A meta-analysis

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Objectives: To examine the impact of depression severity, subtype, anxiety comorbidity and antidepressant treatment on heart rate variability using meta-analysis.
Methods: Studies comparing (1) heart rate variability in patients with major depressive disorder patients and healthy controls, and (2) the heart rate variability of patients with major depressive disorder pre- and post-treatment, were considered for meta-analysis. Means, standard deviations, p-values, and sample sizes were extracted for heart rate variability frequency and time-domain metrics.
Results: Meta-analyses were conducted including 20 sets of data, which comprised up to 606 depressed participants and 511 healthy comparison participants. The combination of mean effect sizes across these studies using a random effects model revealed that participants with depression had a lower heart rate variability (high frequency: Hedges' g = - 0.210, P = 0.027; time frequency: Hedges' g = -0.290, P = 0.006) than healthy controls and that depression severity is negatively correlated with heart rate variability (r = -0.311, P < 0.001). There was no difference in heart rate variability between depressed patients with and without anxiety comorbidity after accounting for depression severity and the data also indicate that heart rate variability does not increase with selective serotonin reuptake inhibitor treatment.
Conclusions: Results highlight a potential role for heart rate variability as a psychopathological endophenotype of depression, the importance of assessing heart rate variability in currently and previously depressed patients, and the possibility that treatment does not resolve these complications, suggesting that selective serotonin reuptake inhibitors may not provide cardioprotective effects as has been suggested previously.

FC-25-002
Social isolation alters the behavior effect of carbamazepine

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Objectives: The aim of the present experiments was to investigate the role of social isolation on the behavior effect of carbamazepine in rats.
Methods: Male Wistar rats were obtained from weaning, and housed either alone (isolation rearing) or in groups of six rats/cage (social rearing). Six weeks later, these rats were tested for their sensitivity to carbamazepine using the forced swimming and the open field tests.
Results: The results from the forced swimming test demonstrated that drug-free isolation reared rats showed significantly less immobility and more struggling in the forced swimming test than socially reared rats. Subchronic administration of carbamazepine (10, 20 and 40 mg/kg i.p.) 24, 5 and 1 h to socially reared rats produced a dose-dependent antidepressant-like effect (reduction of immobility time and elevation in struggling) compared to the vehicle control (2% Tween 80) treated group. However, this effect did not occur in isolation reared rats. The results from the open field tests showed that sub-chronic treatment with carbamazepine (10, 20 and 40 mg/kg i.p.) did not alter the open field behavior and locomotor activity, indicated by no change in total zone transitions compared with vehicle (2% tween 80) treated rats in both socially and isolation reared rats (P > 0.05).
Conclusions: These results suggest that social isolation from weaning reduced the antidepressant-like effect of carbamazepine in the mature rats. Further investigations will need to determine whether there are alterations in the ion channels e.g., Na+ channels and/or the central neurotransmission in the isolation reared rats.

FC-25-003
Effects of antipsychotics and vitamin C on the formation of reactive oxygen species

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Objectives: There is evidence that reactive oxygen species (ROS) are involved in the pathophysiology of psychiatric disorders like schizophrenia. Indirect biochemical alterations of ROS formation have been shown for patients treated with antipsychotics as well as for untreated patients, in which only one study measured directly the ROS formation after treatment with antipsychotics via electro spin resonance spectroscopy (ESR).
Methods: The aim of the present examination was to demonstrate effects of haloperidol, clozapine and olanzapine in concentrations of 18, 90 and 180 µg/ml on the formation of ROS in the whole blood of rats via ESR. To test the protective capacity of vitamin C we incubated the highest concentration of each drug with vitamin C (1 mM).
Results: Under all treatment conditions olanzapine led to a significantly higher formation of ROS compared with control conditions, whereas in the cases of haloperidol and clozapine the two higher concentrations induced a significantly enhanced formation of ROS. Vitamin C reduced the ROS production of all drugs tested and for haloperidol and clozapine the level of significance was reached.
Conclusions: Our study demonstrated that antipsychotics induce the formation of ROS in the whole blood of rats which can be reduced by the application of vitamin C.

FC-25-004
Chronic SSRI treatment in female rats: Dissociation of antidepressant action from hippocampal BDNF expression

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Objectives: A major hypothesis of depression postulates that a deficit in neurotrophine systems is directly involved in the pathophysiology of depression, and that restoration of such deficits may underlie the therapeutic efficacy of antidepressant treatment. One key finding supporting this hypothesis is upregulation of brain derived neurotrophic factor (BDNF) in the hippocampus after antidepressant treatment. Here, we further test the hypothesis of an involvement of BDNF in antidepressant action in female rats of the Flinders sensitive line (FSL), a putative model of depression.
Methods: Adult, female rats of the FSL, Flinders resistant (FRL) and non-selected Sprague–Dawley (SD) lines were treated for 30 days with escitalopram, nortriptyline or placebo admixed to food pellets. At the end of the treatment rats were tested in the elevated plus maze and forced swimming tests for anxiety- and depression-like behavior, respectively. Rats were then sacrificed and BDNF mRNA levels measured in the dentate gyrus of the hippocampus and the medial prefrontal cortex.
Results: Active treatments showed clear antidepressant, but no anxiolytic actions in FSL and SD rats, while FRL rats were unaffected. Escitalopram, but not nortriptyline markedly reduced BDNF mRNA levels in the dentate gyrus of FSL rats. The BDNF down regulation was common to the four major promoters of the gene. Treatment did not affect BDNF in the FRL and SD rats.
Conclusions: The antidepressant effects of escitalopram and nortriptyline, two common medications with different pharmacological profiles, appear to be uncoupled from the regulation of hippocampal BDNF expression in female rats. The downregulation of BDNF by escitalopram is not likely due to a line specific genetic variation at the promoter level, because all promoters appear equally affected. These results do not support an involvement of BDNF in the effects of antidepressant pharmacotherapy and stressing the need of validated disease models of depression to assess potential treatment targets.

FC-25-005

The efficacy of eicosapentaenoic acid for major depression: Results of the OMEGA-3D trial

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Nancy Frasure-Smith, Élise St-André, Gustavo Turecki, Stephen Wisniewski, Paul Lesperance, Louis van Zyl, David Servan-Schreiber

Objectives: Epidemiological studies suggest that lower levels of omega-3 fatty acids are associated with higher rates of depression. There have also been several small trials reporting that omega-3 supplementation may be beneficial in the treatment of major depression. We conducted a randomized clinical trial to evaluate the efficacy of eicosapentaenoic acid treatment for major depression.

Methods: We completed a multi-site, double-blind, randomized clinical trial in 432 individuals with an episode of major depression. Patients were randomized to 3 capsules per day of eicosapentaenoic acid (total of 1050 mg) or matched-placebo masked with fish odor. Eligible participants included those not responding to antidepressants (for whom concomitant use of antidepressants was allowed), and those unable to tolerate antidepressants or who refused antidepressants despite physician recommendation. The primary outcome measure was the Inventory of Depressive Symptoms, Self-Rated (IDS-SR). The secondary efficacy outcome was the Montgomery-Asberg Depression Rating Scale (MADRS).

Results: Recruitment began in October 2005 and the final sample of 432 was completed in December 2008 with follow-up continuing until February 2009. Some 68.5% of participants were women, 40,3% of the patients were taking at least one antidepressant at baseline, 72,7% had a recurrent depressive episode and 55% had a co-morbid anxiety disorder. The mean age was 46 Years.

Conclusions: The final results will be presented at the conference.

FC-26
Affective Disorders (Unipolar) III

FC-26-001
Higher psychological pain during a major depressive episode may be a factor of vulnerability to suicidal ideation and act

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Objectives: It has been suggested that psychological pain ("psychache") is a key factor in the suicide process. In addition, suicidal acts may be best understood within a stress-vulnerability model. We hypothesized that more intense psychache during a major depressive episode would be a factor of vulnerability to suicidal behavior. To test this hypothesis, we compared levels of psychache between recent and past vs. non-suicide attempters. The association between psychache and suicidal ideation was also investigated.
Methods: Patients hospitalized for a major depressive episode, including 87 individuals with a recent history of suicidal acts, 61 individuals with a past history of suicidal acts, and 62 individuals without any suicidal history, were assessed at admission using several Likert scales to measure levels of psychache, physical pain and suicidal ideation.
Results: Patients with a recent or past history of suicide attempts expressed significantly higher levels of current psychological pain, and a higher intensity and frequency of suicidal ideation than patients without any history of suicidal acts. The level of current psychache was significantly and positively associated with intensity and frequency of suicidal ideation. There were no between-group differences for physical pain.
Conclusions: Higher psychological pain during a major depressive episode may be a factor of vulnerability to suicidal behavior, by increasing the propensity to suicidal ideation. Decreasing psychache during a depressive episode should be a major therapeutic target during crisis intervention.

FC-26-002
Association between IL-12 secretion levels in major depressive disorder and symptoms severity, before and after mitogen stimulation

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Objectives: Several studies suggest that Major Depressive Disorder (MDD) is associated with dysregulation of immune mediators and report alterations in cytokine serum levels in patients with MDD. Interleukin 12 (IL-12), a naturally occurring protein produced by T-helper cells to activate and recruit the constituent parts of the immune system, is essential for the proper functioning of the human immune system. The aim of the present study was to investigate whether IL-12 secretion levels before and after mitogenic stimulation differs between depressed patients during treatment and clinical improvement.
Methods: Nineteen subjects, inpatients and outpatients of the Department of Psychiatry who met DSM-IV criteria for a principal diagnosis of Major Depressive Disorder were enrolled. Peripheral Blood Mononuclear cells were isolated and cultured at a concentration of 106 cells/ml for 72 hours in plain culture medium (RPMI / 10% Fetal Calf Serum - 1% Penicillin/Streptomycin) and in the presence of PMA and Ionomycine. Cytokine concentrations were determined by enzyme-linked immunosorbent assay (ELISA). Strict exclusion criteria concerning factors that might have influenced
Results: IL-12 secretion levels were significantly higher in patients suffering from Major Depressive Disorder compared to healthy controls. Higher HAM-D Score was often combined with increased production of the cytokine in a linear way. Mitogen stimulated IL-12 secretion also seems to be affected by symptoms severity and recovery, but not always in a linear way.
Conclusions: Although our study failed to demonstrate a clearly linear association between symptoms severity and IL-12 secretion after mitogen stimulation, our data indicate a significant positive association between MDD and increased IL-12 secretion levels. These findings support the hypothesis that Th-1 cytokines, such as IL-12, secretion, is strongly involved in the pathophysiology of mood disorders. Further studies are necessary to clarify the mechanisms associated with immune system dysregulation mood disorders.

FC-26-003
Localization of white matter lesions and effect of vascular risk factors in late-onset major depression

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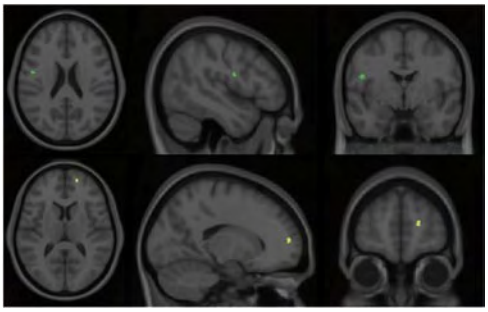
Objectives: Previous studies indicate that patients with late-onset major depression (MD) have an increased frequency of cerebral white matter lesions (WMLs) compared with age-matched controls. However, few of these studies have accounted for vascular risk factors such as hypertension and smoking. The goal of the present study was to investigate the association between the localization, number, and volume of WMLs in MD with respect to vascular risk factors.
Methods: Data on lesion localization, number, and volume were assessed from whole-brain magnetic resonance imaging (MRI) of 22 consecutive patients with late-onset first episode MD and 22 non-depressed, age- and gender-matched controls. The localization of WMLs was compared between patients and controls on a voxel-by-voxel basis, and effects of vascular risk factors on lesion localization were tested using two-tailed unpaired t-tests. The effect of vascular risk factors on lesion load was compared between patients and controls using regression analyses.
Results: Patients and controls showed no difference in vascular risk factors, except for smoking status. Among the subjects with one or more WMLs, the patients displayed a significantly higher white matter lesion density in the left parietal operculum and in the right superior frontal gyrus. There was no significant difference in the number and volume of lesions between the two groups. Smoking had a significant effect on the number and volume of WMLs, whereas life time tobacco load had a significant effect on lesion localization; this effect differed between patients and controls.
Conclusions: Our results indicate that lesion localization is more important than lesion load. Smoking and life time tobacco consumption may play an important role in the pathophysiology of MD. A greater emphasis on vascular risk factors, including smoking, may contribute to a more differentiated diagnostic approach to MD with further implications for future treatment.



FC-26-004
Cognitive effects of electroconvulsive therapy in depression: A meta-analysis

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Objectives: Electroconvulsive therapy (ECT) is the most effective treatment for severe depression. However, cognitive side-effects still limit its use although the nature and extent of these remains unclear. The current meta-analysis aimed to quantify ECT-induced cognitive dysfunctions, specify their configuration and determine their progression over time.
Methods: We searched MEDLINE, EMBASE, PsycARTICLES, PsychINFO, PsychLIT up to July 2008. Eligible studies had a within-subjects design involving depressed patients receiving ECT and assessed with standardised cognitive tests. The main outcome was change in performance on testing after ECT relative to pre-treatment scores. We extracted the delay between end of ECT course and cognitive testing and explored influence of potential moderators.
Results: Eighty three studies including 2888 patients were meta-analysed. Significant decrease in mean effect sizes was observed 0-3 days after ECT in 61% of variables. These were small effect sizes for processing speed and attention variables, moderate effect sizes for memory variables and moderate to large effect sizes for executive functioning variables. Four to 15 days after ECT, 91 % of mean effect sizes were either non significant or positive. No negative effect sizes were observed after 15 days with the majority of variables showing positive mean effect size in the small to moderate range.
Conclusions: Cognitive impairment caused by ECT is probably limited to the first three days after end of treatment. Pre-treatment levels of functioning are subsequently recovered. Heterogeneity, due to either electrode placement or stimulus waveform, was not apparent three days post-ECT. After 15 days post-treatment, processing speed, working memory, anterograde memory and some aspects of executive functioning improve beyond baseline levels.

FC-26-005
Early separations as risk factor for later depressive, panic, generalized anxious and paranoid disorder

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Dusan Lazarevic

Objectives: The subject of this research is the relationship between early separation in childhood and psychopathology in adulthood. We examined three types of separation in relation to the duration(permanent ,intermittent and temporary),and the type of object separation(separation from one or both of parents). We tested zero hypothesis: There is no connections between early separations and psychopathology in adulthood. Sample of this investigation makes 160 subjects who are divided into two groups: experimental and control group.
Methods: Method is comparative. Instruments: ICD 10 criteria for diagnostics, ADIS questionnaire for panic, ADIS questionnaire for generalized anxiety, Hamilton scale for depression ,TCI. Statistical analysis: The results of research we measured by the central tendency -arithmetic Mean and measure of variability of the sample –standard deviation. The statistical significance of differences we counted by unifactor's analysis of variance, Fisher's linear discriminative function s and by logistic regression. We used factor s analysis of the data.
Results: Results shows that permanent separation have statistically significant association with depression of adulthood. Intermittent separation is in connection with generalized anxiety of adulthood, while panic disorder is associated with temporary separation in childhood. TCI shows significant differences of temperament and character, depending of presence of separations in first five years of life. This differences exists in the control group also, and will be discussed in details in the paper.
Conclusions: Early separation and loss of one or both of parents can influence the creation of disposition for a certain disorders in adulthood. Distress of separation has a strong effect on long-term biological characteristics (temperament), where subjects with early separations showed a statistically significant dimension HA (Harm Avoidance). These features are in relation to the dimensions of the character, where we find low self – directness, low cooperativeness in the group that had separations. It is possible to conclude that distress is associated with conditions for development of personality disorders.

FC-26-006
Neurobiological bases of suicidality in major depression

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Objectives: Suicide is a major public health problem that typically occurs in the context of a depression. We used functional magnetic resonance imaging to reveal the neurobiological correlates of suicidality in depressed patients.
Methods: The present 3 Tesla fMRI study was conducted in 14 non-medicated patients with a first episode of unipolar MDD and 14 matched controls. During scanning, subjects performed two tasks imposing two different levels of attentional load at fixation (easy or difficult, i.e. low or high attentional load), while irrelevant stimuli (i.e. faces) were presented in the periphery. To obtain an unbiased measure of suicidality from the Hamilton Rating Scale for Depression (HRSD) scores, we computed their singular value decomposition, a mathematical procedure related to principal component analysis. Functional MRI data were analyzed using a two-step procedure taking into account the intra-individual and inter-individual variance. The summary statistics images of the individual level were entered into a second-level one-way ANOVA implemented in SPM2 (http://www.fil.ion.ucl.ac.uk) to assess random-effects group comparisons. We performed additional whole-brain second-level correlation analyses for the main contrasts of interest using a component of the HDRS as covariates with singular value decomposition of the scale.
Results: When asked to engage attention in a cognitive task (high > low attentional load) depressed patients activated noradrenergic locus coeruleus, serotonergic raphé nuclei and amygdala in proportion of their suicidality. No such correlation was observed in healthy participants, whose suicidality scores were within normal ranges.
Conclusions: In animals, activity in the mesopontine reticular formation and amygdala can promote rapid behavioral shifts in response to cognitive challenges by facilitating the functional reorganization of cortical networks. Our results suggest that, in the context of high attentional demands, depressed patients may be prone to impulsive shifts in behavioral states that could be prevented by a better control over amygdalar activity and its modulation by aminergic neuromodulators.

FC-27
Psychotic Disorders VII

FC-27-001
Some oxidative stress markers in schizophrenic patients with and without history of suicidal behavior

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Objectives: Our aim was to compare the levels of some markers of oxidative stress (total plasma homocysteine - tHcy, superoxide dismutase - SOD, glutathione peroxidase - GPx, and human serum paraoxonase - PON1 arylesterase and paraoxonase activities) in schizophrenic patients with and without history of suicidal behavior.
Methods: 70 patients who met the DSM-IV-TR criteria for the diagnosis of schizophrenia from Psychiatric Clinic No III Cluj-Napoca, Romania were included in the study. 20 patients had a history of suicidal behavior. tHcy concentrations were assessed by RP-HPLC, red blood cell vitamin B12 and serum folate levels were assessed by electrochemiluminiscence, and SOD, GPx and PON1 activities were determined spectrophotometrically. One-way ANOVA was used to compare the variables in the two groups, using age as covariate.
Results: There were no statistically significant differences between the two groups regarding tHcy and PON1 activities. However, significantly lower SOD and GPx activities were found in schizophrenic patients with history of suicidal behavior as compared to schizophrenic patients without suicidal behavior ($p < 0,05$).
Conclusions: Schizophrenic patients with history of suicidal behavior have lower SOD and GPx activities than schizophrenic patients without suicidal behavior.

FC-27-002
Theta Burst stimulation in schizophrenia

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Objectives: Repetitive transcranial magnetic stimulation (rTMS) has been reported to be effective as treatment for negative symptoms and for auditory hallucinations in patients with schizophrenia. Recently, new rTMS protocols have been established in preclinical research, e.g. theta burst rTMS (TBS). Cortical excitability could be either suppressed by continuous TBS (cTBS) or facilitated by intermittent TBS (iTBS). Our aim was to study the effect of TBS on schizophrenic symptoms.
Methods: As negative symptoms of schizophrenia were associated with a "hypoactivity" of the left dorsolateral prefrontal cortex, we investigated the impact of iTBS (33 trains of uninterrupted 3 pulses of stimulation at 50-Hz repeated every 200ms each 10s) applied on this region in a 46-years old patient with resistant negative symptoms of schizophrenia. On the other hand, as auditory hallucinations were associated with a "hyperactivity" of the temporoparietal cortex, we investigated the impact of cTBS in a 40-years-old inpatient with resistant auditory hallucinations. cTBS (40s train of uninterrupted 3 pulses of stimulation at 50-Hz repeated every 200 ms) was applied as a maintenance treatment after a relapse consecutive to a classical 1Hz-rTMS maintenance treatment during 6 months.
Results: Concerning negative symptoms;Three months after 20 sessions of 990 stimuli/day iTBS at 80% of motor threshold over two weeks, we reported a 60% improvement in SANS scale score. This effect is maintaining since October 2008. Concerning auditory hallucinations; After Twice-daily cTBS sessions over 5 days, Audirtory Hallucinations decrease to 50% compared to baseline scores. This effect continued during the 6 months which followed the acute response without any other stimulation.
Conclusions: In these 2 indications, TBS permits prolonged effects and shorter duration of stimulation sessions than rTMS. After these 2 pilot cases, we have undertaking controlled double blind studies; preliminary results will be present at the congress.

FC-27-003
Oscillatory brain dynamics reflected in the frontal auditory evoked potentials in healthy subjects and schizophrenic patients

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Objectives: The goal of the presented study is to apply the oscillatory brain dynamics model to the structural and quantitative analysis of the neuro-cognitive functions considered as a potential marker of schizophrenia.
Methods: A total of 66 male right–handed patients with schizophrenia participated in the study.The event related potentials (ERPs) were elicited in a passive auditory oddball paradigm. Traces of the averaged evoked responses obtained to the standard and to the deviant stimuli were transformed by the WLT analysis. The post-stimulus time course of the WLT(Fo,t) traces obtained in the different frequencies Fo (3-22Hz) was considered conditionally as the EEG activity developed in delta Fo(3Hz), theta Fo(4-6Hz), alpha Fo(7-12Hz) or beta Fo(13-22Hz) frequency bands
Results: The main result of the presented study was the determination of the areas in the time-frequency EEG domain, where concentrated frontal oscillatory activity evoked in response to the auditory stimuli during the passive oddball test in healthy subjects and schizophrenic patients. It was revealed a significant delay of the theta-low alpha responses to standard stimuli in patients, and no difference was revealed between latencies of these responses to deviant. Moreover, the early oscillatory responses to standard and deviant were not differed between them in healthy subjects, and they were closed to the response of patients to deviant.
Conclusions: The fundamental properties of the neuronal oscillatory dynamics as the stability and plasticity of the EEG activity can be elucidated in future studies on the basis of the single trial analysis and provide the basis for the determination of the markers and endophenotypes of the mental disorders. The preliminary results in the discrimination between healthy subjects and schizophrenic patients were hopeful.

FC-27-004
Obsessive-compulsive symptom dimensions in schizophrenia patients with obsessive-compulsive disorder

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Objectives: A substantial proportion of schizophrenia patients also has symptoms of obsessive-compulsive disorder (OCD). Compared to their schizophrenia counterparts, schizo-obsessive patients appear to have distinct patterns of psychopathology, course of illness, neurocognitive deficits and treatment response. In the present study we evaluated whether the revealed factor structure in symptoms of "pure" OCD exists also in schizo-obsessive patients.
Methods: Using the exploratory factor analysis we evaluated obsessive-compulsive symptom dimensions, as assessed by the Yale-Brown Obsessive-Compulsive Scale (Y-BOCS), in 110 patients (83 men, 27 women; age 30.8 ± 8.5 years) who met DSM-IV criteria for schizophrenia and OCD. We also analyzed the interrelationship between OCD and schizophrenia symptom dimensions.
Results: The principal component analysis of 13 Y-BOCS symptom categories yielded a five-factor solution accounted for 58.7% of the total variance: the first factor included aggressive, sexual, religious obsessions and counting compulsions (15.9% of the variance), the second factor, symmetry obsessions, ordering and hoarding compulsions; the third factor- contamination obsession and cleaning compulsion(11.2%); the forth factor-somatic obsession and repeating compulsion(9.8%); the fifth factor hoarding obsession, checking and repeating compulsions (8.2%).
Conclusions: The five symptom dimensions resulting from the analysis are to a large extent comparable to those revealed in factor and cluster analysis studies conducted in patients with "pure" OCD. These findings and lack of inter-correlation between the major OCD symptom categories and schizophrenia symptom dimensions lend additional support to the independent nature of OCD in schizo-obsessive patients and suggest the involvement of universal biological mechanisms in the pathogenesis of OCD regardless of the presence of schizophrenia.

FC-27-005

Fast face recognition in schizophrenia and spatial frequency processing

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Objectives: Visual dysfunctions have been largely described in schizophrenia but less is known about their consequences on the processing of ecological stimuli such as faces. The recognition of facial expression is known to be impaired in schizophrenia, especially in fast presentation conditions. Fast recognition tasks in healthy subjects imply a coarse to fine processing: low spatial frequencies (LSF) provide a rough estimate of the image before a more detailed analysis of high spatial frequencies (HSF). We test here the hypothesis that visual dysfunctions in schizophrenia may impair the coarse to fine processing in a rapid face recognition task.
Methods: 10 patients with schizophrenia and 10 healthy control subjects were recruited. In our main experiment they performed an expression recognition task with hybrid stimuli, combining a face in HSF scale and another face in LSF scale. Because each face presented a different expression, the response allowed us to infer which spatial scale was preferentially perceived. The same set of faces was presented at two presentation times: 30 ms and 120 ms. In a control experiment we used filtered stimuli presenting a single face filtered on HSF or LSF in the same presentation condition.
Results: Patients preferentially used low spatial frequencies in the two conditions, whereas healthy controls presented a normal coarse to fine processing with a preferential use of low spatial frequencies at 30ms and a preferential use of high spatial frequencies at 120ms. Our control experiment verified that the recognition task could be performed in the two conditions.
Conclusions: These results indicate a dysfunction of the coarse to fine processing of visual information in schizophrenia. They suggest that low spatial frequencies may not guide the integration of fine details contained in high spatial frequencies. This result may contribute to understand impairments of expression recognition in schizophrenia.

FC-27-006

Coherent analysis and clinical correlates in patients with first episode of schizophrenia and schizoaffective disorder

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Objectives: Synchronization of brain oscillations, appraised by coherence analysis is appeared to be one of the potential mechanisms of neuronal interconnections which are detected in the lower rates in schizophrenia, few facts exist about schizoaffective disorder. However, the level of coherence is considered as a parameter of stable phase within specified frequency.
Methods: 14 patients (group 1) with first episode of schizophrenia and 14 patients (group 2) with initial diagnosis of schizoaffective disorder were studied by EEG with further analysis of the coherent connections between different brain areas in the Gamma frequency range. Both groups have been treated in the First Episode Psychosis Clinic in Moscow Research Institute of Psychiatry (2005). Clinical status of patients was assessed by PANSS. Results of both groups were compared with normal controls.
Results: Compared to the rates of PANSS of patients with schizophrenia (group 1) where the raters of negative symptoms predominated over positive symptoms rates ($P<0.05$), patients with schizoaffective disorders (group 2) showed no difference between positive and negative symptoms rates. However the average scores were more prominent in group 1 and composed 95, 07143 versus 73, 07143 in group 2. Normal controls showed significant number of coherent inter- and intra- connections between different cortical regions of the brain thought patients of both groups displayed significant decrease of connections. Interhemispheric connections in both groups were absent in the frontal areas of the brain. Performance of the cognitive tasks during the EEG procedure, which require active attention and memory, were accompanied by substantial decrease in synchronization of Gamma-rhythm in different brain areas in both groups.
Conclusions: Despite the prevalence of psychopathological rates in patients with first episode of schizophrenia, coherence analysis showed almost no difference in interconnections of brain areas between two groups. Lack of synchronization in both groups of patients can be one of the reasons of cognitive disturbances in schizophrenia and schizoaffective disorder. (Strelets V.B.,2005).

FC-28
Psychopharmacology IV

FC-28-001
The effect of Ketamine on sensorimotor gating – comparison of human and animal data

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Objectives: With respect to glutamatergic hypothesis of schizophrenia, NMDA antagonists represent the most reliable pharmacological models of this disease. Disruption of sensorimotor gating has been described consistently in schizophrenic patients, however human and animal data in ketamine models of psychosis are inconsistent. In our experiments we have compared sensorimotor gating in human volunteers and in rats in a ketamine model of schizophrenia; we focused on the changes in prepulse inhibition (PPI) of acoustic startle reaction (ASR).
Methods: Animal experiments were carried out on male Wistar rats (200 – 250g). PPI of ASR in rats was analyzed after ketamine 9 and 30 mg/kg i.p. in the startle apparatus SR-LAB, San Diego Instruments (SDI). Measurements of the PPI reaction (SR-HLAB apparatus, SDI) in humans were obtained from 20 healthy subjects under resting conditions in a placebo/ketamine randomized design. Ketamine was applied i.v. at the dose of 0.27 mg/kg within the first 10 min, followed by a maintenance infusion of 0.27 mg/kg/h for 20 min. Two different prepulse intensities (78 and 86dB) and three different prepulse-pulse intervals (30, 60 and 120 ms) were used in our experiments.
Results: Ketamine 30 mg/kg significantly disrupted PPI in rats, with the lower dose of 9 mg/kg being without any effects. In humans, ketamine disrupted PPI only in the 86 dB prepulse intensity for all prepulse-pulse intervals, 78 dB prepulse intensity showed no effect.
Conclusions: Our results indicate that ketamine disrupts PPI both in animals and humans. This contradicts some of the previous findings form other labs, where ketamine increased PPI in humans. This work is supported by the projects CNS MSMT 1M0517 and MZ0PCP2005.

FC-28-002
Treatment resistant catatonia responding to zolpidem: Case reports and literature review

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Objectives: According to recent statistics, 5–9% of all psychiatric inpatients show some catatonic symptoms. Of these, 25–50% are associated with mood disorders, 10–15% are associated with schizophrenia, and the remainder are associated with other mental disorders. Recent developments in the treatment of catatonia are raising the GABAa vs GABAb hypothesis of catatonia.
Methods: This paper describes 7 cases of benzodiazepine-resistant catatonia responding to treatment with zolpidem and critically reviews the current literature on the treatment of catatonia, proposing an algorithm for the diagnosis and treatment of this condition.
Results: The cases discussed, represent patients with a history of psychotic or affective disorders and catatonia showing total or partial lack of response of catatonic symptoms to other treatments, including benzodiazepines and/or ECT, responding to a zolpidem 10 mg challenge and continuing to maintain response to a gradual taper-down of zolpidem. Some of the patients described have relapsed into catatonia upon taper-down or discontinuation of zolpidem. From the review of the literature on catatonia, there is growing evidence suggesting the role of GABAa agonists in the treatment of catatonia, as well as for the possible pro-catatonic effect of the GABAb agonists, with important potential clinical applications in the treatment of this severe condition.
Conclusions: Zolpidem, a GABAa specific agonist appears to be a new and safe therapeutic approach for catatonia, potentially useful in benzodiazepine-resistant patients. More research will be needed in order to replicate and further understand the mechanism and sites of its activity. Various agents described in the literature as useful for the management of catatonia are critically reviewed in terms of mechanism of activity and strength of evidence, and a rational approach to the diagnosis and treatment of catatonia is proposed.

FC-28-003
Rapid metabolism of antipsychotics and akathisia in schizophrenic Court-Order detention patients: A selection bias

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Objectives: Investigate whether prescribed antipsychotics have yielded effective plasma levels.
Methods: In three groups of ten inpatients (Pompe Foundation for Forensic Psychiatry,2007) and in one group of ten inpatients (Forensic Psychiatric Center Oldenkotte,2008) plasma level monitoring was done after informed consent in patients who were using antipsychotic medication in average or high dose. To exclude a possible role of ultra rapid metabolism, pharmacogenetic investigation was carried out in addition in the patients of the last group of ten patients.
Results: In ten out of 30 and in three out of ten patients, respectively, so in one third, plasma levels were subliminal or relatively low. No duplication of the gene for CYP2D6 was found. Based on the pharmacogenetic outcome the hypothesis of ultra rapid metabolism had to be rejected. One might assume, however, that the intensity of metabolism of the CYP2D6 in this special subgroup of patients was at the fast side of the Gaussian distribution. A high percentage of these patients suffered from severe side effects, especially from akathisia, indicative for hypersensitivity for this side effect at even subliminal plasma levels. Both limitations might have led to a selection bias. Probably these patients would have refused, at the time prior to the offence, to accept an increase of dose, out of fear for side effects. By adjustment of the dose and treatment of the akathisia in the present patients, therapeutic effect could be improved.
Conclusions: Special attention should be given from the point of view of prevention in General Mental Hospitals to identify this special subgroup of patients in advance. Plasma level monitoring favours the doctor-patient relationship.

FC-28-004
Acute Stress Responsiveness of BDNF in the rat prefrontal cortex is modulated by antidepressants

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Objectives: The pathophysiology of stress-related disorders such as depression involves reductions in neuronal connectivity in hippocampal and frontal regions and this effect is reversible by antidepressant (AD) treatment strengthening specific neuronal synapses. However not all ADs counteract such alterations. We have demonstrated that this stress-induced impairment is only restored with tianeptine and not imipramine. Neurotrophins, particularly BDNF, play a critical role in AD action. Indeed, ADs rapidly induce trkB autophosphorylation and downstream signalling indicating that ADs induce BDNF release. We here investigated whether these two structurally similar, but pharmacologically distinct, ADs, tianeptine and impramine, alters the modulation of BDNF under an acute stressful condition.
Methods: Stress was evoked by placing rats on an elevated platform during 30 min. Tianeptine (10 mg/kg) and imipramine (10 mg/kg) were injected intraperitoneally just after the end of stress. Rats were killed 30min later, frontal cortices snap-frozen and processed for BDNF using ELISA and immunoblots. Data were analyzed with Student´s T-test to evaluate statistical differences.
Results: Using ELISA and Western blotting, 30 min stress induced a strong reduction in BDNF levels throughout frontal cortex. Using ELISA, only tianeptine could significantly reverse the stress-induced alteration of BDNF. Using western blotting, the decrease in BDNF could be reversed by both tianeptine and imipramine.

Conclusions: Acute stress downregulates BDNF in frontal cortex and acute treatment with tianeptine and imipramine reverse the stress-induced downregulation of BDNF. The reduced levels of BDNF after stress coincided with reductions in MEK/MAPK phosphorylations previously shown in this model suggesting that BDNF may be a first messenger down-regulating this signalling cascade after stress. The data comfort the hypothesis that the critical effect of AD treatment may be the production of trophic effects on the functional organization and connectivity in brain, which improves information processing in critical neuronal networks relevant for mood regulation.

FC-28-005

Dexamphetamine effects on prepulse inhibition of the startle reflex in healthy volunteers

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Objectives: To determine if dexamphetamine affects attentional modulation of prepulse inhibition of the startle reflex in healthy volunteers, similar to the effects associated with Schizophrenia.

Methods: Healthy volunteers (N=16) received an oral dose of dexamphetamine (0.45 mg/kg) in a double-blind placebo-controlled cross-over design. The startle reflex was elicited by acoustic stimuli (40 ms duration white noise ranging from 65-115 dB in 5 dB increments presented in random order) presented in headphones against a constant background white noise (65 dB). On some trials, an acoustic prepulse (10 ms duration at 74 dB), preceded the startling stimuli by 60 or 100 ms. The startle reflex was measured as the peak force of the electromyographic activity of the orbicularis oculi muscle under each of two attention conditions, one in which the participants attended to the acoustic stimuli (counting the number of acoustic stimuli) and a second in which they attended to visual stimuli (counting hidden faces in a neutral photograph displayed on a computer screen). The resulting stimulus intensity: response magnitude curves were fitted to a logistic curve similar to a dose-response analysis, and the fitted parameter of the function, RMAXt (the maximal response or asymptote) was analysed with a repeated-measures Analysis of Variance, followed by pair-wise comparisons made with t-tests, corrected with Sidak's procedure.

Results: Dexamphetamine significantly decreased prepulse inhibition of RMAX when participants attended to the visual stimuli, but not when they attended to the auditory stimuli, as shown by a significant Dexamphetamine X Attention interaction ($F1,15 = 5.129$, $P < 0.05$), and subsequent pair-wise comparisons($p<0.05$).

Conclusions: This finding suggests that dexamphetamine (0.45 mg/kg) alters PPI in an attention-dependent fashion, similar to observations in patients with Schizophrenia.

FC-28-006

Efficacy of amantadine in the treatment of tardive dyskinesia: A randomized, double-blind, placebo-controlled study

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Objectives: Amantadine, a NMDA receptor antagonist, has demonstrated antidyskinetic effect in Parkinson's disease patients with levodopa-induced dyskinesia (PD) and in one open label study in patients with tardive dyskinesia (TD). The aim of this study was to evaluate the efficacy and safety of amantadine in the treatment of TD in schizophrenic patients.

Methods: This double-blind, placebo-controlled, crossover, randomized study involved 22 schizophrenic patients with tardive dyskinesia. Subjects received their usual antipsychotic treatment. Initially, they were randomly assigned to receive 2 weeks of amantadine or placebo, followed by a wash out period of four days. Subsequently, they entered the crossover phase for another 2 weeks. The primary efficacy outcome measure was improvement in the Abnormal Involuntary Movement Scale (AIMS) total score. Safety was assessed with an adverse event scale, psychiatric symptom rating scale and blood tests.

Results: AIMS total scores significantly reduced in the amantadine group as compared to the placebo group. The mean decrease in score from baseline to endpoint in patients treated with amantadine was 22% as opposed to no change in patients treated with placebo ($p=0.000$). Amantadine was well tolerated and did not exacerbate psychosis.

Conclusions: Amantadine appears to be effective in the treatment of tardive dyskinesia. Furthermore, the study highlights the potential role of the glutaminergic system and NMDA receptor antagonists in the pathogenesis and treatment of TD. Further studies are warranted.

FC-29
Childhood & Adolescent Disorders I

FC-29-001

Transcranial brain sonography (TBS), task dependent motor performance and cortical motor excitability measured by transcranial magnetic stimulation (TMS) in children with Tic/Tourette syndrome and in ADHD children

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Objectives: Previous investigations using TMS have shown that intracortically and transcallosally mediated neural inhibitory motor circuits are disturbed as well in ADHD as in Tic/Tourette syndrome. Both diseases are characterized by poor motor skills. Basal ganglia (BG) and corpus callosum (CC) are involved in motor control. To our knowledge, in children the BG and CC were not investigated by TBS so far.
Methods: We aimed to investigate in these and in gender and aged matched children: - size of BG and CC by using TBS - motorcortical excitability by measuring cortical silent period (cSP) and ipsilateral silent period (iSP) with TMS - behavioral cortical motor inhibition and facilitation by using a self generated paradigm, measuring task dependent motor performance. The approval by the local ethics committee was given.
Results: Until now we investigated 2x10 children and seem to found a correlation as well between the size of BG and motor performance as the size of CC and the iSP. Recruitment of patients is continued.
Conclusions: TBS is an excellent fitted method without side effects to quantify brain structures in adults and children. The combination of TBS (quantity), TMS (both quantity and quality) and measurement of task dependent motor performance (quality) allows a multidimensional approach for the investigation of disturbed motor skills in psychiatric disorders like ADHD and Tic/Tourette.

FC-29-002

Contribution of cognitive evaluation of states of awareness associated with memories to the understanding of the clinical features of Asperger's syndrome

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Objectives: Increasing literature has described distinctive features in episodic memory in adults with autism spectrum disorders (ASD). Bowler et al. (2000; Journal of Autism and Developmental Disorders) revealed that recollection was reduced, while the familiarity-based recognition increased. Investigations of contextual memory, typically based on the recollection of every information associated with an item, have yielded mixed results according to task demands and nature of the to-be-remembered material. Our study aimed at investigating states of awareness and source memory using an original task in one child and two adolescents with Asperger's syndrome (AS). Performances were compared to two age matched control groups.
Methods: At the study phase, participants viewed comics presented through an objective context: a windscreen, binoculars or a fence. Memory for comics was subsequently tested using a yes/no recognition task and the "Remember (R)-Know (K)" paradigm, in which participants were asked to give either R responses, when they retrieved items with phenomenological, subjective contextual information (recollection associated with autonoetic consciousness) or K responses when they retrieved items without such details (familiarity associated with noetic consciousness). Participants were asked to justify their R responses by providing the objective context presented at encoding, i.e. the windscreen, the binoculars or the fence.
Results: While performance on recognition task was unimpaired, two participants exhibited significantly fewer R responses and more K responses than controls. However, for source memory, no group difference was found.
Conclusions: These results suggest a disruption of autonoetic consciousness. Moreover, we confirm Bowler's hypothesis that deficits in contextual memory in ASD are masked when the task gives a support at test. These findings have important implications regarding the self identity in autism. Future research concerning autonoetic consciousness and binding processes, which are critical to shape one's own identity and feeling of continuity, will bring essential data to understand this phenomenon.

FC-29-003

Neurofeedback for children with Attention Deficit/ Hyperactivity Disorder (ADHD): Clinical and neurophysiological results of a randomised controlled study

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Objectives: Neurofeedback is a neuro-behavioural, computer-assisted training which could become an important treatment module for children with attention deficit/hyperactivity disorder (ADHD). In a multisite randomised controlled study, we evaluated clinical and neurophysiological effects of a neurofeedback training compared to a control training.
Methods: 102 children with ADHD (age: 8 to 12 years) participated in the study. They either performed a neurofeedback training or a computerised attention skills training (randomised group assignment). The training programs comprised 36 sessions within two blocks of about 4 weeks each. The neurofeedback training consisted of both a theta/beta training and a slow cortical potentials (SCP) training. Pre-training, intermediate and post-training assessment comprised several behaviour rating scales (e.g. the German ADHD rating scale, FBB-HKS) and neurophysiological measurements (EEG, event-related potentials).
Results: For both parent and teacher ratings, the neurofeedback training was superior to the control training. The effect size was .60 for the FBB-HKS total score (parent ratings, primary outcome measure). On the neurophysiological level, specific effects for both types of neurofeedback protocols were found.
Conclusions: Neurofeedback can be considered as a clinically effective method for the treatment of children with ADHD. The neurophysiological effects could reflect correlates of a successful training. Future studies should examine how to optimise a neurofeedback training and how to integrate it into a multimodal treatment program for children with ADHD.
Literature: Gevensleben H, Holl B, Albrecht B, Vogel C, Schlamp D, Kratz O, Studer P, Rothenberger A, Moll GH, Heinrich H: Is neurofeedback an efficacious treatment for ADHD? A randomised controlled clinical trial. J Child Psychol Psychiatry, epub ahead of print, DOI 10.1111/j.1469-7610.2008.02033.x. Funded by the German Research Foundation (HE 4536/2, MO 726/2, RO 698/4)

FC-29-004

QEEG investigation of school-age children with autism

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Objectives: Autism (ASD) is a group of severe lifelong neurodevelopmental disorders characterized by impairment of social interaction, speech and communication. The aim of the current study was to find phenotype and EEG correlations in ASD patients.
Methods: We investigated clinical and QEEG findings in two independent groups of autistic children: 6-15 years, using EEG-mapping package "Brainsys" (Russia). The group 1 (G1) contain 26 autistic children from Mental Health Research Centre, group 2 (G2) - 19 speechless autistic patients from 2 special education Centers. Both groups compared with the age matched healthy children from our normative Database using Z-score transformation. Mental age was significantly higher in G1 group. PEP test was performed in G1and WADIC interview in G2 group.

Results: The increased amount of beta -2 activity and decrease of EEG of fast alpha activity level was found in two independent idiopatic groups of autistic children. There were no significant differences between two group of patients. There was significant negative correlation of beta-1 and beta- 2 activity level with composite PEP test score data in G1. The increase level of beta -1 and beta-2 activity was correlated with severity of autistic manifestation in G2 appreciate using WADIC interview.
Conclusions: Beta activity level correlates with severity of disease and may reflect high excitatory level of cortical networks in autistic patients.

FC-29-005
Preschoolers with behavioral and emotional disorders show increased HPA-axis activity compared to healthy controls

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Objectives: Childhood is the beginning of behavioral and emotional disorders (BED) such as phobias, anxiety, or separation anxiety. The present study aimed at investigating the association between BED and hypothalamic-pituitary-adrenocortical (HPA) axis activity in preschoolers compared to healthy controls. Moreover, gender-related issues were addressed.
Methods: The target group was recruited from the psychiatric outpatient clinic for children and consisted of 21 preschoolers with diagnosed BED (mean age: 4.9 years; 7 females, 14 males). The control group consisted of 98 preschoolers of a non-clinical sample (mean age: 4.85; 43 females, 55 males). To assess HPA-axis activity, saliva cortisol was gathered in the morning after awakening and during a standardized psychological stress-test.
Results: Compared to the control group, the target group showed a highly increased cortisol secretion in the morning (AUC netto: $F(1, 115) = 71.64$, $p = .000$). Moreover, female participants showed also an increased morning cortisol secretion (AUC netto: $F(1, 115) = 8.51$, $p = .00$), and a significant group by gender interaction was observed (AUC netto: $F(1, 115) = 5.96$, $p = .016$), with highest cortisol values for the female target group and lowest cortisol values for male controls. Under stress conditions, the target group exhibited an increased cortisol secretion (AUC total: $F(1, 115) = 29.43$, $p = .00$). No gender by group interaction differences were observed ($Fs < 1.6$).
Conclusions: Findings suggest that BED are reflected by increased neuroendocrine activity already in preschoolers, with a particularly high cortisol secretion in females. This finding points to the hypothesis that among young children with diagnosed psychiatric disorders, children with heightened HPA-axis activity, and especially female preschoolers may be at increased risk for developing or maintaining psychiatric disorders in follow-up.

FC-29-006
Neurobiofeedback in pediatric bipolar disorder and Attention Deficit Hyperactivity Disorder: Is it differential diagnostic tool in child psychiatry?

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Objectives: Introduction: There is no agreement between researchers for diagnostic indicators for of pediatric bipolar disorder and there is no objective instrument in differential diagnosis between Attention Deficit Hyperactivity Disorder (ADHD) and pediatric bipolar disorder (BD). **Objectives:** We supposed that is possible to make clear different diagnosis between those disorders by measuring variation in neurobiophysiological reactions. We hypothesize that children with bipolar disorder will be worse in cognitive tasks when make errors because emotional discontrol in contrast with children with ADHD those will be better because attention discontrol could be improved with negative consequence on task errors.
Methods: Using neurobiofeedback equipment, authors compared the behavioral and psychophysiological correlates of irritability among children with history of drug-free diagnosed ADHD, and phenotype BD as well as those with healthy comparison children from same age as control group. All children completed the neurobiofeedback assessment tasks and working memory task that manipulated emotional demands and induced frustration. Emotion response (appearance of reactions on task errors, EEGtheta/beta ratio, heart rate, respiration frequency, skin conduction and body temperature), and working memory were measured.
Results: The phenotype bipolar disorder children reported significantly more arousal and decline in average EEGbeta/theta ratio after tasks errors in comparison with healthy subjects and children with ADHD. Children with ADHD had significantly better working memory performance and executive attention (average theta/beta ratio) after task errors.
Conclusions: Results indicate that children with bipolar disorder are worse in cognitive tasks after making errors in contrast with children with ADHD whose showed better results after negative consequence on task errors. Using neurobiofeedback equipment we could make clear different diagnosis between those disorders by measuring variation in neurobiophysiological reactions.

FC-30
Neuroimaging III

FC-30-001
Ventral striatal activation during reward anticipation correlates with impulsivity in alcoholics

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Objectives: Alcohol dependence is often associated with impulsivity, which may be correlated with dysfunction of the brain reward system. We explored whether functional brain activation during anticipation of incentive stimuli is associated with impulsiveness in detoxified alcoholics and healthy controls.
Methods: 19 detoxified male alcoholics and 19 age-matched healthy men participated in a functional magnetic resonance imaging (fMRI) study using a monetary incentive delay task (MID), in which visual cues predicted that a rapid response to a subsequent target stimulus would either result in monetary gain, avoidance of monetary loss or no consequence. Impulsivity was assessed with the Barratt Impulsiveness Scale (BIS-10).
Results: Detoxified alcoholics showed reduced activation of the ventral striatum during anticipation of monetary gain relative to healthy controls. Low activation of the ventral striatum and anterior cingulate during gain anticipation was correlated with high impulsivity, significantly in alcoholics and at a trend level in controls.
Conclusions: This study suggests that reduced ventral striatal recruitment during anticipation of conventional rewards in alcoholics may be related to their increased impulsivity, and raise questions about whether this dysfunction might respond to treatment.

FC-30-002
Functional connectivity of right insula during self-face processing

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Objectives: Recent functional imaging findings suggest an integral role for the insula in a wide spectrum of self-relevant processing including interoceptive awareness, personally familiar faces (faces of loved ones), and social cognition such as trustworthiness and empathy. In this study, we examined the functional connectivity of insula during processing of ones own face compared to personally familiar faces to understand the functional role of insula in "self" specific processing.
Methods: A functional connectivity magnetic resonance imaging analysis was performed on data collected from 10 healthy young women during the presentation of three sets of facial pictures: self face, personally familiar face (mother and close, non-sexual female friend), and age and sex matched strangers (younger and older female strangers) while performing three task: passive viewing, salience and emotional evaluation. Based on a prior categorical subtraction analysis showing increased activation of right anterior insula in self face processing versus personally familiar face processing across all tasks, we selected this region as a seed for correlational analysis to investigate the differential functional connectivity of right anterior insula during processing of self face versus personally familiar faces.
Results: During self face processing, the right anterior insula showed positive correlation with left anterior insula/ inferior frontal gyrus, putamen, bilateral temporal and left lateral prefrontal and anterior cingulate regions, whereas during personally familiar face processing, the right anterior insula showed positive correlation with bilateral inferior parietal cortices, bilateral prefrontal and right anterior cingulate regions and to a lesser degree to the left insula/ orbito frontal area.
Conclusions: Self-face specific processing preferentially involves functional connectivity of right anterior insula to brain regions implicated in self awareness, emotional responses and familiarity feelings (left anterior insula, putamen, right superior temporal lobes). This suggests that the emotional aspect of self experience (phenomenological aspect) is crucial to distinguish self from personally familiar others.

FC-30-003
Two days treatment of auditory hallucinations by high frequency rTMS guided by cerebral imaging: A 6 months follow-up study

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Objectives: Auditory hallucinations are a common and disabling problem for many patients with schizophrenia that often fail to respond to optimal antipsychotic therapy. Repetitive transcranial magnetic stimulation (rTMS) has recently been suggested as an alternative treatment for these patients. Until now, rTMS has been used at low frequency and has been most commonly applied to the left temporoparietal cortex. In order to improve the efficiency of this treatment, we conducted a pilot longitudinal study using high frequency rTMS guided by anatomical and functional magnetic resonance imaging (MRI).
Methods: Eleven patients with schizophrenia (DSM-IV) were treated with high frequency (20 Hz) rTMS delivered over 2 days with a 6 months follow-up. The anatomical target was identified by MRI as the highest cluster activation along the posterior part of the left superior temporal sulcus from the BOLD signal contrast map of each subject (listening to French vs Tamil story).
Results: A significant reduction in the global severity and frequency of auditory hallucinations between baseline and post-treatment day 12 was observed. For 2 patients, auditory hallucinations disappeared entirely and persisted at 6 months of follow-up. High frequency rTMS was well tolerated in all patients.
Conclusions: This is the first study reporting the successful treatment of auditory hallucinations with 20 Hz rTMS. The efficacy at short term, the strengh of the therapeutic effect at 6 months for certain patients, the safety and short duration of treatment present a considerable therapeutic gain compared to low frequency rTMS.

FC-30-004
Intention to communicate in schizophrenia: Functional neuroimaging evidence

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Objectives: Theory of Mind is the capacity to recognise, interpret and predict identity, perception, emotion and belief of other people in social interaction. A particular element of this social cognition is the recognition of the "intention to communicate". We aimed to compare brain activation associated with visual and auditory stimuli. We expected that stimuli with intention to communicate would activate specific regions of the brain associated with social cognition, and particularly language.
Methods: Video clips were taken from Bucci et al. (Br. J. Psychol. 47: 232-334; 2008). Auditory stimuli were selected from a novel set of sounds (ToMaS) based on ratings on familiarity, source type, emotional salience, and meaningfulness, thus leading to a subset of 30 stimuli where the intention to communicate was either evident, absent, or ambiguous. Both Gestures and ToMaS were presented whilst collecting fMRI data.
Results: The identification of intentional versus to non-intentional stimuli was associated with differential cortex activation. The identification of stimuli specifically with intention to communicate (both visual and auditory) was closely associated with activation in language processing areas (especially planum temporale).
Conclusions: Our preliminary findings suggest a distinct pattern of brain activation for each of the two tasks.

FC-30-005

Beyond amygdala: 5-HTTLPR polymorphism and the medial prefrontal cortex

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Objectives: The short allele of the polymorphism of the serotonin-transporter-linked promoter region (5-HTTLPR) is associated with an increased risk of depression in relation to life stress, presumably through aberrant interactions between amygdala and the perigenual anterior cingulate cortex (ACC). This study used functional magnetic resonance imaging (fMRI) to examine the effects of the 5-HTTLPR polymorphism on another brain region critically involved in depression, namely the medial prefrontal cortex (MPFC).

Methods: Healthy never-depressed subjects were presented with positive and negative stimuli in fMRI and performed two cognitive tasks known to engage the MPFC. They judged whether the pictures related to themselves or not ('self' condition), or whether the pictures were positive or negative ('general' condition).

Results: The dorsal MPFC (BA9) was less modulated in short allele carriers, resulting in higher MPFC activation in 'general' (versus 'self') condition and for negative (versus positive) stimuli. In contrast with the right amygdala activation, which was driven by a complex interaction between genotype, condition, and recent life stress, the effect of the genotype on the dorsal MPFC was not affected by recent life stress. Additionally, the dorsal MPFC activity predicted the magnitude of the functional connectivity between the amygdala and the perigenual ACC.

Conclusions: Whereas amygdala activity could be a better proxy of near-depressive state at a neural level, reflecting a comprehensive integration of genetic, cognitive, and environmental factors, MPFC activity may play a key role in genetic vulnerability for depression, presumably through self-referential processing.

FC-30-006

Linear and non-linear regional neuroanatomical volume variations due to aging: A voxel-based morphometric MRI study of normal, non-elderly adults

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Objectives: We aimed to ascertain whether it is possible to differentiate, during non-elderly life, patterns of volumetric preservation of limbic/paralimbic structures versus age-related gray matter (GM) reduction in neocortical areas, insula and cerebellum. Specifically, we wished to verify whether age-related volumetric reductions follow different linear or non-linear models.

Methods: Volumetric estimates derived from voxel-based morphometry spatially normalized region of interest masks were used to investigate the relationship between GM volumes and age in 89 healthy individuals (48 males and 41 females, 18-50 years), recruited using epidemiological methods. Multiple regression analyses were performed to assess the goodness of fit of first, second and third order polynomial expansions involving GM volumes (corrected for the total amount of GM in the brain) and age in male and female subgroups.

Results: A linear association between age and relative volume preservation in the left anterior cingulate cortex, left lateral temporal cortex, bilateral temporolimbic region and insula was observed in males. However, several regions revealed a more complex, non-linear relationship between relative GM volume and age. Females also exhibited linear and non-linear associations between relative GM volume and age, encompassing the right dorsolateral prefrontal, lateral temporal and lateral parietal cortices; left temporolimbic region and cerebellum.

Conclusions: This population-based study provided evidence that, in healthy non-elderly individuals, there is a significant, non-linear pattern of age-related decline in GM volumes selectively in the prefrontal cortex, while the volumes of limbic, paralimbic and temporal neocortical areas are largely preserved. The mapping of such variability is crucial to a better understanding of the maturational and degenerative processes that affect the human brain across the lifespan, and provides a framework that may improve our understanding about the structural brain abnormalities that possibly occur in association with neuropsychiatric disorders.

FC-31
Childhood & Adolescent Disorders II

FC-31-001
A month and 5-years follow-up study of postraumatic stress disorder in children

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Objectives: To our knowledge, few studies have addressed prospectively post traumatic stress disorders (PTSD) among children exposed to traumatic events. This report describes a month and 5-years follow-up study of children exposed to a mass shooting incident
Methods: A mass shooting resulting in murder of two men by gunmen driving motorcycles in a busy park from Belen, Boyaca, Colombia has provided a unique opportunity to study acute-phase and five-year follow-up of children responses to a this type of traumatic experience. Diagnostic Interview Schedule/Disaster Supplement and SCARED (parent and child versions) were used to assess 293 children (183 girls and 110 boys) of 8 to 18 years of age (mean age 13 years). Data on family history of anxiety disorders was also collected. Measures at 1-2 months and again five year later, with an 89% reinterview rate.
Results: In the acute postincident period, 32.8% of children reported PTSD symptoms, and in 82.6% of all subjects SCARED scores were >=25. At follow-up, 24.6% of children reported symptoms of PTSD while scores >=25 on the SCARED scale was detected in 62.4% of subjects. There was a positive correlation between SCARED scores and PTSD symptoms in both acute phase and follow-up. Parent-history of anxiety disorders was the best predictor of presence and persistence of PTSD.
Conclusions: Intervention programs for children need to take into account familiar and cultural aspects, as well as characteristics of the communities involved.The association of parental anxiety disorder with persistence of PTSD suggests that victims with a family history of anxiety may deserve special attention, since they may be at heightened risk for developing PTSD after a traumatic event.

FC-31-002
The influence of word meaning on central auditory processing in SLI children as indexed by Mismatch Negativity

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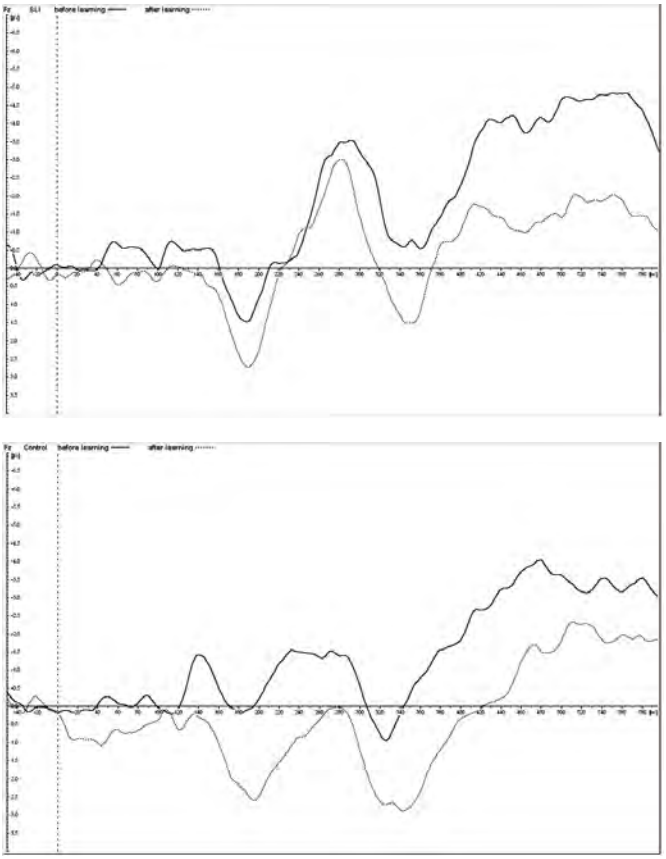
Objectives: For several decades, the aetiology of Specific Language Impairment (SLI) has been associated with central auditory processing deficits disrupting the normal language development of the affected children. Within research on central auditory processing Mismatch Negativity (MMN) is a component of the auditory event-related potential (ERP) that is a useful tool to probe central auditory functions of SLI children (for a review Bishop 2007). The MMN has also been used to study phonological learning effects (Shestakova et al. 2003). It is known that memory processes and meaning effects influence early central auditory processing (Pulvermüller et al. 2001, for a review Näätänen et al. 2007). We wanted to investigate whether semantic learning also influences the central auditory processing in SLI.
Methods: 10 SLI-children and 19 controls participated in a passive oddball paradigm, which comprised two conditions. In both conditions the German pseudoword "fappo" served as standard stimulus, "fappe" as deviant 1 and "fappu" as deviant 2. Before the second condition, subjects learned to connect meaning with the deviant 1. The EEG was digitally recorded with SynAmps amplifiers and Scan 4.0 software. A repeated measure Anova was conducted to compare the MMN mean amplitudes between conditions.
Results: For the deviant 1, we observed a significant reduction of MMN-amplitude after learning in the control group. There was no change concerning the deviant 2. This shows that the reduction of MMN can be ascribed to meaning learning only. In the SLI-group, no change was observed after learning.
Conclusions: The reduction of the MMN-amplitude in the control-group was interpreted as meaning-related MMN effect caused by the possibility to connect the incoming auditory information with conceptual-semantic knowledge. This meaning effect could not be observed in the SLI-group, as no change after learning could be confirmed. We hypothesize that the learning-mechanism of new verbal meaning malfunctions in children with SLI.



FC-31-003
Examination of executive dysfunction as an endophenotype for attention-deficit/ hyperactivity disorder in an ethnic Chinese population

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Objectives: Little is known about executive dysfunction among unaffected siblings of children with attention deficit/hyperactivity disorder (ADHD) and lack of such information in non-Western countries. The authors comprehensively assessed the verbal and non-verbal executive functions in adolescent probands with ADHD, unaffected siblings and the controls.
Methods: We assessed 279 adolescents (range 11-17 years) with childhood diagnosis of DSM-IV ADHD (mean 6.7±2.9 years), 136 biological siblings (108 unaffected. 79.4%)) aged 8 years or older, and 173 unaffected school controls by using psychiatric interviews, the WISC-III including digit spans, and the tasks involving executive functions of the Cambridge Neuropsychological Test Automated Battery (CANTAB): the Intra-dimensional /Extra-dimensional Shifts (IED), Spatial Span (SSP), Spatial Working Memory (SWM), and Stocking of Cambridge (SOC). Linear and nonlinear multi-level models were used for data analyses.

Results: Compared with unaffected controls, probands with ADHD and unaffected siblings had significantly fewer digits recalled in the backward digit span task; more extra-dimensional shift errors in the IED; shorter spatial span length in the SSP; more total errors and strategies utilized in the SWM; and fewer problems solved in the minimum number of moves, fewer mean number of moves; and shorter initial thinking time in the SOC. The magnitudes of SWM and SOC differences increased with increased task difficulties. In general, neither persistent ADHD nor comorbidity was associated with increased deficits in executive functions among probands with ADHD.
Conclusions: As the first study in non-western countries to examine the executive function in unaffected siblings, our findings of executive dysfunctions in unaffected siblings without difference from those in ADHD probands suggest that executive dysfunction may be a useful cognitive endophenotype for ADHD genetic studies.

FC-31-004
Deep brain stimulation for severe head-banging, self-injury, and aggression in adolescent refractory Tourettes

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Objectives: To ascertain if deep brain stimulation (DBS) of the Globus Pallidus Interna (GPi) is a successful treatment for severe head-banging in treatment-resistant Tourettes syndrome.
Methods: Despite her age, a 16 year old female underwent DBS of the GPi as Australia's first Tourettes patient, owing to concerns surrounding the potential for acquired brain injury, or other sequelae, from her recurrent head-banging tics and related episodes of loss of consciousness (LOC). Due to the nature of her severe and bizarre complex motor and phonic tics, attention-deficit hyperactivity disorder, obsessive compulsive symptoms, impulsivity, mood instability and episodic rage attacks, her home had been practically demolished and she required long-term institutionalization in a mental health facility for 18 months. Whilst hospitalized, she accumulated 71 prime incident reports in the ward environment related to injuring herself, others, and significant property damage. Tic scales and head-banging counts were administered pre and post operatively.
Results: At 3 months follow-up, there was noticeable clinical improvement, with post-operative head-banging a rare event (3 witnessed in 3 months, previously multiple episodes daily), and of lesser intensity, with no episodes resulting in LOC. Her Yale Global Tic Severity Scale (YGTSS) improved by 23% (100 to 77), the Tourette Syndrome Global Scale (TSGS) by 37% (95 to 60), and the Tic Syndrome Severity Scale (TSSS) reduced from very severe to severe (9 to 7).
Conclusions: Scale reductions grossly underestimate the magnitude of clinical improvement, due largely to initial ceiling effects. Functionally, she has been able to return home, and attend school and part-time work. The primary gains appear to be in reduced intensity of motor tics, head-banging, self-injury and coprolalia, whilst her underlying impulsivity, affective instability and episodic rage continue, albeit with substantially less injury to herself, others, or property.

FC-31-005
Hyperactivity-inattention symptoms in childhood and later academic achievement: The gazel youth study

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Objectives: Children with Attention Deficit/Hyperactivity Disorder are at risk of negative academic outcomes. However, relatively few studies in this area have been based on long-term longitudinal designs and community-based settings. This study examines the link between childhood hyperactivity-inattention symptoms and subsequent academic achievement in a community setting, controlling for other behavioural symptoms, socioeconomic status and environmental factors at baseline.
Methods: The sample consisted of 1264 subjects (aged 12 to 26 years at follow-up) recruited from the longitudinal GAZEL youth study. Psychopathology, environmental variables and academic outcomes were measured through self-reports. Multivariate modelling was performed to evaluate the effects of childhood hyperactivity-inattention symptoms and other risk factors on academic achievement 8 years later.
Results: Hyperactivity-inattention symptoms independently predicted grade retention (adjusted OR=3.58, 95%CI:[2.38-5.39]), failure to graduate from secondary school (adjusted OR=2.41, 95%CI:[1.43-4.05]), obtaining a lower-level diploma (adjusted OR=3.00, 95%CI:[1.84-4.89]), and lower academic performances. These results remained significant even after accounting for school difficulties at baseline. Negative academic outcomes were also significantly associated with childhood symptoms of conduct disorder, even after accounting for adjustment variables.
Conclusions: This longitudinal survey replicates, in a general population-based setting, the finding of a link between hyperactivity-inattention symptoms and negative academic outcomes. This finding may lead to better detection of Attention Deficit/Hyperactivity Disorder and academic difficulties at school, so that adequate school support may be given and that children may be referred to health professionals.

FC-31-006
Differences in Hypothalamic-Pituitary-Adrenal axis functioning among children with ADHD predominantly inattentive and combined types

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Objectives: Some evidence suggests that the HPA axis may be dysfunctional in children with Attention-Deficit/Hyperactivity Disorder (ADHD). The aim of this study was to investigate whether a different pattern of HPA axis activity is found between the inattentive (I) and combined (C) subtypes of ADHD, in comparison with healthy control children.
Methods: A total of 100 prepubertal subjects (52 children with ADHD combined type [ADHD-C], 23 children with ADHD predominantly inattentive type [ADHD-I]) and 25 healthy control subjects) were studied. The effects of stress were studied by comparing cortisol responses to a psychosocial stressor, consisting of a public speaking task.
Results: Children with ADHD-I showed an elevated cortisol response to the psychosocial stressor, in contrast to children with ADHD-C who showed a blunted cortisol response to the psychosocial stressor. When a distinction was made between responders and non-responders (a subject was classified as a responder when there was an increase in cortisol reactivity), hyperactivity symptoms were clearly related to a lower cortisol reactivity to stress.
Conclusions: The results indicate that a low cortisol responsivity to stress may be a neurobiological marker for children with ADHD-C, but not for those with ADHD-I. Directions for future research and clinical implications are discussed.

FC-32
Psychopharmacology V

FC-32-001
Pisa Syndrome induced by atypical antipsychotics

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Objectives: Pisa syndrome, or tonic flexion of the trunk, long considered a side effect of prolonged exposure to conventional antipsychotics, has been reported as occurring with atypical antipsychotics. The authors report two cases of Pisa syndrome induced by atypical antipsychotics.
Methods: Literature review derived from the MEDLINE and PUBMED database
Results: Case One - 38 years old male with type I Bipolar Disorder, presented with insidious onset tonic truncal flexion with axial rotation and difficulty in walking after exposure to olanzapine in doses up to 20 mg/day for 9 months. An objective causality assessment suggested that Pisa syndrome was probably related to olanzapine. There was improvement in his symptoms after 4 weeks switching olanzapine to zotepine in doses gradually titrated to 200 mg/day. Case two – 26 years old male with moderate mental retardation, treated with long-acting risperidone 25 mg - 15/15 days for is aggressive and self-injurious behavior secondary to mood disorder, developed a acute onset of Pisa syndrome, when prescribed with 50 mg 15/15 dosage. The symptoms disappeared returning to 25 mg of long acting risperidone.
Conclusions: Pisa syndrome is a type of dystonia that has been associated with both typical and atypical antipsychotics. Both acute and insidious onset cases have been described in the literature, which have different course and treatment response. Once the patient presents Pisa syndrome, the treatment may include the reduction in dosage or discontinuation of the antipsychotic drug, associated to the introduction of an anticholinergic medication. In the follow-up drugs with low affinity for dopaminergic D2 receptors should be used.

FC-32-002
Randomized placebo controlled trials of n-acetyl cysteine as adjunct therapy for schizophrenia and bipolar disorder

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Abstract: Glutathione is the principal antioxidant of the brain. There is evidence of oxidative stress, lowered brain glutathione and genetic linkage involve glutathione metabolic genes in schizophrenia and bipolar disorder. N-acetyl cysteine (NAC) is a safe, orally bioavailable, precursor of glutathione. NAC has been shown to reverse animal models of oxidative stress, and raises brain glutathione levels. **Objectives:** To test the efficacy of NAC as an adjunct treatment for schizophrenia and for bipolar disorder. Methods: We performed double-blind, multicenter, randomised placebo-controlled trials, 140 people with schizophrenia and a separate RCT with 75 individuals with bipolar disorder. In both trials subjects received 2g daily of NAC or placebo as add-on therapy to treatment as usual. Outcomes in the schizophrenia trial included the Clinical Global Impression (CGI) Severity and Improvement scales, the Positive and Negative Symptoms Scale (PANSS) and measures of general functioning and extrapyramidal side effects. Outcome measures in the bipolar study included measures of mania, depression, CGI, substance use, quality of life, functioning, and tolerability. The duration of both trials was 6 months. **Results:** Intent-to-treat analysis of the schizophrenia trial revealed that NAC significantly improved PANSS total (p= .009], PANSS negative, (p= .018], and PANSS general (p= .035], CGI-Severity (p= .004], and CGI-Improvement (p= .025) scores. NAC treatment in the bipolar trial caused a significant improvement on the MADRS (p = .002) and most secondary scales at end point. Conclusions: These trials implicate glutathione deficits in the pathophysiology of these disorders, and supports NAC as a novel adjunctive treatment for both conditions. References: Berk et al. N-Acetyl Cysteine as a Glutathione Precursor for Schizophrenia: A Double-Blind, Randomized, Placebo-Controlled Trial. Biological Psychiatry 2008; 64, 361; Berk et al. N-Acetyl Cysteine for Depressive Symptoms in Bipolar Disorder: A Double-Blind, Randomized, Placebo-Controlled Trial. Biological Psychiatry 2008; 64, 468.

FC-32-003
Prevalence of lower-than-expected plasma levels in medicated patients presenting for acute inpatient treatment

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Objectives: Non-compliance or incomplete compliance with psychopharmacological medication by psychiatric patients is a frequent risk, prevalence rates ranging from 18 to 70% (numerical mean 44%).
Methods: All patients who had to be admitted to the psychiatric inpatient wards of the University Clinics of Psychiatry and Psychotherapy I, Paracelsus Medical University, Christian Doppler Clinics from 01 June 2005 to 15 July 2005 were screened for pre-admission psychiatric medication. Plasma levels of antidepressants and antipsychotics were determined after solid-phase extraction by high performance liquid chromatography/mass spectrometry (LC/MS).
Results: A total of 233 acute psychiatric admissions occurred, in the case of 58 admissions, patients did not have any pre-medication. The type of medication could not be determined in one patient, and the dose in 4 patients, nine patients had a pre-medication other than antidepressants or antipsychotics, remaining 161 admissions for the statistical analysis. 52% (83 of 161) of the admissions had actual plasma levels that were >2-fold below the plasma level that could be expected from their prescribed dosage, 21% (34 of 161) had actual plasma levels that were >2-fold above, including 23 (14.3%) patients had a plasma level of 0.0 ng/ml at admission
Conclusions: Our findings show, that under routine conditions, 52% of medicated patients had actual plasma levels that were more than 2-fold lower than the plasma levels that could be expected from the prescribed dosage. Our findings suggest that the risk for a patient of NOT having the intended level of medication in his/her blood is 3:1.

FC-32-004
The anxiolytic etifoxine reduces the physical signs and anxiogenic effects of ethanol withdrawal in mice

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Objectives: Change in the function of gamma-aminobutyric acidA (GABAA) receptors attributable to alterations in receptor subunit composition, is one of main molecular mechanisms with those affecting the glutamatergic system which accompany prolonged ethanol intake. These changes explain in part the central nervous system hyperexcitability consequently to ethanol administration cessation. In animal models as well as in humans, hyperexcitability associated with ethanol withdrawal expresses by physical signs such as convulsions and heightened anxiety. The present work investigated the effects of anxiolytic compound etifoxine on ethanol withdrawal paradigms in a mouse model. The benzodiazepine diazepam was chosen as reference compound.
Methods: Ethanol was given to NMRI mice by a liquid diet at 3% for 8 days then at 4% for 7 days. Under these conditions, ethanol blood level ranged between 0.5 to 2g/l for a daily ethanol intake varying from 24 to 30g/kg. The convulsive behaviour on handling was scored on a rating scale (Watson et al., 1997) whereas anxiety-like behaviour was measured in the light/dark box test. Possible sedative and ataxic effects of etifoxine using the actimeter and rota rod tests were evaluated in normal animals.
Results: Etifoxine (12.5-25mg/kg) and diazepam (1-4mg/kg) injected intraperitoneally 3h30min after ethanol removal, decreased the severity in handling-induced tremors and convulsions in the period of 4 to 6h after ethanol withdrawal. In addition, when administered 30min and 15min respectively before the light/dark box test, etifoxine (50 mg/kg) and diazepam (1mg/kg) inhibited enhanced aversive response 8 h after ethanol withdrawal. Contrary to diazepam, etifoxine had no effects on spontaneous locomotor activity and did not exhibit ataxic effects in normal animals.

Conclusions: These findings demonstrate that the gabaergic compound etifoxine selectively reduces the physical signs and anxiety-like behaviour associated with ethanol withdrawal in a mouse model and may hold promise in the treatment of ethanol-withdrawal syndrome in man.

FC-32-005
Effects of sertindole on MK-801 induced impairment of memory in radial arm maze test

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Objectives: Attention, working memory and long-term memory dysfunctions are mostly seen cognitive impairments in schizophrenic patients (Green et al. 2004, Harvey et al 2004). Controversial results exist about the effects of antipsychotics on cognitive abnormalities. Atypical antipsychotics have been shown to be more effective in improving memory dysfunctions than others. One of the mechanisms for the formation of cognitive impairments in schizophrenia is the hypofunction of N-methyl-D-aspartate (NMDA) receptors. The aim of this study was to investigate the effect of an atypical antipsychotic drug sertindole on spatial reference memory and on MK-801 induced cognitive dysfunction in radial arm maze (RAM) test in mice.
Methods: Animals were divided into six treatment groups: vehicle+vehicle; vehicle+1.3 mg/kg sertindole; vehicle+ 2.5 mg/kg sertindole; vehicle+ 0.2 mg/kg MK-801; 1.3 mg/kg sertindole + 0.2 mg/kg MK-801; 2.5 mg/kg sertindole + 0.2 mg/kg MK-801. Two-way ANOVA post hoc Dunnett-t (2-sided) was used as a statistical analysis.
Results: Sertindole (1.3 and 2.5 mg/kg) had no effect on latency and number of errors of mice in RAM test. 0.2 mg/kg MK-801 significantly increased the number of the errors while it exerted no effect on the latency of the animals compared with the vehicle group. Concurrent administration of sertindole (1.3 or 2.5 mg/kg) with MK-801 (0.2 mg/kg) didn't alter the number of errors compared to MK-801 treated group. Moreover both the velocity of the animals treated with MK-801 and MK-801 plus sertindole was significantly increased compared to control group.
Conclusions: In conclusion, sertindole alone had no disturbing effect on spatial reference memory in the radial arm maze test. Furthermore sertindole failed to improve the cognition disturbing effect of MK-801 at 1.3 and 2.5 mg/kg doses in this task.

FC-32-006
Early perturbation in feeding behavior and energy homeostasis in olanzapine-treated rats

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Objectives: Olanzapine is a new generation antipsychotic drug which has weight promoting effects and often produces glucose metabolism abnormalities, participating in the development of a metabolic syndrome. Feeding patterns abnormalities may be associated with the development of a metabolic syndrome in humans. The aim of the present study was to examine the effects of a chronic olanzapine treatment on feeding patterns in the rat. And to investigate a potential time-related association between abnormal feeding patterns and the appearance of glucose metabolism abnormalities.
Methods: Male rats were treated with olanzapine (2mg/kg/day), haloperidol (1mg/kg/day) or a control solution. In Experiment 1, animals were treated during 26 days, and feeding patterns were measured on day 21. In Experiment 2, animals received the treatments during 46 days, and an OGTT was realized on day 31. At the end of the two experiments, plasma parameters and body composition were analyzed.
Results: Experiment 1: Olanzapine-treated animals showed increased meal numbers, decreased ingestion rates, decreased meal sizes, decreased intermeal intervals and no change in total food intake; Plasma glucose was not altered; The effects of haloperidol were similar to those of the control solution. Experiment 2: At 31 days of treatment fasting blood glucose was increased and OGTT showed alterations; At the end of the experiment, circulating glucose was elevated and adiposity was increased in olanzapine-treated animals.
Conclusions: Chronic olanzapine treatment produces changes in feeding patterns. The fact that olanzapine increases meal number and decreases meal size likely indicates that olanzapine increases incentive drive to eat and has no effect on satiety systems. As a whole, the results raise the hypothesis that long-term alteration of feeding patterns through an alteration of the feeding initiation system could have relationships with the development of a metabolic syndrome during chronic olanzapine treatment.

FC-33
Psychotic Disorders VIII

FC-33-001
Enhanced synaptic plasticity at hippocampal output synapses in the MK-801 model of psychosis

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Objectives: Phencyclidine and other non-competitive antagonists of N-methyl-d-aspartate (NMDA) receptors as MK-801 induce psychotic effects in humans that closely mimic positive, negative and cognitive symptoms of schizophrenia. Some of these symptoms can be reproduced in the MK-801 animal model of psychosis. In the present study, we investigated whether these phenomena go along with changes in hippocampal synaptic plasticity.
Methods: 3 to 5 weeks old Wistar rats received a single intraperitoneal injection of MK-801 (5 mg per kg body weight) or vehicle and their behavior was monitored and scored. 24 hours later, combined entorhinal-hippocampal brain slices were obtained and intracellular recordings were performed in an interface chamber using sharp microelectrodes. Induction of long-term potentiation (LTP) was studied in all subregions of the hippocampus.
Results: Rats treated with MK-801 showed severe behavioral alterations which disappeared within 24 hours. Using a high frequency stimulation protocol that was sub-threshold to induce LTP in control rats resulted in a robust late-onset LTP at CA1-subiculum synapses but failed to induce LTP in the dentate gyrus and hippocampal areas CA3 and CA1. This LTP was blocked by the D1/D5-dopamine receptor-antagonist SCH23390, could be mimicked by application of the specific D1/D5-dopamine receptor-agonist SKF38393 and was independent of metabotropic glutamate I/II and NMDA receptors. Analysis of paired-pulse facilitation indicated a presynaptic expression mechanism.
Conclusions: In the MK-801 model of psychosis we observed a D1/D5-dopamine receptor-dependent facilitation of LTP selectively at hippocampal CA1-subiculum synapses. The subiculum is the major output structure of the hippocampus and plays a key role in the information processing from the hippocampus to the ventral tegmental area (VTA). Hence, we propose that the facilitated synaptic plasticity may contribute to psychotic symptoms that have been attributed to alterations in the hippocampus-VTA loop.

FC-33-002
Temporal processing dysfunction in medicated and unmedicated patients with schizophrenia

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Objectives: Schizophrenia (SCZ) may be associated with a fundamental disturbance in the temporal coordination of information processing in the brain, leading to classic symptoms of schizophrenia such as thought disorder and disorganization and cognitive dysmetria. Following the growing interest and centrality for the time-dependent underpinnings of the pathophysiology of SCZ, the present study investigated timing in SCZ using a well-established task of time reproduction (Rakitin et al, 1998; Fortin et al, 2009).
Methods: Thirty-three patients (22 male, 11 female) that met DSM-IV criteria for Schizophrenia, Schizo-Affective disorder, or Schizoid personality disorder were included in two groups, the "medicated SCZ" (N=20) and the "unmedicated SCZ" group (N=13) that were contrasted to an age-matched control group (N=20). Subjects were asked to reproduce 3 time intervals (2.4, 3.2 & 4.0 sec) with a variant of the peak-interval timing task assessing temporal processing without and with interference from the expectancy of a gap in stimulus presentation, i.e. a brief period during which timing must be interrupted. Gap location and duration were varied. A Word Serial Position Task (WSPT) for an assessment of working memory of serial order and a tone-discrimination (TD) task were also administrated to all subjects and correlations between timing, WM and TD performance were examined.
Results: The unmedicated SCZ were more variable when timing without gaps compared to the medicated SCZ and controls. However, both SCZ groups showed decreased temporal precision when timing with gaps compared to controls. The magnitude of the effect increased with increasing duration of gap expectancy in the patients. The deficit of timing precision was negatively correlated with performance of the WSPT.
Conclusions: These findings provide additional evidence that timing precision is impaired in SCZ and that medication has some effect on this temporal processing dysfunction.

FC-33-003
Schizophrenia, serotonin, gender and age of onset: An association study in a Spanish sample

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Objectives: A high number of studies in schizophrenia have been focusing on searching for causative genes, which might increase predisposition for this disorder or modify its course and outcome. Among such genes, serotoninergic system genes are being selected mainly due to serotonin modulates the activity of dopaminergic neurons, which are affected in this disease.
Methods: In this work, we performed an association study in schizophrenia using 46 polymorphisms from 17 genes of the serotoninergic system. Two different approaches were carried out: a classical case-control design and a comparison between patients grouped by age of onset and gender variables. This study was conducted on a sample from Spanish population, consisted of 196 unrelated patients with schizophrenia (according to DSM-IV), and 374 unrelated healthy subjects without psychiatric records or perceptual abnormalities. All participants gave written informed consent and the study was approved by the Local Ethic Committees.
Results: In the case-control study, the rs888961 polymorphism of the HTR4 gene (serotonin receptor 4) showed a significant association at single marker level (OR = 0,54; 95% CI: 0'38-0'75, corrected p = 0'0077), genotype level adjusted by gender (OR = 0,53; 95% CI: 0'38-0'75, corrected p = 0'004) and at overall haplotype association for HTR4 (rs1862342, rs11956922, rs7700268, rs888961; corrected p = 0'0193). When patients were grouped by the age of onset (< 21 versus ≥21 years), the 1503433 polymorphism of the HTR1F gene (serotonin receptor 1F) was associated at genotype level (corrected p = 0'0456), but not at allelic and overall haplotype level. No positive results were obtained after multiple test correction when the gender variable was taken into account.
Conclusions: In conclusion, our study provided further evidence for association between the serotonin receptor 4 and schizophrenia. On the other hand, the serotonin receptor 1F might contribute to differences of age of onset in this disease.

FC-33-004
Cortical gyrification in twins discordant for schizophrenia

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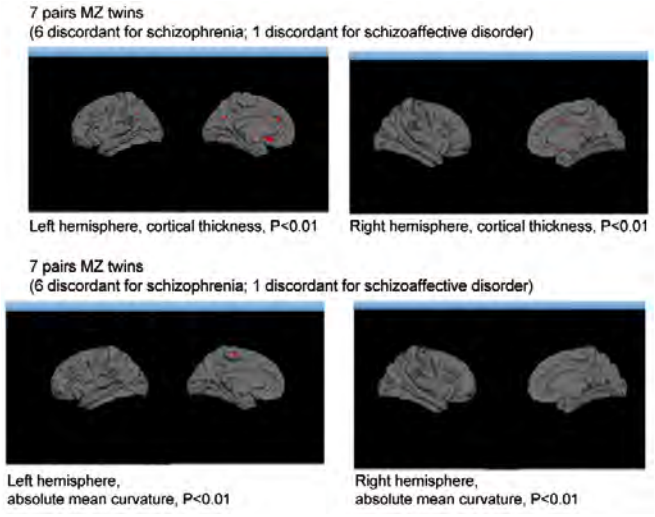
Objectives: Disturbances of gyrification and the cortical folding pattern have been described in schizophrenia in several studies, esp. in the prefrontal cortex. It is generally thought to reflect abnormal neurodevelopment. More recent findings in family members suggest that this abnormality might be related to genetic factors influencing brain development. Here we analyze data from monozygotic discordant twins discordant for schizophrenia to test the hypothesis that abnormal gyrification and cortical thickness is related to genetic factors or the expression of the disease phenotype.

Methods: We analyzed 3D high-resolution (1x1x1mm voxels; 1.5T) MRI scans of 7 pairs of adult monozygotic twins discordant for schizophrenia (6 pairs) or schizoaffective disorder (1 pair). The non-affected co-twins had no other psychiatric or neurological history of condition. Absolute mean curvature, as a measure of local gyrification, and cortical thickness were computed from extracted whole brain cortical surface maps. Gyrification and cortical thickness of each hemisphere separately, was compared between patients and their healthy co-twins using paired t test, with age as a covariate of no interest.
Results: Affected twins showed increased absolute mean curvature in left pars opercularis, increased sulcation of bilateral superior temporal sulci and reduced sulcation of left paracentral sulcus compared to their co-twins. Affected twins showed reduced cortical thickness in left angular gyrus and left precuneus and bilateral cingulate and bilateral subcallosal cortex compared to their healthy co-twins (all results at P<0.01, uncorr.).
Conclusions: Observed gyrification abnormalities in affected twins could be due to early developmental changes underlying disease process, rather than genetic background/risk, which is identical in MZ twin pairs. Absence of changes in dorsolateral prefrontal gyrification would be consistent with the assumption of an additional early developmental abnormality (e.g. peri-natal) or epigenetic mechanisms. Comparison with normal twins and dizygotic pairs discordant for schizophrenia are needed to further clarify genetic effects.



FC-33-005
Silenced and overexpressed genes: Incorporating epigenetic factors in the Etio-Pathology of schizophrenia

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Objectives: The participant should be able to recognize that multiple inherited factors contribute to the liability for schizophrenia.These factors are not just going to be in the protein coding regions.In schizophrenia the role of variation in DNA expression (epigenetics) during the protracted period of brain development suggests that genetic as well as epigenetic factors must be considered.Carefully executed gene expression analysis will be crucial to accelerating the slow progress of genetics research.
Methods: Extensive review of literature from basic sciences to clinical studies.
Results: Discussion:Epigenetics is a term refering to biochemical modifications of chromatin that do not alter the primary sequence of DNA but affect gene transcription.Historically,the search for answers to the etiopathology of schizophrenia had focussed on genetic or enviomental variants, but recent studies in epigenetics have revealed a third mechanism that can influence phenotypic outcomes.The reduced concordence between MZ twins,the temporal delay of schizophrenia onset,the fluctuating coarse and the presence of clinically indistinguishable sporadic and familial cases are indications that aberrent epigenetic regulatory mechanisms operate in the etiology of schizophrenia.In mammals,hypermethylation within promotors is a common epigenetic modification which can lead to gene silencing.The administration of methionine to schizophrenia patients results in a profound excerbation of their symptoms in 60-70% of patients.Valproate produces a dose-related increase in acetylation of histone H3 in the prefrontal cortex which normalizes the methionine-mediated promotor hypermethylation, reversing gene silencing. Indications that epigenetic regulatory mechanisms operate in the etiology of schizophrenia can be garnered from examination of the expression levels of at least three genes. Postmortum studies indicates that the genes that encode Reelin and GAD67 are downregulated at both transcriptional and translation levels in contrast DNMT1,expressed in GABAergic interneurons, is upregulated in schizophrenia.
Conclusions: Epigenetic information might be the missing link for understanding the biological mechanisms in schizophrenia and for prospective pharmacological interventions.

FC-33-006
Modelling thalamo-cortical circuits and auditory processing in schizophrenia

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Objectives: In schizophrenia, disturbances in early information processing involving the thalamo-cortical circuit are well known. Disturbances in the precise timing of coupled brain areas are discussed as the neurophysiological basis of schizophrenia. By using simulations from a mathematical model, which is based on detailed neurophysiological knowledge, we tested several hypothesis concerning disturbances in the thalamo-cortical circuit in schizophrenia.
Methods: We developed a mathematical model describing the dynamics in the auditory pathway of the thalamo-cortical circuit. The model is settled on the level of local field-potentials, but also incorporates dynamics from single neurons. We concentrate on timing processes, which are best modelled by phase-dynamics. The phase-oscillator model enables us to build a compact description and allows detailed mathematical analyses. One focus of the research was to analyze the strength of the connection between the thalamus and the cortex, which in the model is highly connected to synchronization processes in the two brain areas.
Results: The simulations show different aspects of dynamical processing. A reduction of the impact of the thalamus on the cortex produces simulations, which show a similar behaviour as in time-frequency EEG-analyses from a double-click paradigm in chronic schizophrenia patients. To a minor degree, this could also be achieved by changing the impact of cortico-cortical connections. The simulations also show that the thalamic reticular nucleus is highly involved in the sensory gating mechanism, which is disturbed in schizophrenia.
Conclusions: Simulations from a mathematical model based on neurophysiological evidence can give new insights into the understanding of the underlying time-adjusted neuronal processes and therefore enables the formulation and evaluation of hypothesis for disturbances in schizophrenia. This modelling technique complements analyses from EEG/MEG-data by also describing deep brain processes. Additionally, the modelling forms a bridge between the local-field analyses from animal experiments and the time-frequency analyses from EEG data from humans.

FC-34
Affective Disorders (Bipolar/Unipolar)

FC-34-001
State-dependent elevation of interleukin-1 receptor antagonist (IL-1Ra) in bipolar mania

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Objectives: The increase in anti-inflammatory cytokine- interleukin-1 receptor antagonist (IL-1Ra) in schizophrenia has been considered as the physiopathology of schizophrenia or as phenotypic traits of the disorder. However, there is no published report regarding the IL-1Ra in bipolar disorder. The aim of this study is to investigate the IL-1Ra alternation during bipolar mania and its association with symptomatic severity and other clinical features.
Methods: The plasma levels of IL-1Ra and leptin in 30 physically healthy patients with bipolar I disorder, manic (DSM-IV) aged 18-45 years were measured in acute mania, early remission, and full remission. The results were compared with age- and sex-matched healthy normal controls.
Results: The mean plasma levels of IL-1Ra in acute mania and partial remission were significantly elevated in comparison with that in full remission and of control subjects. The mean level of IL-1Ra in acute mania had significantly positive relationship with the scores of Young Mania Rating Scale. The levels of three various affective phases were all positively correlated to body mass index and plasma leptin level. There was no relationship between IL-1Ra level and other clinical variables along with dosage of any psychotropic agent.
Conclusions: As the soluble IL-2R noted in our early work [1], the plasma IL-1Ra level significantly elevates only during bipolar mania and is associated with symptomatic severity of mania. This finding supports a state-dependent inflammatory process of bipolar mania and various immunological physiopathology in different psychotic disorders. Reference: 1.Tsai SY et al: Effects of symptomatic severity on elevation of plasma soluble interleukin-2 receptor in bipolar mania. J Affect Disord 2001; 64:185-193

FC-34-002
The use of background EEG activity to determine stimulus timing as a means of improving rTMS efficacy in the treatment of depression: A controlled comparison with standard techniques

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Objectives: Repetitive transcranial magnetic stimulation (rTMS) treatment of depression utilises numerous pre-determined patterns of stimulation. As an alternative to using invariant repetition parameters, the interactive technique delivers stimuli based on the background EEG activity. This study examines the use of this technique as a means to enhance the efficacy of rTMS in the treatment of depression.
Methods: Forty-four patients with treatment-refractory major depression were treated with two different sets of rTMS parameters (left dorsolateral prefrontal cortex). Standard rTMS utilized 10Hz stimuli, while interactive rTMS applied stimuli in response to a selected pattern of background EEG activity analysed in real-time. Hamilton Depression Rating Scale (HDRS) and the Beck's Depression Inventory-II (BDI) scores were recorded at baseline, two weeks and following the final treatment.
Results: The interactive group showed a trend towards greater efficacy than the standard group in both absolute (t=-1.68; p=.100) and percentage (t=-1.74; p=.090) change in scores on HAMD (and similarly BDI), and in response rates (>50% score reduction). The response rate for interactive parameters of 43% (9/21) was also different to that of the standard parameters (22%; 5/23; Odds-Ratio:2.70).
Conclusions: The use of EEG-based TMS stimuli has been shown to be feasible in an rTMS clinical trial in treatment-resistant depression. The EEG based parameter set showed a trend toward a greater clinical effect than the standard rTMS set, and a higher response rate. The interactive technique thus has the potential to refine the rTMS methodology and to enhance efficacy in the treatment of depression.

FC-34-003
Dopamine-beta-hydroxylase localization and outer membrane disruption of spherical acidophilic inclusions in depression

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Objectives: Lowering of serum cholesterol leads to a decrease in coronary heart disease, but also to increased deaths due to suicide. Lowered cholesterol concentration may contribute to decrease in brain serotonin and also to membrane cholesterol decreases of serotonin receptors (Hawthon et al., 1993). Studies demonstrated disrupted neurochemistry of the noradrenergic locus coeruleus (LC) in major depression (Ordway et al., 2003). In human catecholamine neurons, we have identified abundant somatodendritic spherical acidophilic inclusions, called protein bodies (PB), which originate and grow gradually, as spherical dense cores, in the matrix of mitochondria. We have also shown that PB contain dopamine-β- hydroxylase (DBH), which is a hallmark of noradrenalin (NA) identity (Issidorides et al., 1996; 2004). Since PB are found to be disrupted in LC neurons in depressed individuals (Issidorides, 1983), where NA is biochemically known to be reduced (Bunney and Davis, 1965), this coincidence of ultrastructure and neurochemistry raised the question of PB integrity in depression.
Methods: We studied tissue of LC from 8 controls and 8 cases of depression, applying a) DBH immunogold labeling and b) potassium permanganate (KMnO4) method for the study of membrane ultrastructure.
Results: DBH immunogold labeling was localized in the core and, occasionally, in the double membranes surrounding the PB of controls. However, DBH labeling was also present in PB of the depressed individuals. In patients, KMnO4 method revealed a disrupted outer membrane surrounding the PB, which as a rule resulted from low cholesterol.
Conclusions: Presence of DBH in PB indicates that these bodies are unequivocal NA-synthesis and -storage sites in both control and depressed subjects. The finding that in depression the double-membranes of PB are "blebbing" and fluidizing, suggests a decrease of serotonin receptors, leakage and loss of the neurotransmitter from its storage site, corroborating the biochemical findings of reduced level of NA in the LC neurons in depression.

FC-34-004
DNA methylation profiling of major depression

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Objectives: Emerging evidence suggests that DNA methylation plays an expansive role in the central nervous system, linking this epigenetic process to neurogenesis and neuronal plasticity. DNA methylation may play an important role in the etiology of neuropsychiatric disorders. Our aim is to explore the epigenetic profile of major depressive disorder (MDD).
Methods: Using our methodology Methyl-MAPS (methylation mapping by paired-end sequencing), which couples next-gen sequencing with enzymatic fractionation of DNA by methylation state, we have obtained >80% coverage of the CpGs genome-wide for 4 MDD cases and 4 nonpsychiatric controls.
Results: We limited our study to the prefrontal cortex (PFC) because of converging evidence from neuroimaging studies implicating this region in MDD, and our work showing that genomic methylation patterns differ markedly across regions within the normal human brain. We have identified numerous differentially methylated regions across the genome, and our initial efforts were focused on gene promoters where extant DNA methylation is known to be associated with gene expression. We have identified candidate differentially methylated genes involved in CNS function and are validating these findings via bisulfite sequencing. Following validation, we are expanding our analysis of these regions to a large sample of PFC tissue derived from sixty MDD cases and controls with comprehensive clinical and toxicological profiles in order to identify a panel of MDD-associated DNA methylation alterations.
Conclusions: Evaluation of the frequency of these DNA methylation abnormalities may point to new pathways involved in MDD, and these epigenetic changes may have clinical utility as biomarkers.

FC-34-005

Serotonin Transporter gene polymorphims and it correlation with depressive patients

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Objectives: Study the correlation between Serotonin Transporter gene polymorphims 5HTTPRL and depressive patients.
Methods: Study the correlation between Serotonin Transporter gene polymorphims 5HTTPRL and depressive patients.
Results: Significant differences were found among the patients carrying a short allele in the genotype (ss-ls =n.70) compared with the homocigotes (ll = n.30) depressive patients. The "s" carriers presented earlier onset of depression (aver. 25 years vs. 33.8 years) and more:

- Difficulties in development academic skills (36.5% vs. 14.8%)
- Number of suicidal attempts (rates 10,2 vs. 2,2), in violents ways (57.% vs. 33%.)
- Comorbility with personality disorders (37 % vs 15,%)
- Anxiety disorders (48% vs 37%)
- S ubstance abuse (21% vs. 15%)
- Autoagressivity (62 % vs 33%)
- Impulsivity (67% vs 19%)
- Number of psychiatric hospitalization (52% vs 26 %)
- Past history of stressors events (particulary abandon experiences in early adulthood with lack of attachment figures and sexual abuse (30 % vs 7 %)
- Family background of alcohol abuse history (38 % vs 15 %). Homocygotes "ll" group presented more history of depression in relatives (70 % vs 50%) and succesful suicide attemps (26% vs 15%). Better response to antidepressant treatment (61% vs 44,3) was found in this group of patients.

Conclusions: Patients carrying a short alele in the genotype have presented more vulnerability to depression and comorbility, associated with a reduced response to antidepressant treatment. These factors increased the risk to have a worst development in the course and prognosis of the mental disorder.

FC-34-006

Meta-analytic evidence for familial coaggregation of schizophrenia and bipolar disorder

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Objectives: Several sources of data suggest a link between schizophrenia and bipolar disorder (BD), however family studies have not revealed coaggregation of these disorders. We systematically reviewed family studies of probands with schizophrenia and BD to determine whether these disorders coaggregate in families.
Methods: Prospective studies were identified by searching Medline and PsycInfo databases from January 1, 1980 to December 31, 2006. All family studies reporting morbid risk or raw counts of schizophrenia or BD in first-degree relatives (FDR) of a proband group with DSM-III or later, ICD-9 or 10, or research diagnostic criteria schizophrenia or BD were included. A total of 38 studies were used to investigate rates of BD in FDR of probands with schizophrenia, while 39 studies were used to examine rates of schizophrenia in FDR of BD probands, out of the original 2326 studies identified by the database search. Data were analyzed with a novel random-effects bootstrapping technique that allows for the inclusion of studies lacking a patient or control group, which made up a substantial portion of the available data. Data were also blindly weighted for methodological quality.
Results: The FDR of probands with schizophrenia showed significantly ($p = 0.01$) increased rates of BD relative to control FDR, with an odds ratio (OR) of 2.08. The FDR of probands with BD showed marginally ($p = 0.06$) increased rates of schizophrenia relative to control FDR, with an OR of 2.10—this analysis was significant ($p = 0.02$) when studies not reporting morbid risk estimates were excluded, in which case the OR was 3.49.
Conclusions: The present study provides the first direct evidence for familial coaggregation of schizophrenia and BD, a finding that argues against a view of these disorders as entirely discrete diagnostic entities. Rather, a continuum or overlapping disease entity model is supported.

FC-35
Addictive Disorders II

FC-35-001
Blaming Parkinson's for addiction?

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Objectives: Recently, compulsive behaviour such as extreme reliance on medication, addiction to gambling and others have been described to affect people with Parkinson's disease (PD). At the same time, relationship between dopamine, PD and addictive behaviours has been already illustrated and growing evidences show that the same processes lie behind all addictions, behavioural or chemical. This study has evaluated the prevalence of main aspects of addiction (alcohol, tobacco, gambling, sex, medication) in PD patients on dopamine replacement therapy (DRT) comparing with general population.
Methods: A cross-sectional, self questionnaire-based study was undertaken. The self-report explored quantitative and qualitative addictions (AUDIT, Fagerström, TDAS, SOGS…) with substance (alcohol, tobacco…) or without (gambling, sex) in PD patients and healthy controls. HAD scale was used to assess the contribution of mood disorder.
Results: 138 non-demented patients with PD and 115 age and sex matched control subjects were studied. There are no significant differences between the two groups concerning prevalence of smokers, means alcohol drinking scores, means gambling scores. In contrast, we found that PD patients had significantly higher scores than controls for sex addiction, anxiety and depression but there are significantly higher hazardous or alcohol dependant drinkers in control group. In PD group, there are three times more "probable pathological gamblers" (3.1%); three times more "probable presence of depression disorders (11.4%); more than twice "probable presence of anxiety disorders" (28.9%); 2 cases of "probable sex addict" (1.8%) vs. none in control group. In the total group of PD patients, 13.3% could be diagnosed with Hedonistic Homeostatic Dysregulation (HHD).
Conclusions: This study seems to confirm that PD patients are not affected by all forms of addictions, but preferentially by gambling, sex and dopamine replacement therapy addictions. Further analyses will conduct us to study coaddictions; relation with mood disorders and links between HHD and DRT.

FC-35-002
Treating social anxiety disorder effectively in patients with substance use disorders

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Objectives: Social anxiety disorder (SAD) is frequently co-morbid with other psychiatric disorders including substance use disorders (SUD). Substance users employ alcohol and other drugs as a ‚social lubricant' so often that there is a high prevalence of SAD in this population. There is a reluctance to prescribe benzodiazepines and other anxiolitics because of their addictive properties and risks in this population. Typically, patients are asked to seek treatment for SAD after they have been treated for their co-morbid SUD, and they are regularly excluded from SAD treatment studies because of the belief that their SUD is an obstacle to SAD treatment. However, it is because of their SAD that they use substances and SUD treatment cannot be effective without addressing SAD. This communication presents the efficacy of a 12-week CBT group modified for the treatment of concurrent SAD and substance use from existing CBT protocols for social anxiety (see Heimberg et al., 1999).
Methods: Out-patients in a mental health and addiction treatment center with a DSM-IV diagnosis of SAD and SUD were administered a series of social phobia, anxiety sensitivity, and expectancies on social evaluative situations pre and post SAD treatment. They also completed weekly avoidance and fear hierarchies of social situations from pre to end of treatment. Most had a generalized subtype of SAD (88%) and in most cases (71%) the SAD onset predated the onset of SUD. CBT treatment involved the identification and challenging of cognitive distortions, behavioural experiments and in vivo exposure.
Results: Repeated measures univariate analyses of variance tests conducted with Bonferroni adjustments for multiple comparisons suggested that individuals experienced reduced fear ($p<.007$), avoidance ($p<.009$), and physiological symptoms related to social anxiety ($p<.001$).
Conclusions: CBT can reduce symptoms of SAD in active substance users. Strategies to provide effective SAD treatment with substance users will be presented.

FC-35-003
The psycho-etiological model of alcohol use disorders: A case study in Belarus

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Objectives: Recent epidemiological data show that genetic predisposition, abnormal brain metabolites, endocrine and psychological dysfunctions, including asocial behaviour and environmental influence play significant role in alcoholism. The aim of this study was to identify the psycho-etiology of alcohol use disorders (AUD), determine and examine the psycho-etiological factors that encourage alcohol use above the threshold dose, responsible for the development of alcohol related problems among young people in the general Belarusian population.
Methods: Over 2000 young people (average age 21) in Minsk, Belarus were explained the study aims and objectives. 1599 respondents enrolled for the study. Each participant was administered the AUDIT, a truth test and a validated questionnaire on various initiation patterns and motives of alcohol use. Of them, 82 students could not complete the questionnaire satisfactorily. A total of 1517 (average age = 21) students were considered for analysis. Pearson, $\chi 2$ and t-tests were employed for analysis of results.
Results: Overall, 87.54% alcohol users and 17.67% problem drinkers were identified. The major psycho-etiological factors of AUD were identified as drinking to reduce bad mood (16.41%) ($\chi 2=134.29$); on days of wages (14.89%) ($\chi 2=82.89$); for the sweet qualities of alcohol (24.81%) ($\chi 2=6.39$); to get drunk (26.72%) ($\chi 2=31.14$). The frequency of alcohol use is significantly increased by almost 4 times ($p\leq 0.0001$) among drinkers with AUD.
Conclusions: Drinking to reduce bad mood, on days of wages, for the sweet qualities of alcohol, to get drunk were of great statistical significance in the psycho-etiology of AUD. Recommendation: alcohol doses for one person per month must not exceed 4 standard drinks – 32 g or 40 ml of pure ethanol (1 liter of beer with a composition of 4% alcohol).

FC-35-004
The intergenerational transmission of tobacco smoking – the role of parents' long-term smoking trajectories

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Objectives: Children of smokers have high rates of tobacco smoking. However, it is not clear whether youths' smoking behavior is related to their parents' long-term smoking patterns. In this study, we examined the association between parental smoking trajectory over 11 years and the smoking patterns of their adolescent and young adult offspring.
Methods: Data were collected among 1129 youths (12-26 years) participating in the GAZEL Youth study, a community-based cohort based in France, and from their parents. Youths' regular tobacco smoking (>=1 cigarette/day over the preceding 12 months) was ascertained by self-report. Parental (mother's or father's) smoking trajectory (1989-1999) was measured through parents' yearly reports and classified as follows: non-smoker, intermediate level smoker, persistent smoker. Statistical analyses controlled for youth's sex, age, alcohol use and juvenile behavioral difficulties, parent's sex, as well as family socioeconomic position.

Results: Overall, 27% of study youths were regular smokers. Compared to youths whose reference parent was a long-term non-smoker, offspring of persistent smokers had twofold smoking rates (age and sex-adjusted OR: 1.91, 95% CI: 1.30-2.79, fully-adjusted OR: 1.96, 95% CI 1.31-2.93). Mother's smoking was more strongly associated with offspring smoking than father's smoking (fully-adjusted OR: 3.12, 95% CI 1.58-6.16 vs. OR: 1.47, 95% CI 0.87-2.49). Youths whose reference parents were intermediate level smokers, that is they quit smoking during the follow-up period, had comparable smoking rates to children of non-smokers (fully-adjusted OR: 1.14, 95% CI 0.67-1.96).
Conclusions: Youths' likelihood of tobacco smoking appears associated to their parents' long-term smoking patterns. Parents should be made aware that their smoking behavior may influence their offspring's use of tobacco in adolescence and young adulthood. Efforts that aim to decrease the burden of tobacco smoking among youths should focus on families rather than individuals alone.

FC-35-005
Automatized action schemata in nicotine dependence: Evidence from functional magnetic resonance imaging and a behavioral affordance paradigm

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Objectives: Besides reward- and craving-related processes, habitual mechanisms play an important role in addiction. While the dorsal striatum has been proposed to code for the motivational state of habitual drug-seeking actions, the neural underpinnings of the corresponding drug-taking skills and action knowledge remain poorly understood.
Methods: We used functional magnetic resonance imaging (fMRI) and a behavioral orientation affordance paradigm to investigate the neural and behavioral correlates of automatized drug-taking actions in nicotine dependence.
Results: Smokers (n=15) exhibited higher fMRI activations than non-smokers (n=15) when viewing smoking-related but not when viewing control images. These group differences in fMRI activations were located not only in brain regions associated with craving and habitual learning (left ventral and dorsal striatum, dorsolateral prefrontal cortex, insula, uncus, and medial frontal gyrus; right subcallosal gyrus; bilateral parahippocampal gyrus), but also in a network of brain regions which has been strongly implicated in the encoding of action knowledge and tool use skills (bilateral premotor cortex, left superior parietal lobule, and right lateral cerebellum). A behavioral affordance reaction-time task indicated that smokers (n=8), but not non-smokers (n=8), showed an automatized responsiveness to smoking paraphernalia similar to everyday objects. Moreover, smokers showed strong intercorrelations between fMRI activations in tool use-related brain regions, behavioral responsiveness to smoking-related cues, and severity of nicotine dependence.
Conclusions: Apparently smoking-related action representations in smokers are stored in brain regions typically representing tool use skills and action knowledge. Most importantly, cortical and behavioral correlates of the respective automatized action schemata vary with the individual degree of nicotine dependence.

FC-35-006
Developmental changes in P300 amplitude and risk for substance use disorder

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Objectives: Attenuated amplitude of P300 has been reported on high risk individuals for substance use disorder (SUD). Longitudinal research has not determined whether this trait has developmental basis. We hypothesize that magnitudes of P300 amplitude changes are different in offspring of SUD+ and control parents between end of infancy and mid adolescence.
Methods: Twenty one low average risk (LAR=21) and fifty three high average risk (HAR=53) boys between 10 and 12 years were recruited through their proband biological fathers, qualifying for a lifetime DSM-III-R diagnosis of SUD or no psychiatric disorder. P300 amplitudes were obtained from five electrode sites (Fz, Cz, Pz, P3, P4), and a global average calculated, using an auditory oddball task at baseline and 14 to 16 years. Comparisons were performed by risk group at baseline and endpoint, and on magnitude of change between ages.
Results: P300 amplitude was significantly lower for the HAR group at 14 to 16 years old at the Frontal site (Fz: F=0.502; p=0.03). Percentage of increase in P300 amplitude was a sensitive discriminator by risk group (Fz: t=1.99, p=0.03; P3: t=1.90, p=0.03; Average: t=1.74, p=0.04), as well as, an accurate predictor of number of substances consumed by age 19 (Fz: p=0.004; Cz: p=0.005; Pz: p=0.005; P3: p=0.004; P4: p=0.005; Average: p=0.005).
Conclusions: P300 amplitudes at 14 to 16 years and their ratio of increase since 10 to 12 years, are accurate discriminators across risk groups and ages, respectively. These characteristics could be the result of an altered neurodevelopment of the Prefrontal Cortex, result of an early life environmental stress.

FC-36
Brain Function III

FC-36-001
Sub-thalamic deep brain stimulation decreases metabolic activity in pre-frontal cortex in patients suffering from obsessive compulsive disorder

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Objectives: To highlight the neural substratum of high frequency bilateral subthalamic nucleus (STN) Deep Brain Stimulation (DBS)
Methods: A 18FDG PET study was done in ten patients with highly refractory OCD operated by high frequency bilateral STN DBS. Realization of the neuroimagery procedure took place for each patient in order to compare 18FDG-PET images in "On stimulation" with "Off stimulation" conditions, as well as to compare patients "responders" with those "non responders". PET analysis included three main effects: 1.Comparison of OCD patients on "Off stimulation" status with healthy control (HC) to determinate the modifications of glucose metabolism in refractory OCD; 2. Comparison of "On stimulation" and "Off stimulation" conditions to determine direct STN DBS effects; 3. Comparison of "responders" (decrease > 25 % at the Yale Brown Obsessive Compulsive Scale (YBOCS)) versus "non responders".
Results: In "Off stimulation" condition, an hypermetabolism in OCD patients was observed in the right orbito-frontal cortex (Brodmann Area (BA) 10 and BA 47), right parietal lobe (BA 7), post central gyrus (BA 43) and in the bilateral putamen, when comparing to HC. Comparison of "On stimulation" versus "Off stimulation" conditions showed a significant decrease of cerebral metabolism ($p<0.001$) in the left limbic lobe: cingulate gyrus (BA 24, BA 32), and in the left frontal lobe: medial gyrus (BA 6). Comparison of "responders" versus "non responders" groups showed a significant hypo activation in the "responders" group ($p = 0.05$) in the right orbito-frontal gyrus (BA 10).
Conclusions: STN DBS would have a beneficial impact via circuits connecting subthalamic nucleus and OFC.

FC-36-002
Effects of isolation-rearing on hippocampal cytoskeletal microtubular proteins, synaptic markers and behavioural phenotype in Sprague Dawley and Flinders Sensitive Line rats

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Objectives: The Flinders Sensitive Line (FSL) obtained by selective breeding of Sprague Dawley (SD) has been used as a genetic model of depressive disorders (Overstreet et al., Neurosci. Biobehav. Rev. 2005, 29, 739-759). Growing evidence suggest that neuronal alterations at cytoskeletal microtubules may be involved in the pathogenesis of depressive disorders. This study investigated the effects of isolation on hippocampal microtubular and synaptic proteins in SD and FSL rats.
Methods: Male SD (n=8) and FSL (n=10) rats (post natal day 21-28) were housed in groups or in isolation for 39 days. Animals were exposed to the elevated plus maze (EPM; housing day 35) or the open field (housing day 36) and sacrificed on housing day 39. The hippocampus was dissected for the western blot analyses of acetylated alpha-tubulin (Acet-Tub; microtubule stability marker), tyrosinated/detyrosinated alpha-tubulin ratio (Tyr/Glu-Tub; microtubule dynamics index), synaptophysin (pre-synaptic marker) and spinophillin (dendritic-spines marker).
Results: Grouped SD and FSL showed similar anxiety in the EPM (i.e. time spent in the open arms). However, isolated SD showed increased anxiety compared to grouped SD. In contrast, anxiety was decreased in isolated FSL compared to grouped FSL. Locomotor activity in the open field was lower ($p<0.05$) in FSL compared SD independently from the housing conditions. Moreover, isolated SD showed increased hippocampal Tyr/Glu-Tub ($p<0.01$) and decreased spinophilin ($p<0.05$) compared to group housed SD. Oppositely, Tyr/Glu-Tub and spinophilin were decreased ($p<0.01$) and increased ($p<0.05$), respectively, in isolated compared to grouped FSL. Acet-Tub and synaptophysin were unchanged by isolation in both strains.
Conclusions: Isolation induces anxiety in the EPM and decreased markers of microtubule stabilization and dendritic-spines in the hippocampus of SD rats. However, isolated FSL showed opposite phenomena. These findings show that the effects of early adverse experience on cytoskeletal and synaptic remodelling can be influenced by the rat strain genetic background.

FC-36-003
Psychiatric disorder biomarker discovery – from differential expression to isoforms to pathways

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Objectives: A major problem in the area of psychiatric disorders is the fact that current diagnosis is mainly based on categorizing the signs and symptoms of the syndrome, which limits the ability to reliably identify biological causes and develop specific treatments. The research of the ‚Proteomics and Biomarkers' group is therefore aimed at the identification of biomarkers that can categorize subsets of subjects in a more consistent manner than is presently achievable. This will allow a more precise definition and categorization of mood disorders and in turn facilitate investigations of the pathogenesis of the diseases and enhance our ability for treatment.
Methods: Proteomic technologies promise to be of great value in molecular medicine, particularly in the detection and discovery of disease markers. The proteome is thought to be directly related to the phenotype of an organism and hence protein profiling will result in the most precise understanding of disease mechanisms as well as the molecular effects of drugs.
Results: A particular focus of our research efforts is the use of animal models that represent selected endophenotypes characteristic for the respective clinical phenotype in humans. Classical proteomics approaches have resulted in a limited number of biomarkers in a mouse model for trait anxiety. A more comprehensive and sensitive proteomics platform that is based on metabolic labeling of mouse models with stable isotopes has been used next and has allowed a precise relative protein quantitation by mass spectrometry. In addition, the method has resulted in the characterization of brain protein metabolic activity. In a complementary approach we have analyzed human CSF specimens from patient groups that have been characterized according to their clinical as well as endophenotypes. An antibody array platform was established and allows the stratification of psychiatric patient groups.
Conclusions: Proteomic analysis of mouse models and human specimens combined with pathway analysis of the identified biomarkers aids in disease diagnosis and an improved understanding of disease pathobiology.

FC-36-004
Determination of T-Cell subpopulations in CSF and peripheral blood in patients with affective and schizophrenic spectrum disorders to assess immunosurveillance and to apply as a diagnostic approach

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Objectives: Various research approaches indicate inflammatory mechanisms contribute to the pathogenesis of major psychiatric disorders (MPD). However, the specific nature of the inflammatory abnormalities remains to be elucidated, though providing yet a basis for therapy trials. To investigate lymphocyte activation and T regulatory cells (Tregs) cell surface markers in patients with psychiatric disorders and subgroups of patients with neurological diseases in paired samples of CSF and blood (PB) to detect aberration in immunosurveillance and to use as a differential diagnostic tool.
Methods: CSF and PBMC were collected simultaneously from 45 patients, 17 patients with major psychoses (MPD), 16 with non-inflammatory neurological diseases (NIND), 7 with meningitis (MEN) and 5 with chronic inflammatory diseases (CIND). Peripheral Blood Mononuclear Cells (PBMC) were isolated by Ficoll, CSF-cells were centrifuged. Samples were stained with monoclonal antibodies directed against CD4, CD8, CD25, CD45, CD69, CD127 (BD and Caltag-Invitrogen). Stained cell samples were analysed using BD FACSAria™ cytometer and BD FACSDiva software.
Results: Significant differences ($p<0.05$) were observed in PB for CD4+ cells (MEN: 45.8% versus NIND: 33.06% / CIND: 31.03%); in PB for CD4+CD45RO+ cells (MEN: 24.08% versus CIND:11.12%); in PB for CD4+CD25+ (MEN:0.89% versus CIND: 0.28% / MPD: 0.39%); and in CSF for CD4+CD127dim cells (MEN: 5.15% versus MPD: 10.18%). A significantly higher frequency of CD4+CD25+CD127dim, representing Tregs were observed in PB of MEN (0.25%) versus CIND (0.09%). Cluster analysis revealed 6 out of 17 MPD displaying a ratio of CD4+/CD8+ cells in PB >3.2, but only 2 NIND patients. Another cluster of patients with Tregs in CSF >10% and in PB < 15% included 7/17 MPD versus 2 NIND patients.
Conclusions: In summary, multiparameter FACS analysis of CSF versus PB is feasible and distinct patterns of T cell subsets were identified in both neurological and psychiatric disorders.

FC-36-005
A cytokine model of cognitive function

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Objectives: A formulation of a cytokine model of cognitive function under immunologically unchallenged physiological conditions.
Methods: The proposed cytokine model of cognitive function under unchallenged conditions is based on empirical work by this group investigating the effects of cytokines at the protein and genetic level on cognitive function as well as experimental animal models investigating the effects of TNF in transgenic mice.
Results: In a study among 369 healthy elderly from the general population, we found the chemokine IL-8 to be significantly associated with poor cognitive performance in the memory, attention and motor domains. In a similar study among 369 healthy individuals, genetic variants of IL-1beta were related to poor memory, whereas TNF-alpha was related to better cognitive speed performance. In contrast, genetic variants of IL-6 showed no association with cognitive performance in humans. Animal studies of our group show that the absence of TNF (B.6TNF-/-; N=10) is detrimental of cognitive function during neurodevelopment, while during aging the absence of TNF (B.6TNF-/-; N=10) is related to improved cognitive performance as opposed to wt mice (C57BL/6; N=10). The cytokines IL-1β, IL-6 and TNF-α have effects on complex cognitive processes at the molecular level, such as synaptic plasticity, neurogenesis, as well as neuromodulation.
Conclusions: The findings provide evidence for a cytokine model of cognitive function, which shows that cytokines play an intimate role in the molecular and cellular mechanisms sub-serving learning, memory and cognition under physiological conditions.

FC-36-006
Repetitive Transcranial Magnetic Stimulation (rTMS) in treatment of resistant obsessive-compulsive disorder

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Objectives: To investigate the efficacy and tolerability of repetitive transcranial magnetic stimulation (rTMS) as an adjunctive treatment to medication and cognitive behavioral therapy (CBT) in patients with resistant obsessive-compulsive disorder (OCD).
Methods: 27 outpatients with resistant OCD (defined as a 30% or less reduction in Y-BOCS scores after adequate treatment with 3 or more different serotonin reuptake inhibitors, including clomipramime, and CBT) were maintained in stable treatment regimens for at least 8 weeks, and then submitted to 6 weeks (30 treatment days) of either active or sham rTMS delivered in the right dorsolateral prefrontal cortex. rTMS was applied at 10Hz frequency, 40 trains with 5s duration and 25s interval (2000 pulses/day). All patients were evaluated before, in weeks 2 and 6 during treatment and in weeks 2 and 6 following treatment, with Y-BOCS, clinical global impression (CGI), HAM-A, HAM-D21 and SF-36 (quality of life) scales. The groups were compared using 2-way repeated measures ANOVA.
Results: 23 patients completed the study and all evaluation process. rTMS was safe and well tolerated. Dropouts happened mainly due to lack of improvement and difficulty to attend rTMS or evaluation sessions. Y-BOCS scores decreased significantly in both groups (p=0,026), but no significant difference between groups was observed (p=0,253). The same results applied to CGI scores, with p values of 0,009 and 0,978 respectively. No significant difference in time or between groups was observed in the SF-36 functional capacity domain.
Conclusions: High frequency rTMS applied to the DLPFC as adjunctive treatment in resistant OCD patients was not superior to placebo for reduction of obsessive-compulsive symptoms or improvement in clinical global impression and functional capacity. We consider disease severity in our sample and the involvement of deep brain structures in OCD as mainly responsible for such results. Good safety and tolerability encourage further studies enrolling less severely affected patients.

Poster Presentations

P-01
Addictive Disorders I

P-01-001
Investigation of ventromedial prefrontal cortex associated decision-making skills at the beginning of abstinence in alcohol addicted patients

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Objectives: Recent studies observed impairments of ventromedial prefrontal cortex (VMPFC) associated neurocognitive functions in alcohol addicted patients: when they make a decision, they neglect the long term negative consequences and prefer short term rewards. Although this phenomenon may influence the success of alcohol cessation attempts, small body of data is available about these decision-making skills at the beginning of alcohol withdrawal. In this on-going study this function of VMPFC was examined in relation to the characteristics of alcohol dependence.
Methods: All participants (15 short term abstinent patients-STAP, 26 healthy controls-HC) were scored in the "ABCD" (reward sensitivity) and "EFGH" (punishment sensitivity) versions of the Iowa Gambling Task. The STAP matched for the criteria of alcoholism set by DSM-IV. Furthermore in the group of STAP the following measurements were taken: Addiction Severity Index 1.2., Alcohol Use Disorders Identification Test, and Severity of Alcohol Dependence Questionnaire. All of the patients were hospitalized and assessed in seven days of abstinence.
Results: STAP scored significantly lower on both IGT ABCD ($t=-3,2$, $p<0,01$, $df=39$) and EFGH ($t=-3,8$, $p<0,01$, $df=39$) compared to controls. The pattern of performance was also different: while HC showed improvement already at the first fifth of the task, the STAP stayed at the same level. To measure correlation of variants Spearman correlation was used because of the small sample size. Negative correlation was found between the amount of alcohol intake in the last 30 days and IGT ABCD scores, but results of the cognitive tests were independent from the lifetime alcohol consumption.
Conclusions: Our results support the findings that dysfunction of VMPFC can be observed in alcohol addiction. In addition, at the beginning of the abstinent period the impairment of reward sensitivity is notably influenced by the amount of alcohol intake in the recent past, which may bear consequences regarding alcohol cessation.

P-01-002
Attentional bias associated with cocaine cues: Differences among cocaine dependents, occasional cocaine users and controls

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Objectives: Rationale: Previous research has shown an attentional bias toward drug-related stimuli in cocaine addicts. Cocaine-dependent individuals demonstrate attentional bias when measured by Stroop color-naming tasks that have been modified to include cocaine-related words. However, these cognitive procedures may not represent appropriate measures of attentional allocation. The primary aim of this study was to investigate whether cocaine addicts would differ in their selective attention towards cocaine-related stimuli in comparison with a group of occasional cocaine users and with a control group.
Methods: Attentional bias was assessed using cocaine-related pictures in a dot probe detection task. Picture pairs were visually presented, followed by a dot probe that replaced one of the items. Attentional bias was determined from latencies in responding to the dot probe. Questionnaires were used to examine the relationships among attention, outcome expectancies after cocaine consumption, and personality traits. Higher-order executive function was also measured with cognitive tasks.
Results: Cocaine-dependent subjects showed an attentional bias towards the cocaine-related stimuli when compared to the occasional users ($p<0.05$) and controls ($p<0.001$).
Conclusions: The results support cognitive theories of addictive behaviour in which the ability of drug-related stimuli to capture attention is suggested to play a part in drug dependence, craving and relapse.

P-01-003
Neurofeedback for treating substance use disorders: A review

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Objectives: The aim of the review is to determine the clinical potential capacity of neurofeedback in the treatment of substance use disorders (SUD). Neurofeedback can be seen as a forward-looking adjunctive psychophysiological approach for treating various mental disorders, e.g. hyperkinetic, emotional and addictive disorders. It is a special form of biofeedback enabling individuals to control their neuroelelctrical brain activity. Participants learn (operant conditioning) to produce desirable brain wave patterns by receiving contingent visual, auditory or tactile feedback given simultaneously to the neuroelelctrical activity that indicates a special brain wave frequency. Depending on the protocol and the treated disorder the rewarding feedback is given for producing a particular state of brain activity. The review wants to appraise 1.) whether neurofeedback is effective as an adjunctive treatment for SUD and 2.) to what extent the effects on various SUD are associated with a specific neurofeedback protocol.
Methods: We got the data by electronic literature search (Medline, Web of Science, Cochrane Library databases) supplemented by manual reference checks (important journals, references of most important articles) and included studies conducted between 1970 and 2008.
Results: The meta-analysis shows that patients treated with neurofeedback (in addition to traditional psychotherapy) show higher abstinence rates than those who only received traditional addiction therapy. Furthermore, the treatment was found to lead to sustained prevention of relapse and marked reductions in comorbid symptoms.
Conclusions: Neurofeedback is a promising adjunctive psychophysiological approach which consistently provides positive outcomes and effects regarding different measures. Moreover, up to now no adverse effects could be found. Limitations and future research questions are discussed.

P-01-004
Experience of Gabapentin (Tebantin®) application for treatment of alcohol cancellation in intact condition

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Objectives: Study of Gabapentin (Tebantin®) medical effects in intermediate symptom and syndrome structure during intact condition of alcohol cancellation.
Methods: Observation of 73 patients with intact condition of alcohol cancellation, taking medical treatment in Republican Narcology Centre under Public Health Ministry, detoxification department, Bishkek city. Observation was conduced by means of ICD 10 indication, CIWA-ar enquirer and original semi-formalized interview.
Results: Creation of alcohol cancellation syndrome structure typology, which includes condition severity, presence or absence of complications, as well as domination in clinical presentation of such blocks as self-vegetative and affective disorder, obsessive-compulsive alcohol attraction, disorder of consciousness and perceptual disorder. The research exposed that Gabapentin could be effectively used for mono-therapy in case of affective disorder (15.34 ± 4.94, $p<0.05$) and obsessive-compulsive alcohol attraction (12.51 ± 5.10, $p<0.05$) dominancy. In other cases it could be mixed with benzodiazepine and antipsychotic drugs (13.05 ± 3.84, $p<0.05$).
Conclusions: Suggested research has pilot character. Obtained results are ambiguous. Attempt to consolidate phenomenological and biological approaches could lead to unexpected and often positive results, particularly indication extension of already known drugs.

P-01-005

Inhibition of anandamide hydrolysis reduces reinstatement of nicotine seeking but not motivation for nicotine – Comparison with CB1 receptor blockade

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Objectives: The endocannabinoid system has been recently identified as having critical involvement in drug taking and relapse phenomenon for various drugs of abuse, and notably nicotine. The endocannabinoid system consists of endocannabinoids (such as anandamide), their target receptors (mostly cannabinoid CB1 receptors) and the enzymes that degrade those endocannabinoids (fatty-acid-amide-hydrolase (FAAH) for anandamide). The objective of the study is to explore the effect of inhibiting FAAH enzyme by URB597 on motivation for nicotine (nicotine self-administration under a progressive ratio schedule) and reinstatement of nicotine seeking; in comparison with the effect of the CB1 antagonist Rimonabant.
Methods: After the acquisition of the nicotine (0.03 mg/kg/injection) self-administration in Long-Evans rats in progressive ratio (PR) schedule of reinforcement, the rats have been tested for the effect of acute or repeated (3 consecutive sessions) administration of Rimonabant (0.3-3 mg/kg) or URB597 (0.1-1 mg/kg) on the breaking point for nicotine. After this testing, the rats have been submitted to extinction sessions and the effect of URB597 and Rimonabant has been compared on cue- and nicotine (0.15 mg/kg, s.c.)-induced reinstatement of nicotine seeking.
Results: Rimonabant, but not URB597, dose-dependently reduced the breaking point for nicotine, an effect that was stable over repeated administrations. Rimonabant and URB597 significantly decreased the reinstatement of nicotine seeking induced either by presentation of nicotine-associated stimuli or by nicotine priming.
Conclusions: These results indicate that the integrity of the CB1 receptors is necessary for the rats to exhibit motivation for nicotine and that FAAH inhibition may be as effective as CB1 receptor blockade to prevent reinstatement of nicotine seeking. Due to its potential antidepressant and anxiolytic properties, it appears likely that URB597 may be better tolerated than Rimonabant to prevent relapse for tobacco smoking.

P-01-007

Tobacco smoking and motivation to quit in psychiatric patients

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Objectives: Find the prevalence of tobacco smoking, nicotine dependence and motivation to quit smoking in a sample of psychiatric outpatients.
Methods: Cross sectional study. A questionnaire was randomly distributed to a total of 210 patients of two outpatient psychiatric units in a suburban area of Lisbon, Portugal, between November 2008 and January 2009. Nicotine Dependence was measured using Fagerström Test. Motivation to stop smoking was measured using Richmond Questionnaire.
Results: Most of the patients in the sample are women, have a partner, live with family, are employed and have a mood disorder. Mean age 49.4 years old. 26% smoke. Higher smoking prevalence is found in patients with schizophrenia and other psychotic disorders, although it isn't statistically significant. Most of the patients have moderate (54%) / high (24%) nicotine dependence and 81% have low motivation to quit smoking.
Conclusions: Tobacco smoking prevalence is similar in a sample of psychiatric outpatients and the general portuguese population. High prevalence of moderate/high nicotine dependence suggests the need for pharmacological and cognitive behavioural approaches. Low motivation to quit smoking reinforces the need to encourage patients to seek smoking cessation programs - psychiatrists and other mental health professionals should do that and such programs should be implemented in psychiatric facilities.

P-01-008

Cocaine induced psychotic symptoms in a French sample of cocaine addicts

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Objectives: Background:Cocaine use has been described to induced psychotic symptoms (Post 1975). These symptoms are associated with aggression and disruptive behaviours. **Objectives:** To assess the frequency of cocaine-induced psychosis in a sample of 90 French cocaine users (mostly crack smokers) and to test the effect of plausible risk factors.
Methods: We translated the CIP, a questionnaire evaluating cocaine induced psychosis, derived from the SADS inventory, into French. We administrated this questionnaire in 90 cocaine users along with a structured clinical interview. Plausible risk factors (sex, cocaine dose, type of cocaine (chlorhydrate, crack) and route of administration (inhaled or smoked versus IV injection)) were recorded. Statistical analysis: Frequency of cocaine-induced psychotic symptoms (hallucinations, paranoid ideation, delusions) is described with a 0-5 score for each item, and with a total score. The correlations of age and dose with the total score were tested with spearman's correlation. The effects of sex, type of cocaine, and route of administration on the mean of CIP total score were tested with one-way ANOVAs.
Results: The sample was composed of 90 subjects, (among which 76% were men). The mean age was 38± 8 years old [19-68]. At least one psychotic symptom was found in 85% of the sample. The mean of the CIP total score was 10.5 ± 10 points [0-51]. There was no association between the tested factors (age, dose, sex, type of cocaine used and the CIP total score except for a significant effect of IV route (20 ± 13 versus 8 ± 8, ANOVA : $F(1df) = 22$, $p < .001$). This result is discussed.
Conclusions: References: 1. Cubells JF, Feinn R, Pearson D, et al. Rating the severity and character of transient cocaine-induced delusions and hallucinations with a new instrument, the Scale for Assessment of Positive Symptoms for Cocaine-Induced Psychosis (SAPS-CIP). Drug Alcohol Depend. 2005; 80(1):23-33. 2. Post RM. Cocaine psychoses: a continuum model. Am J Psychiatry. 1975;132(3):225-31.

P-01-009

Assessment of denial and insight in patients with nicotine and alcohol dependence

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Objectives: Denial and poor insight are common in addictive disorder. They may prevent patients from using care facilities or be the cause of early drop-out from treatments. However, few studies have been conducted on the subject. This is why we decided to measure these dimensions.
Methods: We adapted the Insight Q8 (Bourgeois, 2002) a questionnaire assessing insight in schizophrenia, and the Denial Rating Scale (Goldsmith & Green, 1988) assessing denial in alcoholic patients to measure insight and denial of various addictions. The effect of the drug (cannabis, tobacco) on Insight and Denial scores was tested with an ANOVA. Setting: Sixty patients in an outpatient addiction clinic were recruited.
Results: The feasibility and internal consistency of Insight and Denial questionnaires are presented. The correlation of both measurements is tested and discussed, as well as a drug effect.
Conclusions: References: - Bourgeois, M.L. (2002). Validation de l'échelle d'insight Q8 et évaluation de la conscience de la maladie chez 121 patients hospitalisés en psychiatrie. Annales Médico Psychologiques, 160, 512-517. - Goldsmith, R.J., Green, B.L. (1988). A rating scale for alcoholic denial. Journal of Nervous and Mental Disease, 176 (10), 614-620.

ADDICTIVE DISORDERS - Poster Presentations

P-01-010
Adaptation of the MOPS (Measurement of Parental Styles) in French: Preliminary results in drug dependant outpatients

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Objectives: Dysfunctional parenting seem to dispose people to the development of psychiatric disorder as well as to the development of addictions. Nevertheless, it is not easily evaluated with standardized questionnaires in clinical setting. This is why we decided to adapt in French a measure of dysfunctional parenting (Parker, 1997).
Methods: This questionnaire is composed of three sub-scales measuring for each parent: indifference, over-control and abuse. The MOPS is based on refined PBI (Parental Bonding Instrument). Setting: Sixty outpatients of an addiction clinic were recruited.
Results: Preliminary results regarding parental style, as well as the scores on the three dimensions (indifference, over-control and abuse) are described. Reliability and construct validity of this questionnaire are discussed. The links between dysfunctional parenting and age of first use of illicit drug are tested with one-way ANOVA. The MOPS passation was feasible in addicted patients.
Conclusions: Reference: Parker, G., Roussos, J., Hadzi-Pavlovic, D., Mitchell, P., Wilhelm, K., & Austin, M.-P. (1997). The development of a refined measure of dysfunctional parenting and assessment of its relevance in patients with affective disorders. Psychological Medicine, 27, 1193-1203..

P-01-011
Alcohol use end anxious depressive disorders

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P-01-012
Differential characteristics between substance – induced and primary psychotic disorders

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Objectives: To describe differential characteristics between PP (primary psychotic disorders) and SIP (substance-induced psychotic disorders) in a dual diagnosis unit.
Methods: - We studied the psychotic patients admitted into a dual diagnosis unit by collecting sociedemographical and clinical characteristics. - Psychiatric disorders were diagnosed according DSM-IV criteria using the Spanish version of PRISM. - Descriptive statistics were Fisher's exact test for categorical variables and Mann-Whitney U test for scaled variables. Statistical significance was established at 0.05 level.
Results: - We show results of 120 patients that were admitted with psychosis and substance use disorders. Most of the patients were males (78,3%); mean age 36,7+10). Patients were grouped into two categories based on whether they had substance induced psychotic symptoms or not according with DSM-IV criteria: 98 cases were diagnosed as PP amb 22 as SIP. - Most prevalent co-occurrent diagnoses were psychotic disorders-cocaine use disorders (35%). - We found some significant differences referring SIP versus PP: younger age (years: mean [s.d]) (32,7 + 8,2 vs. 37,6 +10,1), shorter length of admission (days: mean [s.d]) (16,2 + 9,1 vs. 24,3 + 16,4), increased employment rates (42,9% vs. 10,4%), main drug of abuse: cocaine (50% vs. 35,1%), amphetamines and related drugs (13,6% vs. 3,1%), cannabis (27,3% vs. 10,3%), alcohol (4,5% vs. 39,2%) and methadone (0% vs. 5,2%); grouping this variable in psychostimulant or sedative we observed a significant primacy of the former group in SIP cases. - A diferential trend in admittance clinical presentation was observed: hallucinations/delusions (55,1% vs. 86,4%), conductual impairment (9% vs, 29,6%) and suicide ideation (0% vs. 9,2%).
Conclusions: - SIP were younger and showed earlier clinical improvement and increased employment rates than PP. - Psychostimulant profile drugs (mainly cocaine, amphetamines and related drugs) were more prevalent in SIP.

P-01-013
A flow-cytometric and electron – microscopic study of the combined effect of human immunodeficiency virus (HIV)-1 Tat and methamphetamine on the human neuroblastoma cell line SH-SY5Y

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Objectives: Tat (transactivator of transcription) protein is crucial to HIV-1 for its replication. In addition, Tat is toxic when released from infected cells: Tat may interact with neuronal surface receptors, leading to calcium influx, oxidative stress and eventually cell death. Tat may also induce glial cells to release factors that are detrimental to neurons. Methamphetamine (MA) reverses the reuptake of dopamine (DA) by DA neurons and disrupts the vesicular storage of DA; oxidation of the accumulating cytosolic DA causes an increase in reactive oxygen species. Recent publications suggest that Tat and MA when administered together result in greater neuronal damage than when administered separately, and it has been suggested that they act through the glial cells (astrocytes or microglia or both) to produce such a synergistic effect. It is not clear whether Tat and MA have a direct synergistic effect on neurons. In addition, the cellular events of the combined Tat-MA effect have not been morphologically characterised. We therefore have carried out an in vitro study on these problems, using SH-SY5Y, a neuroblastoma cell line which is known to display morphological, biochemical and electrophysiological properties of dopaminergic neuron.
Methods: SH-SY5Y cells were incubated with medium only (control), Tat (50 ng/ml), MA (500 μM), or Tat+MA for 18 to 24 hours, and then used for flow cytometry or processed for electron microscopy.
Results: Flow-cytometric data showed apoptosis following Tat+MA and MA treatments, but not Tat treatment, and it was more extensive with Tat+MA treatment. Electron-microscopic observation showed vacuolation which was most pronounced with Tat+MA treatment, less so with MA treatment, and was infrequent with Tat treatment. Autophagia was observed (18 hr) preceding cell death (24 hr), which was observed in the Tat+MA treatment.
Conclusions: These results demonstrate morphologically the synergistic action of Tat and MA, and confirmed that these molecules induce apoptosis.

P-01-014
Drug addiction among schizophrenic inpatients

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Objectives: to study the impact of addictives behaviours on schizophrenic disorders
Methods: It is about a retrospective study recuperating a period of five years. Included were all schizophrenic patients having among their antecedents or presented in their admission an abuse or a dependency to a substance (DSM IV-Trcriteria). Patients with tobacco addiction, intoxication in a substance and the presence of a cerebral organic pathology or of a marked mental deficiency were exluded.
Results: 59 patients have been assembled, that is 16,43 % of the group of schizophrenic patients hospitalised during the period of study. Results allowed to reveal an average of age of 31,5 years, an exclusively male sex, a marital status of a single man in 84,7 % cases, a 66,1 % unemployment rate and a presence of antecedents of suicide attempts and of criminal records respectively to 23,7 and 33,9 % patients. Dependency was estimated at 37,3 %. The most consumed product was alcohol (69 %) and poly-intoxication was noted in 34,5 % cases. The average age at the beginning of the disturbance linked to the use of a substance was 21,2 years old. Schizophrenia of undifferentiated type was most represented (61 %) with an average of age at the beginning of the disturbance estimated at 24 years. The addiction preceded the appearance of schizophrenia in 74,6 % and simultaneously in 13,6 % cases.

Conclusions: Even if the existence of a direct causal relation between comorbid addiction and worsening of the prognosis of schizophrenia is not definitely established, the highlighting of such association shows the need to a specific and precocious health care of addictives comorbid behaviours.

P-01-015
Personality characters as a predictor of tendency to addiction

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Objectives: The aim of this research is to test this question that are there especific personality characters that lead to addiction?
Methods: 153 addicted people and 153 nonaddicted people were randomly selected and MoKioly´s Characterlogy Inventory (MCI) was administered on them. The inventory assess personality based on eight characters: sanguine, indifferent, nervous, indolent, indignant, passionate, sentimentee, amorphous.
Results: Findings showed addicted people are much more indifferent, sanguine and passionate than nonaddicted people.
Conclusions: In regard to people with these characters are much more at risk, they should be trained with special plans and be cared so that tendency to addiction in them decrease or control.

P-01-016
The role of the relationship between therapist and patient in an individual outpatient program for drug addiction treatment by the administration of naltrexone

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Objectives: We will present how the development of a positive relationship between therapist and patient (therapeutic alliance) influences the effectiveness of a treatment program with naltrexone for heroin users.
Methods: The Counseling Center provides a program of naltrexone administration to heroin users in an individual outpatient drug counseling program. The users selected for this program are particularly motivated to abstain from drug use, and have an efficiently supportive environment, since supervision of naltrexone administration is necessary. The administration has to be continued for at least four months after detoxification, although in many cases administration is necessary for a much longer period, usually for a year (Tai & Blane, 1997). The user attends an individual psychotherapeutic program twice a week, while counseling services are provided to the family.
Results: The therapeutic alliance is one of the most important factors for the user's retention, and for a successful therapeutic outcome (Conners et al, 1997). It reduces relapse probability, and gives therapist the possibility to handle relapse as an opportunity for a new negotiation of the therapeutic process and its objectives. Finally, it enables therapist to intervene in the family, for a successful naltrexone administration. A productive relationship includes appropriate emotional response from the therapist to the patient needs, with parallel avoidance of emotional involvement. This presupposes therapist's familiarization with the problem of dependence, and also specialization in working with drug users and dealing with negative behaviors of psychopathetic type which are related to addiction (Washton and Stone-Washton, 1990). The sincere interest for the user and his problems will help therapeutic alliance be consolidated.
Conclusions: The quality of the therapeutic alliance is one of the most important factors for successful therapy because the sincerity which is secured through it, protects user from therapy interruption, parallel drug use, and allows better supervision of administration.

P-01-017
Effects of microwave resonance therapy on oxidative modification of proteins and lipids of blood plasma and erythrocyte in alcoholism

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Objectives: Positive effect of microwave resonance therapy (MRT) in withdrawal syndrome is well-known. Improvement of clinical parameters is usually accompanied by metabolic changes, particularly by changes of parameters characterizing patient's oxidative status. MRT effect on oxidative modifications of alcoholics' proteins and lipids has not been studied. Purpose of the work is to study MRT effects on content of lipid peroxidation products (LPP) and protein carbonyls in blood plasma and erythrocytes in alcoholism.
Methods: Blood plasma and erythrocytes were obtained from: 30 adult male alcoholic patients before and after MRT course (7 sessions) (basic group), 16 adult male alcoholic patients before and after 7 days of traditional detoxicating therapy (comparison group) and 15 adult male donors in normal health (control group). All of the alcoholic patients in the study had abstained from alcohol consumption for between 1 to 5 days before investigation.
Results: It is revealed that protein carbonyls and LPP of both blood plasma and erythrocytes are increased in alcoholism, which is evidence of oxidative stress. Reliable decrease of protein carbonyls of erythrocytes and blood plasma is revealed in basic group after MRT influence on acupuncture point AT55 (power < 3MW/cm2, frequency 59-61 Hz, session time 30 minutes every 24 hours). At that, protein carbonyls content in erythrocytes becomes equal to control parameter, whilst blood plasma carbonyls content remains higher than control. Reliable decrease of the same parameter was not detected in comparison group. LPP range of blood plasma decreases both in basic and comparison groups. LPP range of erythrocytes decreases in basic group, whilst in comparison group decrease is not reliable.
Conclusions: Thus, MRT alleviates withdrawal alcoholics' oxidative stress symptoms, its effect on erythrocytes is more distinct than on blood plasma.

P-01-018
Factors associated with relapse of drug addiction among males in Selangor, Malaysia

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Objectives: to determine factors associated with relapse of drug addiction among males in Selangor, Malaysia.
Methods: This was a case control study, conducted from June 2005 till February 2007 at all public Drug Rehabilitation Centres (DRC) for cases and the National Agency of Anti Narcotic (NAAN) for controls in Selangor. When a drug addict was caught by the authority for the first time, he was sent to the public DRC. Upon discharge, he would be follow-up by NAAN. In the case of relapse, the drug addiction would be sent again to the DRC. Those without relapse would be continued under the supervision of NAAN for two years. The total sample size was 174 subjects. The study population was male subjects with history of drug addiction. The dependant variable was relapse of drug addiction. Relapse was defined as having past history of drug addiction which was recorded by NAAN. Cases were defined as all new relapse cases or first time relapse. Controls were defined as all male cases with no history of relapse and on more than 6 months follow up by NAAN after being released from a public DRC. The independent variables were (1)sociodemographic characteristics (2) pattern of drug use (3) severity rating of major risks variables which include family/social relationship, employment/support status, pattern of drug use, psychiatric status, medical status and legal status. Modified Addiction Severity Index (ASI) was used to assess information regarding the nature and severity of respondent's problems.
Results: The significant independence risk factors were age OR 9.3 (95%CI 3.5, 24.9), criminal activity OR15.3 (95%CI 6.3, 37.5), employment / support status severity OR 2.7 (95%CI 1.1, 6.8) and pattern of drug use severity OR 23.9 (95%CI 8.2, 69.9).

Conclusions: This study had identified risk factors that contribute to relapse of drug addiction.

P-01-019
Event-related potential subsequent memory effect dysfunction in chronic cannabis users

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Objectives: The aim of the study was to investigate the subsequent memory effect (SME) in a group of chronic heavy cannabis users via recording of event related brain potentials (ERPs) during encoding of words. Characterised by a 400ms post-stimulus negative electrical component followed by a late developing positive wave, the SME is predictive of later word recall and is believed to originate in brain structures sensitive to interference from acute exposure to exogenous cannabinoids (eg. hippocampus and parahippocampus). Given the persistence of cannabinoids within fatty tissue, effects of residues, as well as potential cumulative effects of chronic exposure, may be reflected in the time course and/or voltage changes of the SME. The extent to which cannabis users might engage compensatory processes in response to impairment was also explored.
Methods: A verbal memory task compared performance between 24 cannabis users (mean 17 years of near daily use) and 24 non-using controls. The task involved the presentation of ten categorised word lists, each with a short delay recall. ERPs were recorded at word presentation (during encoding) and later grouped by recall outcome (success/failure).
Results: Cannabis users showed poorer recall performance and altered patterns of SME brain activation ($p<.05$). Specifically, a decrease in the negative component and an increase in the late positive wave were observed for the cannabis group. Characteristics of cannabis use history, including duration of use and age of initial use, correlated significantly with SME component amplitudes.
Conclusions: The results indicate chronic users of cannabis to have altered brain activation relative to non-using controls, that may be indicative of dysfunctional SME production and/or compensatory brain activation, and is associated with poorer recall. A longer history of use and onset of use at an earlier age were related to greater disruption, suggesting implications for age-related cognitive development and decline.

P-01-020
Visuospatial memory deficits, subclinical psychotic symptoms and structural brain changes in long term heavy cannabis users

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Objectives: Visuospatial memory has been less well studied than verbal memory in chronic cannabis users. We recently found reduced hippocampal and amygdala volumes in long term heavy cannabis users to be associated with subclinical psychotic symptoms. This study assessed visuospatial memory in relation to symptoms and neural substrates.
Methods: 100 healthy participants (51 cannabis users, 49 non-user controls) completed five tests of visuospatial memory function from the Cambridge Neuropsychological Test Automated Battery (CANTAB): Pattern Recognition Memory (PRM), Spatial Recognition Memory (SRM), Spatial Span (SSP), Spatial Working Memory (SWM) and visuospatial Paired Associate Learning (PAL). Groups were matched on demographic characteristics with minimal other substance use. Subthreshold psychotic symptoms were assessed using the Scales for the Assessment of Positive and Negative Symptoms (SAPS and SANS) and the Brief Symptom Inventory. 15 users and 16 controls also underwent detailed anatomical brain scans.
Results: Cannabis users' performance was significantly worse than controls on most visuospatial memory outcome measures ($p<0.05$). Duration of cannabis use correlated with PRM latency ($p<0.007$), SWM errors ($p<0.05$) and PAL errors ($p<0.01$). Quantity of cannabis used per month correlated with SRM latency ($p<0.05$). In cannabis users only SSP errors correlated positively with SAPS scores ($p<0.03$) and reduced hippocampal volume. Volumetric measures of the orbitofrontal and anterior cingulate cortices mostly did not differ between groups, yet associations were observed between poor memory indices and smaller subregional volumes in cannabis users, which also correlated with various cannabis use parameters.
Conclusions: Long-term heavy cannabis use is associated with poor visuospatial memory and subclinical psychotic symptoms. These functional indices are related to volumetric measures of hippocampal, orbitofrontal and anterior cingulate cortices. The results suggest complex relationships between cumulative exposure to cannabis, the subsequent development of memory deficits and subclinical psychotic symptoms, and structural changes in the brain.

P-01-021
The effect of 3,4-Methylendioxymetamphetamine (MDMA) on proliferation and survival of neurons in hippocampus in adult rats

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Objectives: New generated cells can be imunohistochemically stained against the mitotic marker Ki-67 or by bromodeoxyuridin (BrdU). BrdU is a thymidine analog, which is incorporated into the DNA during cell division. Many factors as stress, physical exertion, learning and pharmacs have influence on adult neurogenesis. Neurogenesis is important to provide neuroadaptation on varied endogen and exogen conditions. It was repeatly noticed, that application of psychoactive drugs as alcohol or morfin decrease proliferation and survival of newly generated nerve cells.
Methods: In our study, we monitor the effect of weekly aplication of MDMA (5 mg/kg 2x day) or 0.9 % saline on birth and survival of newly generated neurons in the dentate gyrus of rats. MDMA was apply (5 mg/kg 2x day after 8h, s.c.) to Wistar rats (250-300 g). BrdU (50 mg/kg i.p.) was apply 1x day same as MDMA. Quantity of BrdU (1:100, Santa Cruz) and Ki-67 (1:100 Santa Cruz) positive cells was observe 9 days after end of application. We used antibody against neuronal factor NeuN (1:500 Chemicon) to identify neurons.
Results: Semi-quantification of BrdU and Ki-67 positive cells in dentate gyrus determined, that the application of MDMA did not modify quantity of BrdU and Ki-67 positive cells to the control groups.
Conclusions: Our results shows, that administration of MDMA did not influence the proliferation as well as survival of new neurons in rat hippocampus.

P-12
Addictive Disorders II

P-12-001
Smoking is associated with psychosis

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Objectives: Association between smoking and particular symptoms in people with mental disorders is a conflicting issue. A reliable evaluation of smoking based on biological measures may be a key element required to respond appropriately to that objective.
Methods: Nicotine extraction from cigarettes was measured in 492 consecutively hospitalized psychiatric patients with various diagnoses. A nicotine extraction index (urinary cotinine/creatinine ratio referred to the number of cigarettes smoked per day) was calculated for each patient. All patients were evaluated with the Brief Psychiatric Rating Scale (18 items).

Results: For all patients, a positive correlation was found between the nicotine extraction index and two major symptoms of psychosis, "grandiosity" and "unusual thought content." For patients with diagnoses other than schizophrenia, the nicotine extraction index correlated positively with six symptoms: "somatic concern", "grandiosity", "hostility", "hallucinatory behavior", "unusual thought content" and "excitement." Patients with schizophrenia also extracted significantly more nicotine from cigarettes than patients with mood disorder and drinkers with problems. Patients with the paranoid form of schizophrenia extracted almost 3 times more nicotine from their cigarettes than patients with diagnoses other than schizophrenia, but the difference did not reach statistical significance.
Conclusions: Smoking is associated with psychosis. This may have implications for the treatment of smokers who wish to quit.

P-12-002
Concurrent disorders: Substance use disorders, eating disorders, and post-traumatic stress disorders

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Objectives: There is a high commorbidity of substance use disorders (SUDs) with eating disorders (ED). This communication presents a recent study that investigated the prevalence of post-traumatic stress disorder (PTSD) in treatment seekers for concurrent substance use and eating disorders and associated concerns.
Methods: 110 individuals with concurrent SUD and ED responded to a structured interview and standardized questionnaires. Data were analyses with frequency analyses: to assess prevalence rates on variables of interest; analyses of variance: to identify group differences on SUD, PTSD, ED; and Scheffe: to identify individual mean differences among groups.
Results: Results suggested that 58.2% of sample met DSM-IV criteria for PTSD at time of assessment. Individuals with concurrent SUD, ED, and PTSD experienced more alcohol and opioid induced psychiatric disorders, had a higher prevalence of panic disorder with agoraphobia, and paranoid personality disorder, reported more opiate use ($p<.002$), more problems related to alcohol ($p<.003$), less confidence in resisting substances ($p<.005$), a higher incidence of binge eating when upset ($p<.007$), eating moderately in front of others and stuffing themselves in secret ($p<.003$); and they were less able to describe their feelings to others ($p<.041$) than their counterparts without PTSD.
Conclusions: Concurrent PTSD, ED, and SUD can be negatively associated with a patient's ability to cope with substance-related difficulties. These patients may require intensified attention from therapists to their problems with the use of substances. Cognitive restructuring, exposure and relapse prevention strategies may help clients manage their symptoms enabling them to focus treatment. Assessment and treatment issues will be discussed

P-12-004
Influence of acute hemoexfusion on severity and length of withdrawal syndrome in heroin addiction

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Objectives: To reveal influence of acute hemoexfusion on activity of HPAS and on behavioral reactions in rats in period of development of withdrawal syndrome in heroin addiction.
Methods: Investigation was conducted on pedigreeless mature male rats. Drug dependence and withdrawal syndrome formed with method of daily intraperitonial injections of 1% solution of heroin, with gradual heightening dose for 20 days. Severity of withdrawal syndrome was assessed in 24 hours after last heroin injection. In course of investigation we assessed behavioral reactions, identified level of corticotrophin releasing factor (CRF), adrenocorticotropic hormone (ACTH), cortisol and b-endorphin in rats after initial introduction of heroin in period of development of withdrawal syndrome and after conducting of the acute hemoexfusion. Acute hemoexfusion was created with amputation of tip of tail. Exfusion of blood constituted 15% of total blood volume.
Results: Period of formation and manifestation of withdrawal syndrome was characterized by alteration of behavioral reactions of animals. During initial introduction of heroin we observed increase of level of activity of CRF, ACTH, cortisol and b-endorphin. Systematic introduction of heroin was accompanied by gradual decrease of level of activity of CRF, ACTH, cortisol and b-endorphin. In period of withdrawal syndrome development, we observed abrupt increase of level of activity of HPAS and moderate increase of level of activity of b-endorphin. Conducting of acute hemoexfusion during withdrawal syndrome resulted in significant decrease of severity and length of abstinent syndrome and normalized level of activity of HPAS and b-endorphin.
Conclusions: Thus, conducted investigation shows that acute hemoexfusion in period of withdrawal syndrome development in heroin addiction results in decrease of severity and length of this syndrome and normalization of level of activity of HPAS and b-endorphin.

P-12-005
Cigarettes smoking, lipid profile and paraoxonase 1 activity

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Objectives: this study aims to examine the effect of cigarettes smoking on lipid profile and paraoxonase (PON1) activity in a healthy population.
Methods: Our study included 200 subjects among which 98 non-smokers aged 38.47 ± 21.91 years and 102 smokers aged 35.55 ±16.03 years, classified as mild (≤10 cigarettes/ day), moderate (11–20 cigarettes/day) and heavy (>20 cigarettes/day). Triglycerides, total cholesterol, c-HDL, c-LDL and PON1 activity were determined by enzymatic colorimetric method; ApoA1, ApoB, Lp(a) were determined by immunoturbidimetry on Konélab 30™. Statistical analysis was performed using SPSS version 11.0
Results: We noted a significant increase in smokers compared to non smokers, in TG (1.79 ± 1.03 Vs 1.40 ± 1.24 mmol/L), CT (4.13 ± 118 Vs 3.70 ± 1.04 mmol/L), c-LDL (1.35 ± 0.56 Vs 1.16 ± 0.61 mmol/L), Lp (a) (230 ± 226 Vs 179 ± 190 UI/L) and ApoB/ApoA1 (0.83 ± 0.52 Vs 0.52 ± 0.15) and significant decrease in c-HDL (0.94 ± 0.25 Vs 1.07 ± 0.27 mmol/L). TG values were higher in heavy than mild smokers (2.30 ± 0. 96 Vs 1.63 ± 1.11 mmol/L) and c-HDL levels decreased particularly in heavy smokers. We noted a significant decrease of PON1 activity in smokers compared to non smokers (94 ± 104 Vs 158 ± 133 IU/L, $p = 1.17$ 10-4). In smokers we found a significant correlation between PON1 activity and c-HDL concentration ($r = 0.172$; $p < 10$-14).
Conclusions: Cigarette smoking is associated with perturbations in lipid profile, especially low levels of c-HDL, high levels of TG, and significant decrease of PON1 activity correlated with decrease of c-HDL which can explain the atherosclerosis risk.

P-12-006
Psychopharmacotherapy of pathological gambling comorbid with affective disorder

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Objectives: The aim of this research is to evaluate current psychiatric comorbidity in gamblers and estimate safety and efficacy of psychopharmacotherapy.
Methods: Sample contained 157 pathological gamblers. Comorbid affective disorder was shown in 97 cases (44 with bipolar disorder, 24 with cyclothymia, 16 with hypomania and 12 with major depression). Selective serotonin-reuptake inhibitors (Fluoxetine 40 mg a day, Sertraline 50 mg a day) make the first-line treatment of PD. Clinical experience has shown that they are more effective than noradrenalin-reuptake inhibitors or tricyclic antidepressants. Antipsychotics, especially butyrophenones (Haloperidol 1-3 mg a day, Trifluperidol 0.5-2 mg a day), have been shown effective in PD patients with compulsive characteristics or refractoriness to other treatments. Mood stabilizers (Carbamazepine to 1200 mg) seem to reduce mostly autonomous overreactions to stress.

Results: For 12 months in our patients by 56% frequency of episodes of game activity has decreased, and 32 from them in general have ceased to game. In 72 persons affective background was stabilized. Other groups of medications, such as serotonin agonists and antagonists, new antidepressants, dual inhibitors of serotonin- and noradrenalin-reuptake, valproats, and opiate antagonists are also sometimes used in PD treatment. However, as shown in our clinical experience, most clinical studies performed to date investigate effectiveness of different psychopharmacological agents in therapy of PD have serious limitations in terms of small sample size, lack of blinding and randomization, and small effect size.
Conclusions: More rigorously designed, comparative studies are needed to identify usefulness, efficacy, tolerability, and safety of particular psychopharmaceutical agents in treatment of this therapeutically and functionally challenging disorder.

P-12-007
Assessing the psychometric properties of the 6th Brazilian version of the Addiction Severity Index (ASI 6): Family-social area

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Objectives: There is a strong association between family/social problems and substance abuse. Considering the need for a standardized instrument, available in Brazilian Portuguese, to evaluate patients with alcohol and other drugs related problems, this study aimed assessing the psychometric properties of the "family/social" area of the sixth version of the Addiction Severity Index (ASI6). This work is part of the validation study of the ASI 6.
Methods: A cross sectional study was conducted in which 740 patients under treatment at specialized centers were evaluated. In order to assess the dimensions evaluated by each subscale of the Family/Social area of the ASI (family relationship, violence, children's custody) we carried out a factorial analysis. The Test-retest reliability (N=50) and Inter-rater reliability evaluated the stability of the instrument.
Results: In the subscale of family relationship, we identified 4 factors related to severity scores, family support, relationship problems and aggressiveness of partner. In the subscale of family relationship, we detected 4 factors related to severity scores, family support, relationship problems and aggressiveness of partner. In the subscale of violence, we detected 4 factors related to severity scores, life endangerment, aggression to himself/herself and to others. The subscale of children custody presented 3 factors, related to problems in the contact with children, legal and behavioral problems. We found good correlations in the inter-rater reliability (r=0.71-problems) and test-retest reliability (r=0.79 - support).
Conclusions: The family/social area of the ASI 6 presented good psychometric properties, showing good stability and well-defined dimensions. Therefore, it is useful in the evaluation of drug users.

P-12-008
Common pathogenetic mechanisms of alcoholic and food addiction

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Objectives: Constitutional-biological and social factors participate in addictive behavior and dependent states, but just neuro-physiological peculiarities determine the type of reaction on irritation and rate of fixation of certain behavioral stereotypes. We suggest that common mechanisms are background of addictive disorders.
Methods: We tested twenty people alcoholic addicts, twenty people food addicts and twenty people control group. The neurophysiologic tests (definition of functional asymmetry of a brain, its visually-spatial opportunities, and estimation of the right and left hemispheres participation in speech functions, reproduction of the specific speech information and definition of inversion) have been lead.
Results: The right hemisphere is active at addicts. It is expressed in good reproduction the emotional words, directed to the left ear, and infringement of carry emotional information from the right to the left hemisphere. It leads to inversion of normal interrelations of hemispheres which are peculiar in healthy persons and to formation of the excitation center in the right hemisphere. This center starts to dominate and suppresses other inclinations. The person concentrates on the alcoholic or food experiences. The existential organization of mental activity of addicts does not give into the likelihood forecast, does not install relationships of cause and effect and provides greater freedom in manipulation of information and in this connection requires smaller physiological expenses. An addict is peculiar inversion of emotional reflection.
Conclusions: addiction is such property of the person which is caused neurophysiology by the mechanisms connected with domination of the right hemisphere on a background of deficiency of function of the left hemisphere. Thus, there is an infringement of the coordinated activity of hemispheres and carry of emotional information.

P-12-009
Naltrexone for the treatment of amphetamine dependence: A randomized placebo controlled trial

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Objectives: To investigate the effect of treatment with naltrexone for amphetamine dependence, in particular the efficacy of naltrexone in comparison to placebo in increasing weeks of abstinence in amphetamine dependent patients.
Methods: Randomised double-blind placebo-controlled 12 week trial. Patients visited the clinic twice weekly to receive medication and relapse prevention therapy. Urine samples were submitted twice weekly for analysis, to detect illicit drug use. Study was conducted at the outpatient treatment and research unit, Addiction clinic, Karolinska University Hospital. Eighty patients, meeting the DSM IV criteria for amphetamine dependence, were included.The main outcome was abstinence from amphetamine use, as measured by the total number of negative amphetamine urine samples during 12 weeks of treatment. All missing samples were defined as positive for amphetamine.
Results: Overall, 55 patients (68.7%) completed study. The ITT analysis showed that the naltrexone group had a significantly higher number of amphetamine negative urine samples, compared to the placebo treated group ($p<0.05$). Survival analyses examining the course of continuous rates of abstinence from amphetamine, showed that the treatment groups differed in continuous abstinence rates, both in the ITT ($p<0.05$) and completer analysis ($p<0.05$), in favor of NTX treatment. There was a significant reduction in craving levels ($p<0.05$) and self reported weekly consumption of amphetamine in the NTX group compared to placebo. Treatment with NTX was well tolerated in this population.
Conclusions: The results suggest that NTX is efficaceous in reducing relapse to amphetamine use in amphetamine dependent individuals, The potential of naltrexone as an adjunct pharacotherapy in amphetmaine dependence is promising.

P-12-010
Prevalence of alcohol related problems in Belarusian universities: The survey of students at five campuses

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Objectives: There is a dearth of data concerning the prevalence of alcohol problems in the general students' population in Belarus. We therefore screen for the prevalence of alcohol related problems in the general students' population and examine the differences in alcohol related problems between the Native Belarusian and foreign students in Minsk, Belarus.

Methods: Respondents were 1613 university students in the 2007/2008 academic session, from five different campuses in Minsk (Belarus). The Belarusians and foreign students were administered questionnaire, containing the AUDIT, MAST, CAGE and other alcohol related questions. The cut-off point on the AUDIT was set at 8. Statistical calculations were performed using SPSS 16.0; the Pearson and Student's t-tests. The probability value for significance was set at $p<0.05$.
Results: Overall, 86.67% alcohol users and 17.48% problem drinkers were identified using the AUDIT. 61.34% prevalence of alcohol use among foreigners was indirectly proportional to 28.35% cases of alcohol related problems in comparison with the Belarusians that had relatively higher prevalence of alcohol use (90.13%), but lower cases of alcohol related problems (16.00%). The dose-dependent effect of alcohol was also proven. The moderate drinkers use doses of 29-37 ml of pure alcohol for one person per month. The problem drinkers had 2.39-50.00 times higher alcohol related problems than the moderate drinkers.
Conclusions: Alcohol problems in Belarusian universities are high. The problem drinkers experience higher alcohol related violence, injury, hangover, guilt, blackouts and asocial behaviour, compared to the moderate drinkers. In accordance with the recommendations of Welcome MO et al.[Psychotherapy and Clinical Psychology. 2008; 25 (2): 19-22 & Bulletin of Smolensk Medical Academy. 2008; 3: 28-33], alcohol doses for one person per month must not exceed 4 standard drinks - 32g or 40ml of pure ethanol.

P-12-011
The concept of safe psychophysiological dose of exogenous ethanol

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Objectives: Alcohol use causes over 60 types of diseases (including cancer) worldwide. Usually, the 1-2 standard drinks/day are normally generalized as safe dose of alcohol. The aim of this review was to extensively analyze both long and short term alcohol related problems resulting from the use of alcohol in various doses and to determine both a long and short-term safe dose of exogenous ethanol for young adults.
Methods: This study involved over 500 peer reviewed literatures from the year 1960 to 2008, which included epidemiological data, clinical studies and case studies. Various forms of the disease-alcoholism, etiology, alcohol related problems in relation to the dose-time dependent effect of alcohol use were critically analyzed.
Results: The vast majority of data suggests that "regular" (with 1-2 alcohol-free days per week) alcohol doses of 1-2 drinks/day give the least health risk for cardiovascular diseases (CVD), especially for adults. Higher doses might result in increase health risk for cancer, liver cirrhosis, psychophysiological dysfunctions. A dose of 40ml pure ethanol/person/month which is the safe monthly exogenous dose of alcohol is recommended for young adults (≤25 yrs). This recomendation was based on the psychophysiological functions of undergraduates over a 3 year period of study.
Conclusions: Recommendations of alcohol dose should be strictly based on the individual's health status, the disease for which the population/individual is at risk, including long and short-term effects of alcohol. Abstinence is recommended for pregnant women and children up to 18 yrs of age. For undergraduates (18-25 yrs), alcohol dose must not exceed the safe psychophysiological dose of 40ml/person/month. Alcohol dose should be strictly based not only on the individual's health state/risk for CVD, but also for cancer, liver cirrhosis and other long-term effects like psychophysiological dysfunctions.

P-12-012
Glucose homeostasis disturbances as an important factor in the decrease in effectiveness of mental activities of alcohol users

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P-12-013
Treatment of sleep disturbances in the alcohol dependence – comparative effects of Zolpidem vs. Benzodiazepines hypnotics

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Objectives: Sleep disturbance in alcoholics is a well recognized problem. The aim of this examination is the hypnotic effect of Zolpidem, Placebo and benzodiazepines hypnotics at patients treated of alcoholism in the post – detoxification period when physical apstinencial crisis were overcome.
Methods: We analysed 48 inpatients, alcohol addicted, male, who were hospitalized and psycho and socio – therapeutic method were applied. None of the patients suffered severe somatic or physic diseases and all suffered from insomnia with prolonged sleep induction, short sleeping period with frequent awakenings and bed sleep quality. The patients were followed in the period if six weeks in 3 phases. In the first phase of two weeks Zolpidem (10 mg), was administrated, in the second period placebo therapy was ordinared and the third phase, Flurazepam (15-30 mg) or Nitrazepam (5-10mg) was administrated. Besides the above mentioned medicaments, the patents didn't get any other psychotropic medicaments in the survey period. The effects were evaluated by self evaluating scale each week.
Results: More of the patients had shorter induction in the sleeping period, it's longer better quality and subjective feeling for better rest with benzodiazepines hypnotics than with Placebo. The achieved results showed that more of the patients didn't have shorter induction in the sleeping period and it's longer duration, but they had better quality and subjective feeling for better rest with Zolpidem than with Benzodiazepines hypnotics. The termination of the therapy with Zolpidem didn't lead to appearance of apstinential difficulties. Zolpidem induces sleep quickly, allows a restful sleep with a rapid onset of an action. Adverse events and residual effect in the next day are comparable to placebo, without serious rebound insomnia.
Conclusions: Usage of Zolpidem as a hypnotic is also beneficial and efficient treating insomnia as Benzodiazepines hypnotics with minimal next-day effects on cognition and psychomotor performance.

P-12-014
Differences in use of wait-and-see strategy in the stop signal task between non-chemical and chemical addictions

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Objectives: Pathological gamblers (PG) and polysubstance users (PSU) perform differently than normal controls in neurocognitive tests. Although both disorders are thought to be inhibitory disorders, the question remains of how specific the inhibitory deficit is in PG and whether it distinguishes PG from PSU, with which it shares several clinical features, particularly impulsiveness.
Methods: The aim of this study was to assess inhibitory motor control efficiency a major component of executive control functions – using a Stop Signal task in a male population with PG (N=56; representing non-substance-related disorders), PSU (N=58; representing substance-related disorders), and healthy subjects (N=43).
Results: Our results demonstrated that PSU use a significantly less effective "wait-and-see" strategy compared to healthy controls ($P=0.001$) and PG ($P<0.0001$). PSU had a significantly higher number of false alarms ($P=0.012$) and misses ($P=0.020$) than PG in the Stop Signals task.
Conclusions: Further studies to investigate neurobiological mechanisms underlying differences in performance in the Stop signal task between PG and PSU patients are necessary to confirm our results.

P-12-015
Sensitivity of the dopaminergic neurotransmision to opioidergic stimulation in alcoholism: A PET study with [18F] fallypride

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Objectives: The mesolimbic dopamine (DA) pathway which includes dopaminergic neurons in the ventral tegmental area of the midbrain and their targets, especially the nucleus accumbens, in the limbic forebrain, plays a major role in rewarding effects of alcohol consumption. Chronic alcohol intake seems to be associated with changes in central dopamine D2-receptor availability and delayed recovery of D2-receptor sensitivity after detoxification is positively correlated with high risk for relapse. In addition, alcoholic patients display an increase in μ-opioid receptors in the ventral striatum. The aim of the present study was to explore differences in sensitivity of dopaminergic neuro-transmission to opioidergic stimulation in alcohol-dependent patients and healthy controls using the μ-opioid-receptor agonist remifentanil.
Methods: [18F]fallypride positron emission tomography (PET) was used to compare 11 detoxified male alcoholics and 11 healthy controls. The subjects underwent two dynamic PET scans of 180 minutes. To test for a group difference in D2/3 receptor availability between baseline and stimulated condition, participants were scanned twice, the second time after application of the short-acting μ-opioid agonist remifentanil. Binding potentials (BP-ND) were calculated by means of the simplified reference tissue model. DA release was calculated as percent change in BP-ND
Results: Preliminary data analysis shows no group difference in D2/3 receptor availability at baseline. However, opioidergic stimulation using remifentanil seems to lead to a differential response in alcoholics and healthy controls: while D2/3 availability was unchanged by remifentanil in healthy controls, it was decreased in the bilateral caudate and in the right putamen in alcohol-dependent patients.
Conclusions: These preliminary results point to increased sensitivity of dopaminergic systems to opioider-gic stimulation via μ-opiate receptors in alcohol-dependent patients. This finding could be the basis for the relapse-preventing effects of μ-opiate receptor antagonists in a subpopulation of alcohol-dependent patients. However, these findings await confirmation in larger subject samples.

P-12-016
Impairment in the prepulse inhibition (PPI) in abstinent alcoholics

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Objectives: The objective of this study was to prove if there are impairments in PPI in abstinents alcoholics patients.
Methods: 50 alcoholic patients (40 males and 10 females), with ages comprised between the 18 and 65 years (mean age= 47.72), and who had met DSM-IV criteria for alcohol use disorders and were abstinent more than one month, were exposed to PPI test and compared with 25 equal controls. In this study, the amplitude of the startle reflex, the habituation of the startle reflex and the PPI when the prestimuli is presented 30, 60 and 120 msec before the startle-elicitng stimuli, were used as dependent variables.
Results: Magnitudes of the startle reflex of abstinent alcoholic patients were higher than controls at different trials. There was a lower percentage of prepulse inhibition at 60 mseg trials in abstinent alcoholic patients respect to control subjects. The differences were significant when comparing the two groups (p<0,01). No significant differences were observed at 30 msec and 120 msec trials.
Conclusions: Abstinent alcoholic patients show a decrease in PPI. PPI is an operational measure of sensoriomotor gating and attention. These data suggest that early stages of sensory information processing are abnormal in abstinent alcoholic patients. These observed deficits in PPI could reflect a more generalized difficulty in suppressing or gating information in abstinent alcoholic patients. Further studies are needed to prove if impairments in PPI in alcoholic patients can be used as a vulnerability marker for the development of alcoholism.

P-12-017
Considerations about the influence of age and duration of opiate use on the condition and symptoms of opiate addicts

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Objectives: Background/ Aim: To overcome the lack of data describing the course of the illness Addiction in a population of Drug- Addicts the Department for Drug-Addiction Otto Wagner Hospital, Vienna established an electronic documentation system 5 years ago. All patients attending the department were investigated physically, examined by a psychiatrist and underwent psychological tests, and a widespread social anamnesis.
Methods: The data of 937 persons (male 697, female 240), recorded from Dec. 2004 till (including) April 2008 looking for treatment were evaluated. The correlation of the variables in respect to age and duration of opiate use was statistically calculated. Groups of 5-year steps of age and duration of opiate use were formed and a big number of variables were graphically displayed. The data were used either as metrical variables or, after transformation, as categorical variables representing prevalence. Differences in prevalence between groups were compared by Chi2 tests. Metrical variables are described by mean and standard deviation; the significance of average differences between groups was assessed with independent two-sample t-tests.
Results: The evaluations give a detailed description of the conditions and symptoms in the different age groups and groups of different duration of opiate use. There is an impressive gender difference. A variety of psychiatric symptoms and results of psychological tests correlate toage or display in the graphs increasing means with higher age and not in the same amount with longer duration of Opiate use Other Items do this according to the duration of opiate use.
Conclusions: Considerations about the development of symptoms and conditions should be done seperatly concerning female and male As several items correlate to age, considerations in direction of a chronic illness underlaying addiction can be based on these items. Other Items correlate to the duration of opiate use. Explanations of these findings also are a useful base for further calculations.

P-12-018
Epidemiological characteristics of clinicaly treated heroin addicts

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Objectives: To assess the frequency of epidemiological characteristics amongst heroin dependant psychiatric patients in post war Bosnia and Herzegovina.
Methods: We analyzed seventy heroin addicts (57 males; χ^2-test=27.657, P<0.001) who were treated in the Department of Psychiatry Tuzla, during the period January 2008-January 2009), and were tested with Pompidou questionnaire. The results were analyzed using descriptive statistics and χ^2-test.
Results: Average age of the group of patients studied was 26.2±5.4 years (min. 14- max. 43 years), the age of the first intake of heroin was 20.4±4.3 year and average duration of heroin addiction was 5.1±4.3 years. 51of them (72.9%) started treatment following own decision, and coming from town's environments, 48 (68.6%) were unemployed, 16 (22.9%) finished elementary school and 51 (72.9%) finished secondary school. 43 (61.4%) own driver's licenses, males significantly more frequently 41/57 than females 2/13 (χ^2-test=15.8, P<0.001). 51 (72.9%) had no marriage experience. 13 (18.6%) had own children (1-3 kids). 11 (15.7%) had experience of parents' divorce, 10 (14.3%) had lost one parent and 2 (2.9%) lost both parents. Material status of parents was below average for 17 (24.3%), and average for 49 (70%). 25 (35.7%) had parent(s) who suffered from certain psychiatric disorder(s). 36 (51.45) had judicial proceedings, and 18 (25.7%) were imprisoned. 23 (32.9%) experienced one or more overdosing. Hepatitis "C" virus infections were reported from 12 (17.1%) heroin addicts.

Conclusions: Majority of heroin addicts who were treated in Psychiatry Clinic in Tuzla were males, from towns, unemployed, not married, with finished secondary schools, owners of driver licenses, had average material status of parents. Majority of them had judicial proceedings with imprisonment. Hepatitis "C" infection was highly presented.

P-12-019
Addictive disorder

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Objectives: To incorporate educational reflection techniques in an addiction psychiatry postgraduate core rotation in order to increase critical self-awareness of attitudes, values and beliefs related to working with people with substance use and other addictive disorders
Methods: After 1 year of this new curriculum, 28 reflection papers from PGY I psychiatry residents were collected and analyzed for themes. Content analysis using "open coding" was conducted in order to determine themes that emerged from the papers submitted17,18. The papers were coded twice; once manually, and once using N-Vivo software.
Results: 40 nodes were identified using N-Vivo (see Table A). Many comments contained within the nodes are repetitive but illustrate slightly different themes within the data. Numerous constructs emerged that demonstrated the attitudes, beliefs, stereotypes and stigmas learners have regarding addictive disorders. Many constructs also highlighted that learners felt much more comfortable dealing with addictive disorders due to the training and would treat individuals with these conditions in a more effective manner. Please see analysis document for further details (attached next to poster)
Conclusions: As a final note, the authors wish to share that by creating a learning climate of trust and discovery where reflections can be discussed, the educational experiences are not only enriched for the students but for the teacher as well. Often the teacher will also share reflections and be able to gain valuable insight into the actual teaching program from the students' perspectives often unseen and unheard by the traditional feedback techniques. The interactive opportunity this provides optimizes the learning experience for both learner and mentor.

P-12-020
Effects of methadone therapy on changing of positive and negative mood affect in addicted

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Objectives: The pharmacology of methadone is so straightforward, so unequivocal, so simple for medical professionals. The benefits of such short-term addiction treatment with methadone are substantial. It is a safe, effective, relatively inexpensive medical intervention in the solving problems of addiction. However, some physicians and doctors and even healthcare providers who themselves prescribe methadone to addicts often have inadequate information and are unfamiliar with psychiatric and psychological aspects of how it works. So for better understanding of this aspects the study aimed to investigate effects of Methadone on changing of positive and negative mood affect in addicted.
Methods: 19 addicted people were randomly selected and before methadone therapy with a pretest, Watson's Positive Affect and Negative Affect (PANAS) was administered on them. One month later after methadone therapy again Watson's Positive Affect and Negative affect (PANAS) was administered on them. PANAS assesses: interest, distress, powerfulness, fear, enthusiasm, proud, agitation, nervous and panic. Data were analyzed with dependent T test.
Results: Findings showed significant differences between PANAS components. Methadone therapy increased interest, powerfulness, enthusiasm, proud and decreased distress, panic and agitation in addicted. But there is not any significant difference between nervous component.
Conclusions: The findings indicated that using methadone drug in addition to reduce physical symptoms of addition, can reduce significantly mental problems in addicted and can be regarded as a proficient drug for treating of addiction and as a results individuals can have a normal, productive, healthy, socially acceptable and self-fulfilling life style.

P-12-021
What is the first cause of tendency to addiction? Psychological, environmental or physical

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Objectives: The aim of the research is to test this question what is the first cause of addiction? Psychological, Environmental or Physical causes.
Methods: 70 addicted people were randomly selected and Abuse Drug Assessment Inventory (ADAI) was administered on them. Chi Square formula was used to analyze the results.
Results: Results showed 55 percent of tendency to addiction was psychological. Also more analyzing showed 70 percent of continuing causes of addiction were psychological factors such as anxiety ,sorrow.
Conclusions: In regard to result we should put more emphasis on psychological prevention and treatment methods so that both tendency to addiction and continuing causes of addiction decrease and control.

P-32
Addictive Disorders III

P-32-001
Pain, personality and addiction: Pain coping strategies related to personality traits in substance abusers

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Objectives: According to recent research about treatment of diseases, pain coping strategies or management of pain can play important role in pain decrease and treatment of disease. But there is a few documented article or reference that imply to pain coping strategies specially in relation to personality in substance abusers. So this pilot study was to assess the relationship between pain coping strategies and personality traits in substance abusers.
Methods: 50 addicted were randomly selected and Rosenstein & Keefe's Pain Coping Strategies Questionnaire (PCSQ) and Mc Care & Costa´s NEO PI-R inventory were administered on them. PCSQ assesses six pain coping strategies: diverting attention, reinterpretation pain sensation, self -negotiation, ignoring pain, disastrous thought and praying-hoping and NEO assesses five personality traits: Neuroticism, Extroversion, Agreeableness, Conscientiousness, Openness to experience.
Results: Finding showed there are positive significant relationship between neuroticism and disastrous thought, negative significant relationship between agreeableness and disastrous thought, negative significant relationship between neuroticism and diverting attention, positive significant relationship between extroversion and conscientiousness with diverting attention.
Conclusions: With regard to findings it is recommended that in addition to drug treatment, for changing the attitudes and thinking in addicts, psychiatrists and psychologists apply psychological treatments specially cognitive - behavior therapy to reduce bad and abnormal thinking level about pain so that the length during of treatment decline and as a results reduce the personality problems that is related with addiction before and in during of drug treatment.

P-32-002
Personality and tendency to addiction: Comparison between addicts and nonaddicts

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Objectives: Since the introduction of Diagnostic and Statistical Manual of Mental Disorders, Third Edition (DSM-III) in 1980, there has been a growing interest in the study of patients with substance use disorders (SUD). The driving force behind this field has been, and still is, the high clinical pessimism about the prognosis, and the difficulties in the clinical management of the characteristics of diagnosed patients. In this way the important matter to study is the evaluation of co-occurring personality problems and substance abuse. So the study investigated the personality traits of addicted and nonadicted people.
Methods: 90 addicted people and 90 nonaddicted people were randomly selected and Mc Care & Costa's NEO PI-R inventory was administered on them. Mean scores were compared with T independent tests.
Results: Findings indicated that there are differences among means of personality traits in two groups. Addicted people are more neurotic and open to experience than nonaddicted people and nonaddicted people are more extroverted, agreeable and conscientiousness than addicted people.
Conclusions: Findings showed addicted people are more neurotic and open to experience than nonaddicted people and nonaddicted people are more extroverted, agreeable and conscientiousness than addicted people. It indicates that evaluating with reliable measures and with more attentions to personality traits can help the psychiatrists and psychologists to diagnose the cause of tendency to addiction and also reduce the psychological problems that is related with addiction before and in during drug treatment and can reduce duration of treatment and enhance efficacy of treatment methods.

P-32-003
Family burden in alcohol dependence

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Objectives: There are no published data on how family burden changes over time in alcoholism. We present 6-month follow-up data on the burden of families of alcohol dependent individuals.
Methods: The sample comprised 115 caregivers (83 females, 32 males) of alcohol dependent individuals who completed a 4-6 week inpatient alcohol detoxification in the Specialized Drug and Alcohol Addiction Clinic at the Eginition Hospital, Athens University Medical School. During hospitalization, a brief supportive intervention for the relatives took place. After detoxification all participants were followed-up as outpatients for a 6-month period in an affiliated service. Burden and psychopathology of caregivers were assessed with the Burden of Care Scale, and the General Health Questionnaire (GHQ-28). T-tests for paired samples were used for comparisons between different time points (admission-discharge-six months). A logistic regression model was used to identify factors which influence relatives' relief.
Results: Caregivers exhibited high scores of burden in terms of financial, household, interpersonal relations and parental roles at admission; mild psychopathological symptoms were also recorded. By the end of detoxification scores significantly decreased in most relatives (admission vs. discharge, p<.000); this improvement was determined by the patients' soberness.
Conclusions: Alcohol dependence may have a considerable impact on family interaction as shown by the high scores of burden and mild psychopathology recorded in the caregivers. Our findings suggest that the relatives' relief was dependent on the achievement of abstinence and the number of relapses. Therefore, a brief supportive intervention is recommended.

P-32-004
Tiagabine in the management of collateral psychopathology during alcohol detoxification

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Objectives: The objective of the present study was to compare the effects of the administration of tiagabine as detoxification adjunct, on anxiety and depressive symptoms and global functioning in a sample of alcohol dependent subjects.
Methods: Two age-matched groups, comprising 80 subjects each, were treated with psychotherapy and adjunctive tiagabine. The Hamilton Depression Rating Scale, the Hamilton Anxiety Rating Scale and the Global Assessment Scale were administered at the beginning and at the end of a 4-6 week detoxification period for the assessment of psychopathology. ANOVAs were used for comparisons between groups.
Results: The results were: Tiagabine: HARS=32.4±9.4, HDRS=41.1±8.3, GAS=45.7±4.4; Control group: HARS=31.8±9.1, HDRS=40.2±8.5, GAS=46.1±4.6; (T-test NS). By the end of the detoxification period psychopathology significantly subsided in both groups. However this reduction was more marked in the tiagabine treatment group: Tiagabine: HARS=4.4±5.4, HDRS=4.6±4.4, GAS=89,8±5,1; Control group: HARS=9.7±6.3, HDRS=9.9±7.7, GAS=79.3±7.6; Thus, the tiagabine augmentation group differed significantly from the control group (p<.000).
Conclusions: Moderate to severe anxiety and depressive symptoms with concomitant low functioning were present in all subjects before treatment. Following 4-6 weeks of alcohol detoxification a considerable improvement in terms of anxiety and depressive symptoms was observed in both groups. However, in our study, a significantly more robust decrease was recorded in the tiagabine augmentation group. Therefore, tiagabine in conjunction with a short-term psychotherapeutic treatment appears to help the detoxification process by minimizing physical and subjective discomfort.

P-32-005
Personality of polysubstance abusers with the acute psychotic episode

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Objectives: Among young drug addicts in Serbia trend of use of many substances was observed. Also, appearances of psychotic episodes were noticed in this group of young patients. The aim of this study is to try to find characteristic dimensions of personality for the polysubstance abusers who developed acute psychotic episode not related to intoxication with substances.
Methods: The sample consisted of 100 patients, 51 male and 49 female. It was divided into 4 groups, experimental and 3 controls. Experimental group consisted of 30 polysubstance users with psychotic episode (18-27 years of age, 22.93±2.48 years). The first control group consisted of 30 polysubstance users without psychotic symptoms (23.97±4.07 years), the second of 20 patients with acute psychotic disorder with polymorphic symptoms (25.40±6.64) and the third consists of 20 patients with first manic episode with psychotic symptoms (25.90±6.22 years). Before filling in the battery of tests, patients with psychotic symptoms were examined with BPRS (Brief Psychiatry Rating Scale) at the beginning and at the end of treatment in order to check the clinical condition and ability to fulfill other scales. The next instruments of self-examination were used: MCMI (The Millon Clinical Multiaxial Inventory), TPQ (Three-dimensional Personality Questionnaire). For the analysis of data we used various methods of univariant statistical analysis.
Results: Our results showed that polysubstance users with psychotic episode have normal profile of personality with higher passive-aggressive dimension. Emotional instability was confirmed (novelty seeking (NS) component is high), but less than with the other polysubstance abusers.

Conclusions: Paradoxically more expressed pathology of personality and more severe patterns of addiction less often lead to appearance of psychotic symptoms. Experimental group does not have histrionic dimensions and clinical syndromes of alcohol and substance addiction as polysubstance users without psychoses, but they have more prominent passive-aggressive, schizoid, avoiding and schizotypal dimensions.

P-32-006
Apoptosis of immune competent cells in alcoholic patients

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Objectives: Apoptosis (programmed cell death) is known to play an important role in mechanisms of realization of organism adaptation to influence of various stressful factors, including chronic intoxication. Aim of this investigation was to study processes of apoptosis in lymphocytes and neutrophils in alcoholic patients during withdrawal syndrome therapy.
Methods: Study of immune competent cells apoptosis has been performed in 30 alcoholic patients (the age of 31-57 years) in dynamic of withdrawal syndrome therapy. Expression of FAS receptors on lymphocytes was assessed using indirect immunofluorescence microscopy with monoclonal antibodies to CD95 antigen. The proportion of cells with sings of apoptosis was evaluated by light microscopy of blood smears in terms of morphological changes typical of apoptosis in neutrophils and lymphocytes. Concentration of cortisol was identified in serum of blood using an immunoenzyme method. The control group was constituted by 30 mentally and somatically healthy persons.
Results: We observed significantly increased cells' apoptosis of alcoholic patients as the percentage of lymphocytes with expression of FAS-receptors, also as cells with morphological changes characteristic for apoptosis (nuclear condensation, vacuolation, and blebbing). Stimulation of apoptosis in alcoholic patients has been observed against elevation of serum cortisol. Positive correlation between cortisol concentration and apoptosis receptor expression has been revealed. Ethanol has been shown to induce programmed death in neutrophiles but not in lymphocytes population in vitro. After the therapy the apoptosis realization index in alcoholic patients has been shown to be decreased.
Conclusions: According to obtained results it may by assumed that alcohol increases readiness of lymphocytes to apoptosis but activation of mechanisms controlling and limiting the processes of programmed cell death during the therapy results in decrease of apoptosis realization index in alcoholic patients

P-32-007
Alcoholism, comunication and family

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Objectives: We want to reflect on the family effects alcoholism, as well as the psychological and physical implications. The effects extend beyond the medical implications and demand the intervention of a multidisciplinary team.
Methods: We will present a study case of a 40 year old patient, married with three children that having done desintoxication therapy successfully, his recover brought lack of communication (as people still thought of him as a drunk man) and after struggling against alcohol he had to fight through his painful divorce.
Results: Each family is unique and special, but there are certain movements, certain standarts and barriers that seem to reflect some types of families (Minuchin, S. (1990) (in this case a family with a alcoholic patient).
Conclusions: Although presenting just one case, it seems to us that its singularity reflects the influence of an addiction in the family system as well as in its communication, as all families have their own communication models (Watzlawick, P., Beavin, J., & Jackson, D. (1997). In this case family communication system end up working in an established way: the eldest sun took over parental functions, being his siblings' counselor as the mother took over the head of the family.

P-32-008
Correlates of lifetime alcohol misuse among older community residents in Brazil

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Objectives: Little is known about the sociodemographic correlates and health effects associated with lifetime alcohol misuse in community resident elderly in Brazil.
Methods: Data came from a representative sample of 6961 residents aged 60+ in the State of Rio Grande do Sul, Brazil. The structured interview included a five-item lifetime alcohol use questionnaire addressing abuse and dependence, and enquiry regarding sociodemographic characteristics, lifestyle and social support, and health conditions.
Results: Of the sample, 10.6% (25.3% men, 2.9% women) endorsed at least one lifetime alcohol misuse question. Controlled analyses comparing a gradient of alcohol misuse (none, one, more than one item endorsed), found that men, people age 60-69 (compared to older persons), and tobacco users were more likely to endorse alcohol misuse items. Persons reporting lower income, and of nonWhite race/ethnicity did not differ from their comparison groups with respect to endorsing one item, but they were more likely to endorse two or more items. Endorsing more than one item was associated with impaired activities of daily living, the presence of respiratory problems and psychiatric disorder, but was protective against vascular conditions.
Conclusions: Major lifetime alcohol misuse (defined as endorsing more than one of five items reflecting alcohol abuse or dependence) is more common in certain sociodemographic groups (men, younger elderly, lower income, nonWhites). With the exception of vascular conditions, it is associated with smoking, poorer functional status, respiratory problems, and psychiatric disorder. Endorsing only one item has a reduced association, significant only for male gender, smoking, and psychiatric disorder.

P-32-009
The influence of alcohol metabolizng enzymes and their combinations on drinking behaviors of Korean young adults

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Objectives: It is well-known that Koreans show distinctive drinking behaviors depending on the ALDH2 gene polymorphism. However, there are other alcohol metabolizing enzymes affecting drinking behaviors such as ADH, CYP2E1. This study examined the gene polymorphisms of alcohol metabolizing enzymes and their combinations on the drinking behaviors of Korean young adults in their twenties.
Methods: Through a follow-up survey performed for a cohort consisting of 551 freshmen at Chungbuk National University for six years since 2000, the authors attempted to identify genetic factors affecting drinking behaviors and their changes. In 2000, degree of drinking, drinking behaviors and CAGE were assessed and ALDH2 gene polymorphism was determined with PCR-RFLP. In 2001(n=323), degree of drinking and drinking behaviors were reassessed and in 2006(n=150), AUDIT-K was assessed in addition to the above as a 6-year follow-up survey. Using the in-kept DNA, the gene polymorphisms of ADH1B, ADH1C and CYP2E1 were determined through SNaPshot method.
Results: While ALDH2*2 allele was associated with increased degree of drinking in all of the three observation periods, the combination of active form of ADH1B(*2) and the active form of ALDH2(*1) was associated specific problem drinking behaviors in 2006. When both enzymes were active, the possibility to be classified into the risk group by the screening tools for alcohol dependence such as AUDIT-K(>12) and CAGE(>2) was high. Among those with problem drinking from the first year in university, those who had ALDH2*2 allele showed a increase in CYP2E1*c2 allele frequency.
Conclusions: The ALDH2 genotype had a significant effect on drinking behaviors and degree of drinking during early adulthood. However, the combination of the active ADH1B and the active ALDH2 can be risk factor for problem drinking in Korean young adults. And CYP2E1 genotype affects on drinking behaviors of those who had ALDH2 protective allele for alcoholism but had problem drinking.

P-32-010
Serotonin 5-HT2B receptors are required for MDMA-induced hyperlocomotion, locomotor sensitization, CPP and serotonin release in vivo

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Objectives: The 'club drug' 3,4-methylenedioxymethamphetamine (MDMA, Ecstasy) binds preferentially to and reverses the activity of the serotonin transporter, causing release of serotonin (5- hydroxytryptamine, 5-HT) stores from nerve terminals. Subsequent activation of post-synaptic serotonin receptors by released serotonin has been shown to be critical for the unique psychostimulatory effects of MDMA. In contrast, the effects of direct activation of pre- and/or post-synaptic receptors by MDMA have received far less attention, despite the agonist actions of the drug itself at 5-HT2 receptors-in particular the 5-HT2B receptor.
Methods: We employed parallel pharmacological and genetic approaches using a highly selective 5-HT2B receptor antagonist 2-amino-4-(4-fluoronaphth-1-yl)-6-isopropylpyrimidine (RS127445) and 5-HT2B KO mice in different behaviour paradigm: locomotor activity and sensitization, conditioned place preference (extinction and reinstatement).
Results: We will present recent evidence that mice lacking functional 5-HT2B receptor do not exhibit sensitization to repeated injections of MDMA (10mg/kg). In addition, reinstatement after conditioned place preference extinction is abolish by a selective 5-HT2B receptor antagonist in mice. However, toxic dose of MDMA (30mg/kg) induces DA release without 5-HT release and the downstream behavioral effects (locomotion, locomotor sensitization and CPP) in mice lacking functional 5-HT2B receptor.
Conclusions: These results highlights two independent, but converging pathways used in response to different dose of MDMA, one purely serotonergic at low dose, triggering secondarily dopamine release and one mixed, serotonergic and dopaminergic at high dose. These findings reveal a novel regulatory component in the actions of MDMA and highlight the 5-HT2B receptor as a potential therapeutic target for MDMA abusers. Future studies of the serotonergic system in the brain should now consider the potential involvement of this previously underappreciated receptor.

P-32-011
Steroid hormones and aggression in alcohol dependent patients in the conditions of social isolation

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Objectives: The research aims to investigate the correlations between steroid hormones level alterations and aggression level among alcoholic patients in conditions of social isolation.
Methods: Serum levels of cortisol and testosterone were measured in alcohol dependent males with aggressive behavior (n=60) and in alcohol-dependent non aggressive males (n=27) being in conditions of social isolation. The control group consisted of 24 alcoholic patients during alcohol withdrawal period. The hormone serum levels were measured by immunoenzyme method. Data was statistically processed using a software package SPSS for Windows.
Results: In comparison with the control group, increase of cortisol concentration in patients in conditions of social isolation have been observed. Patients with aggressive behavior have shown a trend toward cortisol level increase as against non-aggressive alcohol-dependent males. Concentration of testosterone in the investigated groups did not differ from one of the control group.
Conclusions: Increase of cortisol level in the investigated groups is apparently a consequence of influence of factor of social isolation, but also it might be associated with aggressively tendency of alcoholic patients. Steroid hormones may play a significant role in aggressive behavior of alcohol-dependent patients in conditions of social isolation. Our results conform with literature data that steroid hormones are involved in developments of aggressive behavior. Also it is shown that alcoholism is associated with alterations in the activity of hypothalamic–pituitary–adrenal axis.

P-32-012
Trazadone in the treatment of insomnia in patients on methadone maintenance

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Objectives: Chronic insomnia is most commonly and sever symptom caused by opioide addiction. Insomnia during methadone maintenance, as a long-lasting complication, frequently is resistant to pharmacotherapy. Trazodone, as an antidepressant, has a short half-life and significantly increases deep sleep without greatly affecting normal sleep architecture. The aim of this study was to evaluate the efficacy and safety of trazadone that improves sleep in patients on methadone maintenance.
Methods: A total of 20 patients, both gender, aged 40 ±7,5 years, with addiction period of 20±4 years, on substitution treatment with methadone (average 3,6 year) were enrolled in this prospective clinical study in Special Hospital for Addictions, Belgrade. Separated in two groups, patients received trazadone treatment 150-300mg/day (n =10) or midazolam 15mg/day (n=10) during 4 weeks period. The efficacy for sleep inducing and prolonged sleeping were clinical monitored. Sleep was assessed by means of Pittsburgh Insomnia Raiting Scale,Pittsburgh Sleep Quality Index and three insomnia items of the Hamilton Depression Rating Scale.
Results: The scores of two sleep measures demonstrated statistically significant difference between trazadone 62,7 % and midazolam 28,9% for all aspects of sleep. The result showed highest range of sleep inducing effects in the first days of administration for trazodone 49, 5 % and slight 35, 7 % for midazolam.Although, trazodone showed effectiveness not only as a sleep inducer but also after prolonged unsuccessful attempt to sleep after 4 weeks period

P-32-013
Alcohol modulates the properties of benzodiazepine receptors peripheral type

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Objectives: The complex central actions of various benzodiazepine and perhaps ethanol could include effects on neurosteroid production mediated through centrally located mitochondrial PBRs. Recent observations on the steroid synthetic capability within the brain open the possibility that benzodiazepines may influence steroid synthesis in nervous tissue through interactions with peripheral-type benzodiazepine recognition sites, which are highly expressed in steroidogenic cells and associated with the outer mitochondrial membrane.
Methods: Methods: for the investigation well be study binding of 3H-PK11195 with mitochondrial membranes prepared from different brain regions and the binding of 3H-PK 11195 with peripheral blood trombocytes were separated from fresh blood.
Results: Results: A comparative studies of 3H-PK11195 binding to PBR from brain cortex, caudatus and cerebellum in alcoholics (A) and non-alcoholics (NA) post-mortem showed that properties of PBR are not identical in different brain regions. The largest density of binding sites was found in brain cortex, the less one - in cerebellum and in nucleus caudatus (in A and in NA). The highest binding affinity for the PBR was found in nucleus caudatus than for PBR in brain cortex and in cerebellum (in A and in NA). Study of the properties of PBR in NA (non-alcoholic)and A (alcoholic) in different brain structures showed the reduction of the affinity and increasing of PBR binding sites in A. We found similar alterations of PBR in peripheral blood trombocytes that suggests close connection between central and peripheral benzodiazepine receptor systems
Conclusions: Conclusions: complex central actions of ethanol could include effects on neurosteroid production mediated through peripheral types of benzodiazepine receptors located in mitochondrial membranes in nervous tissue and plasmatic membrane of trombocytes.

P-32-014
Reduced serum concentrations of nerve growth factor, but not brain-derived neurotrophic factor, in chronic cannabis abusers

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Objectives: The aim of this study is to investigate whether cannabis dependence alters the serum levels of nerve growth factor and brain derived neurotrophic factor
Methods: In this study we measured by enzyme-linked immunosorbent assay (ELISA) the NGF and BDNF serum levels in two groups of subjects: cannabis-dependent patients and healthy subjects.
Results: We found that NGF serum levels were significantly reduced in cannabis abusers as compared to healthy subjects.
Conclusions: These findings indicate that NGF may have a role in the central action of cannabis and potentially in the neurotoxicity induced by this drug. These data also suggest that chronic cannabis consumption may be a risk factor for developing psychosis among drug users.

P-32-015
Low self-esteem as a risk factor for alcohol abuse in undergraduate students

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Objectives: To determine levels of self-esteem in undergraduate students of the National University of Mexico, whose alcohol intake is excessive (cases) or moderate/absent (controls).
Methods: In total 185 undergraduate students were analyzed, 137 with alcohol abuse and 48 controls. The Coopersmith Self-esteem inventory, which consists of 58 items.
Results: In general, controls have a higher self-esteem, as well as a higher self-esteem relatated with home and school. However, alcohol abusers have a tendency to higher self-esteem related with social aspects, but this was not statistically significant.
Conclusions: A higher self-esteem was identified in controls with respect to alcohol abusers (68.8% vs. 41.6%). This report shows an association between a lower self-esteem and a higher alcohol intake in undergraduate students. This may represent a non-genetic risk for alcohol abuse

P-32-016
Variability of the human MPDZ gene sequence and association with alcoholism

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Objectives: Mpdz gene variability contributes to alcohol withdrawal severity and seizures in mice. To investigate the relevance of these findings for human alcoholism, we resequenced human MPDZ gene and compared it with the Mpdz sequences of three mouse strains with different propensity to alcohol withdrawal seizures (AWS).
Methods: 46 exons, exon-intron boundaries and 2 kilobases in the 5' region of the human MPDZ gene were resequenced in 61 alcoholics with AWS, 59 alcoholics without AWS and 64 Coriell DNA samples from self-reported non-alcoholics (all European Americans). Single SNP and haplotype analyses using 13 common variants were performed to explore potential associations of the human MPDZ gene with alcoholism and AWS.
Results: 67 new, mostly rare variants were discovered. Sequence comparison revealed that the human gene does not have variations identical to those associated with AWS in mice. We also found no significant association between MPDZ haplotypes and AWS in humans. However, a global test of haplotype association revealed a significant difference in haplotype frequencies between alcoholics without AWS and controls ($p = 0.015$), suggesting a potential role of MPDZ in alcoholism and/or related phenotypes other than AWS. Haplotype-specific tests for the common haplotypes (frequency > 0.05), revealed a high risk haplotype ($p = 0.006$, maximum statistic $p = 0.051$), containing rs13297480 G allele also found to be significantly more prevalent in alcoholics without AWS compared to non-alcoholic controls ($p = 0.019$).
Conclusions: Sequencing of MPDZ gene in individuals with European American ancestry revealed no variations identical to those associated with AWS in mice. Exploratory haplotype and single SNP association analyses suggest a possible association between the MPDZ gene and alcohol dependence but not AWS. Further functional genomic analysis of MPDZ variants and investigation of their association with a broader array of alcoholism-related phenotypes could reveal additional genetic markers of alcoholism.

P-32-017
Paroxetine compared to Alprazolam in the treatment of alcohol dependence

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Objectives: This study is referred to our experiences in treating alcohol dependence with psychic apstinential difficulties by therapy with Paroxetine and Alprazolam
Methods: We have analysed 27 alcoholic patients, male, who were hospitalized in their second phase of treatment when physic abstinent crisis were overcome and when psycho and socio - therapeutic method were applied. Besides the alcoholism effects (hepatopathia, polyneuropathia), none of the patients suffered severe somatic disease. After the alcohol detoxification, the patients were given Paroxetine (20 mg), or Alprazolam (0,5- 2 mg), over a third months period. The following symptoms were examined with all patients: psychic abstinent symptoms (anxiety, depression), craving for alcohol, neurovegetative and psychosomatic symptoms. None of the patients never showed other psychotropic substances and practically all got hepatoprotectives and vitamins. As a matter of fact, it was followed whether certain symptoms disappeared or were soothed while treated by certain medicaments. For the evaluation of the therapeutic efficacy we used the rating instrument CGI, HAMA scale, and alcohol withdrawal scale with 10 items.
Results: Statistical test have shown significant differences regarding the influence of Paroxetine on the psychic apstinential symptoms, but no differences were observed between Paroxetine and Alprazolam with respect to their efficiency to suppress craving for alcohol and neurovegetative phenomena. But, with patients whose continuous craving for alcohol was accompanied with fear of recidives, anxiety and depression, Paroxetine has shown as more efficient than Alprazolam. Investigation of psychosomatic difficulties has indicated that Paroxetine is faster and more efficient in coping with them than Alprazolam.
Conclusions: The data permit us to recommend Paroxetine to be used for alcoholism treatment, especially for remission stabilization and relapse prevent in patients with alcohol dependence, where anxious-depressive simptomatology and craving for alcohol are dominate symptoms.

ADDICTIVE DISORDERS - Poster Presentations

P-32-018
Dopamine partial agonist effect on the craving for smoking in patients with schizophrenia

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Objectives: The high rate smoker in schizophrenic patients with antipsychotics treatment has sometimes been thought as a form of self-medication to alleviate extrapyramidal symptoms (EPS). In addition, the functional imbalance in the neural circuitry mediating reward and reinforcement was thought to be a higher vulnerability to smoking in patients with schizophrenia. We compared the effects of four antipsychotics (haloperidol, risperidone, olanzapine, and aripiprazole) on the craving for smoking and number of cigarette.
Methods: The influence of antipsychotics for craving for smoking and number of cigarette was assessed in 139 first onset schizophrenic patients with antipsychotic treatment (35 patients treated with haloperidol, 41 patients with risperidone, 32 patients with olanzapine, and 31 patients with aripiprazole). The craving for smoking (Fager-strom Smoking Sclae Score) and number of cigarette was assessed at baseline and following 8 weeks of treatment.
Results: In the comparison of four groups controlling EPS, there was a significant difference in the change of craving for smoking ($F=49.2$, $p<0.01$) and number of cigarette ($F=36.9$, $p<0.01$) over 8 weeks of treatment. While the craving for smoking and number of cigarette were increased in haloperidol ($t=2.26$, $p=0.03$) and risperidone group ($t=2.72$, $p=0.03$), there was no significant change in olanzapine group ($t=0.06$, $p=0.95$). Aripiprazole group showed the reduction in the craving for smoking and number of cigarette ($t=2.84$, $p<0.01$). There was no significant difference in the change of symptoms between four groups over the 8-week period.
Conclusions: These results demonstrate that the partial agonist effects of aripiprazole on neural circuitry mediating reward and reinforcement would reduce the craving for smoking in patients with schizophrenia.

P-32-019
Psychiatric comorbidity of internet addiction in Romanian teenagers: An observational study

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Objectives: The purpose of this study is to investigate issues related to clinical analysis of patients with IAD (internet addiction disorder), we focusing on clinical, demographic features, and comorbidities.
Methods: The survey included a representative sample of 439 school students of ages 11 to 18. All of the students came from 3 gymnasium schools and 5 high schools of Iasi, Romania. The students answered to a questionnaire comprising 34 questions related to computer activities. Nine girls and 21 boys constituted the sample of Internet addicts. All participants were diagnosed based on psychiatric diagnostic interview and psychiatric scales.
Results: Clinical diagnoses included 10% attention deficit and hyperactivity disorder, 9% hypomania, 25% generalized anxiety disorder, 15% social anxiety disorder; 9% dysthymia, 6% obsessive compulsive personality disorder, 14% personality disorder, 10% met criteria for eating disorder. Severity measures of IAD were associated with higher perception of family disability ($r = 0.618$; $P \leq .001$) Adolescents with Internet addiction were more likely to have substance use experience.
Conclusions: With these results, it seems reasonable to suggest that effective evaluation of, and treatment for comorbidities disorders is required for college students with Internet addiction.

P-13
Affective Disorders (Bipolar) I

P-13-001
Validity of the "National Institutes of Mental Health Life Chart – self version" (NIHM-sLCM)

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Objectives: The Lifechart-Methodology of the NIMH is widely used. While the clinician-rated version of the lifechart has shown good validity and reliability validity of the patient rated lifechart has not been demonstrated yet. We tested the selfrated-version against the clinician rated-Lifechart and several other clinician rated psychometric scales.
Methods: Data is derived from participants of the "Naturalistic follow-up study" (Nfs) at both german sites of the "Stanley Foundation Bipolar Network" (SFBN). The protocol of the Nfs includes usage of the retrospective and prospective form of the lifechart as well as several scales for documentation of symptomatology. First, we compared the self-rated and the clinician-rated versions of the lifechart. Second, we examined correlations between the selfrated-version and IDS-C, YMRS, and CGI-BP. Statistical calculation was performed using the program SAS. For comparison of demographics the chi-square test and the t test were used. To estimate the correlation Pearson´s coefficient was calculated.
Results: Data of about 108 patients were available for this evaluation. Because of missing data number of patients differed slightly among the several calculations. Comparison of patient-rated and clinician-rated lifecharts revealed corresponding ratings between 63% and 91% for each mood level. Greatest differences were observed for slight hypomania and subdepression. We found good correlation between patient lifechart and clinician rated IDS, the YMRS, and the CGI-BP (Pearson´s correlation r = -.72, r = .72, r = .65; p<.001).
Conclusions: The selfrated version of the lifechart shows good concordance with the clinician rated lifechart. Cross-validation results are of similar quality as the clinician rated lifechart. Therefore the selfrated lifechart might offer a cost effective alternative to clinican rated lifecharts. Limitation: The cohort of this trial was highly motivated participators of the Nfs and had specific training on how to use the daily life chart. We gratefully acknowledge the support of the Stanley Medical Research Institute.

P-13-002
Lamotrigine in the treatment of bipolar disorder in women of reproductive age

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Abstract: Weight gain, hyperlipidemia, and insulin resistance are among the most concerning metabolic effects of mood stabilizing medications in Bipolar Disorder (BD). Lamotrigine (LTG) is an effective mood stabilizer, with potentially neutral metabolic effects as evidenced by studies in women with epilepsy. The objective of this study was to assess the effects of add-on LTG on body mass index (BMI) and other markers of metabolic and reproductive function among reproductive-age women with BD who were receiving a stable course of psychiatric medication. Exclusion criteria included history of diabetes, cardiovascular disease, or dyslipidemia. A 6-mo. course of lamotrigine was initiated in addition to each patient's medication schedule, with an initial dose of 25mg/day, titrated up to 200mg/day. Prior to initiation of LTG and at the end of 6-month follow-up, BMI and fasting morning blood level of lipids, glucose, insulin, free and total testosterone, and sex hormone binding globulin (SHBG) were measured. Clinical mood ratings (Hamilton Depression Rating Scale (HDRS), Young Mania Rating Scale (YMRS), and Clinicians Global Impression (CGI) were collected at monthly intervals. A total of 46 patients completed the complete baseline assessment; 30 completed the 6-month study and are included in the present analysis. Mean baseline BMI was 26.6 kg/m2, +/-6.5. Analysis of data showed no changes in BMI, fasting insulin, fasting glucose, total cholesterol, triglycerides, low-density-lipoproteins, free and total testosterone, or SHBG. High-density-lipoproteins actually significantly increased (p=.005). Overall mood appeared to improve, with trend decreases in HDRS and YMRS, and a significant decrease in CGI score. Age was not found to be correlated with changes in any metabolic biomarkers nor with clinical response to LTG treatment. In summary, add-on LTG has antidepressant effects in reproductive-age women BD, with neutral or possibly beneficial metabolic effects.

P-13-003
Differences in clinical features between bipolar I and II disorders

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Objectives: Whether bipolar II disorder (BP-II) is simply a milder form of bipolar I disorder (BP-I) or a valid diagnostic category that could be separated from BP-I is a nosologic issue still under controversy. Investigations exploring differential features of the two conditions in clinical and biological aspects are needed to resolve the controversies. This study aimed to obtain a comprehensive view of differences in clinical courses and symptoms characteristics between BP-I and BP-II.
Methods: 44 BP-I, 26 BP-II patients were assessed using Diagnostic interview for Genetic Studies(DIGS), Korean version. Demographic data, age at onset, number of (hypo)manic/ depressive episode, duration of illness, polarity at onset, seasonality, rapid cycling, atypical depression and symptom profiles of each episode were evaluated.
Results: BP-II patients have experienced more depressive episodes than BP-I patients after adjusting for duration of illness (U=240.5, p=0.008). More BP-II patients showed seasonality (34.9% vs. 61.5%). When comparing symptom profile of manic/hypomanic episodes, irritable mood, decreased sleep need, inattention, reckless behavior, arrogant/provocative attitude, frequent outburst of anger, psychotic symptom were less encountered in BP-II patients. In depressive episodes, leaden paralysis and psychomotor agitation are more frequently observed in BP-II patients. There's no significant difference between the two groups in psychotic symptoms of depressive episode.
Conclusions: BP-I and BP-II disorders showed distinct clinical courses and symptom profiles. BP-II disorder seems to be less severe than BP-I disorder with regard to the intensity of manic-side symptoms, but more severe with respect to frequencies of depressive episodes. These results provide additional evidences supporting the distinction of BP-I and BP-II as separate diagnostic categories that might have different genetic liabilities and biological mechanisms.

P-13-004
Subsyndromical symptoms as manifestation of alarm in the patients with bipolar disorder

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Objectives: The present paper is aimed to stress the importance of recognizing subthreshold manifestations associated with bipolar patients' clinical symptomatology.
Methods: An experimental study on a sample of 40 patients (22 women and 18 men) affected by Bipolar Disorder (Bipolar I Disorder, Bipolar II Disorder and Cyclothymia) was conducted at the Operational Unit of Bipolar Disorders of the Catholic University of Sacred Heart and at Lucio Bini Centre, sited in Rome, Italy. All patients were evaluated by the MOOD-SR, a clinical self-reported interview, that is specific for the spectrum of subthreshold pathology, by the GSM-5 an interview specific for the spectrum of anxiety and eating disorders' pathology and by the Quality of Life (QoL), that investigates patient's quality of life.

Results: The total average for the MOOD of the 4 humour domains (humour, energy, cognitive function and rhythmicity) was 64,9 while the total standard deviation is 27,5. Instead the total average and the standard deviation of the GSM domains were: panic-agoraphobia (2,6 - 2,8), depressive mood (3,8 - 3,6), hypomania (2,2 - 2,1), social anxiety (2,8 - 3,0), obsessive-compulsive disorders (2,4 - 2,8) and eating disorders (2,5 - 3,4), respectively. All those data will be compared with symptomatic scales' results (Hamilton Depression Rating Scale and Young Mania Rating Scale).
Conclusions: The model of humour spectrum consider maniacal and depressive aspects of Bipolar Disorders gathering peculiar aspects inside them. The model for other spectrum underlines the presence of concomitant symptoms of spectrum. Spectrum manifestations might represent an indicator of both course and response to treatment, but they are also predictive for relapse.

P-13-005
Late onset bipolar disorder differential characteristics

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Objectives: The aim of the present study is to analyze those peculiar characteristics in a late onset subgroup, of Bipolar Disorders, and to compare it, with a group of classical age onset, the cut age considered was 55 years old.
Methods: We studied retrospectively an aleatorial sample of clinical histories of patients attending to our Lithium Clinic, we included in the study patients diagnosed with DSM – IV of Bipolar Disorder Type I, Type II, and Schizoaffective Disorder, we considered the age of onset of the disorder, the moment when the patients were diagnosed. Neurological symptomatology was recorded by neurologists.
Results: The sample consisted in 50 patients with a mean age of 57.28 years old with a (SD 14.5), being 63% women. The mean length of evolution with the illness was 22.76 years with a (SD 9.86). Only 6% of the sample was diagnosed of Bipolar Disorder after 55 years of age. The mean age in the classical onset group was 56 years (SD 14.003) and 77.33 years in the late onset group (SD3.055). (U Mann-Whitney=11.5; p=0.008). The mean number of hospitalizations in the classical onset group was 1.21 (SD 1.742), and in the late onset group 4 (SD 1.414). (U Mann-Whitney=10; p=0.07). Moderate cognitive impairment was found in 66.6% of the late onset group and in 6.4% of the classical onset patient group (p=0.259).
Conclusions: The late onset group of this sample of Bipolar Disorder had more neurological associated pathology, more number of hospitalizations and less familial antecedents than the comparison group, with classical onset age. Although it could be suggested that the later onset group could have a worse prognosis, none of the statistical data analyzed reached significance to support that affirmation, perhaps due to a sort sample.

P-13-006
Subclinical anxiety as an endophenotypic marker in Costa Rican bipolar I patients

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Objectives: To determine whether quantitative subclinical anxiety is a candidate endophenotype for bipolar I patients.
Methods: We analyzed 30 bipolar I extended families (300 subjects, average family size 10.34 members, range: 2-31) and 20 unrelated healthy controls from a Costa Rican sample. Heritability and genetic correlation of the state and trait scale from the Anxiety State and Trait Inventory was computed by using the general linear model (Solar package software). We also assessed variation of both scores among groups (patients, relatives and controls) and tested independence of affection status.
Results: Heritability for state is 0.45 (SE=0.11, p=0.0000001) and for trait is 0.89 (SE=0.06, p=6.22e-29). Genetic correlation for state and trait is 0.29, (SE=0.12, p: 0.038-3.19e-8). Bipolar I patients showed the highest trait score (F[5,24], p=.002), (bipolar I patients > relatives with other pathologies, > healthy relatives > unrelated healthy controls) with normal distribution in healthy individuals and no difference regarding depression and mania current status, (F[,230], p=.632) and (F[1,401], p=.238) respectively, contrary to the state score.
Conclusions: Anxiety state and trait are heritable and share some genetic factors but only trait showed normal distribution in healthy subjects, mood current status independence and significant liability for bipolar I disorder. This suggests that subclinical anxiety trait can be considered a candidate endophenotype for Costa Rican bipolar I patients.

P-13-007
Bipolar disorder in patients with a current diagnosis of major depressive episode

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Objectives: To estimate the frequency of bipolar disorders (BD) in patients with a diagnosis of major depressive episode (MDE) and to identify other psychiatric comorbidities in these patients.
Methods: An international cross-sectional epidemiological study was performed in eighteen countries in Europe, Asia and North Africa. These data come from a prespecified interim analysis of patients recruited between April and October 2008 (when half of the target sample had been recruited). Community- and hospital- based psychiatrists included consecutively all adult patients consulting with a diagnosis of MDE (DSM-IV criteria) into a patient registry. At this consultation, participating physicians completed a questionnaire on clinical features of the patient (including the modified DSM-IV criteria for BD, Diagnostic Checklist of Lifetime Manic and Hypomanic Episodes for BD), medical history and treatments.The patients completed the Hypomania Self-Rating Scale (HCL-32-R2).
Results: A total of 2729 patients were included, of whom 2694 completed the HCL-32-R2. Their mean age was 41.7 years and 63% were female. 15.7% fulfilled DSM-IV criteria for BD and 50.8% scored >=14 on the HCL-32-R2. 12.9% had previously received a diagnosis of type 1 BD and 14.3% a diagnosis of type 2 BD. 92.7% were currently prescribed antidepressant drugs and 34.1% mood stabilisers. The most frequent current psychiatric comorbidities encountered were generalised anxiety disorder (10.4%), borderline personality disorder (9.6%), panic disorder (9.4%) and obsessive compulsive disorder (5.5%). Alcohol and other substance abuse, social phobia, borderline personality disorder and ADHD were significantly more frequent in patients fulfilling modified DSM-IV criteria for BD than in those with unipolar depression.
Conclusions: Bipolar disorder is frequent in patients with MDE and is associated with higher comorbidity of others psychiatric disorders. Patients with MDE and alcohol and other substance abuse, social phobia, borderline personality disorder or ADHD should be screened for BD before initiating antidepressant therapy.

P-13-008
A naturalistic study of olanzapine in the treatment of patients with manic or mixed episodes of bipolar disorder: Results from 12-weeks acute phase treatment with olanzapine in monotherapy and in combination

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Objectives: The aim of this study was to evaluate outcomes of olanzapine treatment of manic or mixed episode of bipolar affective disorder in 24 psychiatric clinics in the Czech Republic after 12 weeks as a part of 24-months observational study in naturalistic setting conducted between November 2003 and May 2007.

Methods: Olanzapine was used in monotherapy or in combination with other antipsychotics, anticonvulsants, and/or lithium and antidepressants. Primary objective included evaluation of changes in symptoms of mania in both groups according Clinical Global Impression – Bipolar Disorder scale (overall, mania, depression, hallucinations, dellusions). Patterns of use of antimanic medication were evaluated.
Results: 251 patients were enrolled. 90.8% (228 patients) completed 12-weeks acute phase observation. 35.1% (88) patients received olanzapine in monotherapy (M-group) and 64.9% (163) patients in combination (C-group). 24.3% (61 patients) had no previous antimanic medication for index episode. One previous medication had 30.7% (27) in M-group and 17.2% (28) in C-group. Two or more medications had 26.1% (23) in M-group and 68.7% (112) in C-group. The main reason for medication change was lack of efficacy for 58.3% (95) in C-group and 31.8% (28) in M-group. There was significant improvement in all efficacy measures in both treatment groups in week 12 compared to baseline. In C-group 35% (57) patients used three and more medications; anticonvulsants were used by 37.4% (65) patients and lithium by 8% (13) of patients. A proportion of patients with concomitant therapy (benzodiazepines, hypnotics, anticholinergics, others) was 63.8% (104) in C-group and 48.8% (43) in M-group.
Conclusions: Olanzapine in monotherapy or in combination showed significant improvement of manic symptoms within both groups. Combination therapy and use of concomitant medication is highly prevalent in this sample of patients with manic/mixed episode treated in a naturalistic setting in the Czech Republic.

P-13-009
Neurological comorbidities in patients with bipolar disorder: A systematic review

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Objectives: To synthesize the available knowledge on neurological comorbid disorders in patients with bipolar disorder (BD).
Methods: Relevant studies were identified by a MEDLINE search from 1966 to January 2008, and supplemented by a manual review of reference lists of the articles identified and previous review articles. We included studies with any design, in patients with BD as diagnosed by any criteria, with sample size ≥30 patients, and reporting any measure of frequency or association about comorbidities. Priority was given to comparative studies.
Results: We identified 21 studies: 11(52.4%) were comparative; 10 (47.6%) were cross-sectional and 11 (52.4%) were retrospective cohort studies; 2 (9.5%) were a population-based studies; and 2 (9.5%) used a probabilistic sampling. An increased point-prevalence of migraine in patients with BD, compared with the general population, was reported in two studies (24-24.8% vs 10.3-11%). One study also reported a higher lifetime-prevalence of migraine in patients with BD than in the general population (15.2% vs 7%). Two studies reported a higher point-prevalence of dementia in patients with BD as compared with that of the general population (1.8% vs 1%) or with that of patients with arthrosis/diabetes (1.9% vs 1.1/1%), respectively. However, in one study the point-prevalence of Alzheimer disease did not differ between patients with BD and the general population (0.7% vs 0.6%). Data on other neurological comorbidities such as epilepsy, Parkinson disease or multiple sclerosis, are very limited.
Conclusions: BD seems to be associated with an increased frequency of migraine. The possible association between BD and dementia should be further investigated.

P-13-010
Spatial working memory function in bipolar disorder and schizophrenia

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Objectives: Spatial Working Memory (SWM) impairment has been consistently described as a candidate endophenotypic marker in schizophrenia, but findings in bipolar disorder have been contradictory. We previously reported how SWM significantly differed between BP patients with and without a history of psychosis (Glahn et al, 2007). We anticipate that patients with a history of psychosis will show poorer performance on SWM.
Methods: Individuals chosen for this analysis participated in two genetics projects carried out in Costa Rica. Subjects received a lifetime diagnosis according to DSM-IV criteria. The South Texas Assessment of Neurocognition Battery was administered to each subject by trained, local psychologists. SWM functioning was measured by the Spatial Capacity Delayed Response Test (SCAP). 18 patients with schizophrenia (SCZ), 18 with bipolar disorder type I with a lifetime history of psychosis (BPP), 17 subjects with bipolar disorder type I without a lifetime history of psychosis (BPNP), and 20 controls (HC) completed the assessment described above. All subjects were unrelated to each other. A p value of $<.05$ was considered statistically significant. All analyses were performed with SPSS, version 17.0. ANCOVA analysis was performed co-varying for age, gender, and education.
Results: Differences in SWM performance were observed among all groups. Schizophrenic patients obtained the lowest performance, followed by BPP patients (SCZ<BPP<BPNP<HC). Patients with schizophrenia were significantly impaired when compared to controls (p=0.001), when compared to BPNP (p=0.001), and to BPP (p=0.024). Patients with bipolar disorder were not impaired in SWM when compared to HC (p=0.243). A lifetime history of psychosis in the bipolar group did not determine any difference in SWM functioning (p=0.359). Patients with bipolar disorder were not significantly impaired in SWM when compared with HC (p=0.476).
Conclusions: Our results support that SWM impairment constitutes a clear trait marker for schizophrenia but less clearly to bipolar disorder. SWM performance did not distinguish BPP from BPNP. SWM might be influenced by state in bipolar disorder.

P-13-011
Illness experience and reasons for non-adherence among individuals with bipolar disorder who are poorly adherent with medication

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Objectives: Characterization of factors underlying poor adherence in bipolar disorder (BD) is essential in order to develop appropriate interventions. This mixed-methods analysis evaluated illness experience in relation to adherence among 20 poorly adherent Community Mental Health Clinic patients with BD.
Methods: A qualitative instrument (SEMI TAD BD) evaluated selected patient, social/environmental, and provider-relationship factors likely to affect adherence. Quantitative assessments measured symptoms (HAMD, YMRS), psychopathology (BPRS), adherence (Tablets Routine Questionnaire/TRQ and pill counts) and attitudes (Attitude toward Mood Stabilizers Questionnaire (AMSQ), the Drug Attitude Inventory (DAI), and the Rating of Medication Influences (ROMI). Poor adherence was defined as missing 30% or more of medication.

Results: Minorities (80%), unmarried individuals (95%), and those with substance abuse (60%) predominated. Individuals were substantially depressed (mean HAMD 19.2, range 12-28), had at least some manic symptoms (YMRS mean 13.6, range 12-28) and moderate global psychopathology (Mean BPRS 41.2, range 29-60). Rates of missing prescribed medications were in the order of 41%. Standardized attitudinal scales (AMSQ, DAI, ROMI) found generally negative attitudes towards medication and limited insight into illness. Forgetting to take medications was the top reason for non-adherence (55%), followed by side effects (20%). Half of individuals had difficulty paying for medications at times, while 35% (N=7) felt they had insufficient information about BD. Interestingly, all individuals reported good relationships with their providers.
Conclusions: Poorly adherent BD patients report that forgetting medication and side effects are primary drivers of non-adherence. Access to medications, insufficient illness knowledge, and limited insight may likewise affect overall adherence.

P-13-012
Depressive symptom ratings in geriatric patients with type I bipolar mania

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Objectives: It has been reported that 7%-40% of mixed-age individuals with bipolar disorder (BD) experience depressive symptoms in the context of acute manic states. Mania with substantial concurrent depressive symptoms has been reported to be associated with greater mania severity and is suggested to be more common in older individuals. A recent European College of Neuropsychopharmacology (ECNP) consensus suggested that individuals with bipolar depression have a 17-item Hamilton Depression Rating Scale (HAMD-17) score above 20. Depression ratings have not been reviewed in geriatric mania, and this is an exploratory analysis of clinical features in bipolar elders who met the ECNP criterion.
Methods: The subjects were the first 106 individuals enrolled in an RCT designed to compare acute treatment with lithium or valproate in geriatric patients (age 60 and older) with Type I Bipolar mania, mixed-manic episode or hypomania. Individuals had at least moderate manic symptoms as defined by a Young Mania Rating Scale (YMRS) score of 18 or greater. Individuals who met the ECNP criterion (at least moderate depression ratings) were compared to those with lower depression ratings.
Results: These patients had a mean HAMD-17 score of 9.6 ± SD 6.8. A subgroup (N=12; 11.3 %) had HAMD scores meeting the ECNP criterion. There were no significant differences in age, gender, ethnicity, education, residential or marital status, medical co-morbidity or age of bipolar onset between the criterion and non-criterion groups. YMRS severity was similar between groups.
Conclusions: A preliminary analysis found that the proportion of bipolar manic elders with at least moderate depression rating on the HAMD-17 by the ECNP criterion appeared similar to the range reported for mixed-age populations. These patients did not have greater overall mania severity.

P-13-013
Mood disorders associated with interferon treatment: Development and validation of a mood disorders diagnostic screening questionnaire: The DETHEC questionnaire

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Objectives: The antiviral, immunomodulatory, and antiproliferative properties of interferon alfa give this cytokine potential therapeutic effects in chronic viral infections and cancers. A major limitation of interferon alfa therapy is its serious side effects, which include fever, headache, myalgias, sleep disturbances, fatigue, anorexia, and neuropsychiatric effects. Usually observed, depressive symptoms are detrimental to the patient's quality of life and may justify adjustment or interruption of the treatment. Identifying patients at risk for these mood disturbances early in the treatment would permit the adoption of corrective measures.
Objectives: Development and validation of a Mood disorders diagnostic screening questionnaire based on issues pertinent to patients with hepatitis C treated or not by interferon were performed.
Methods: During a first phase, identical pattern were identified among interviews of patients infected with hepatitis C virus, (n=141) conducted by psychologists (1 hr). More questions were asked concerning a least 38 sub-domains. The data gathered in first phase were discussed and organized, by 11 experts For the second stage, questionnaire development pertained to construct a psychometrically sound Mood disorders measure taking into account the existing state of the art by using literature searches, expert consulting and Delphi method.
Results: Items (n=488) were developed by conducting with patients infected with hepatitis C virus to identify relevant Mood disorders dimensions and acceptable wording. Five questions - rounds were administered to a multidisciplinary group of 11 experts. The first Delphi round consisted largely of open questions, and answers to this round provided the basis for later versions. Consensus was considered to be reached when at least 80% of experts either agreed or disagreed with a given item. Responses were received from 20 respondents in the 5 rounds. There was agreement that each new instrument should be a multidimensional, profile measure with 30-45 items covering 4 to 8 dimensions, taking 10-15 min. to complete. The consensus was generally against having an individualised quest. Finally, for the five stage (validation study) the instrument included less than 70 items. The 7 major domains were "Sensory, pleasure, hedonism, relationship with food"; "Ability and emotional control, emotional state, fear, anxiety", "Philosophy of life, risk of suicide"; "Living conditions, daily functional aspect and in general"; "Intellectual capacity, cognitive function"; "Relations with other, family friend"; "Ability to cope (in life, disease)"
Conclusions: The next phase consisting, from a prospective epidemiological study (n=1500) in a validation analysis of structural and psychometric proprieties of "The DETHEC questionnaire".

P-13-014
Impact of psychoeducation in bipolar disorder on the quality of life

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Objectives: To assess the impact of a psychoéducative therapy,on QDV of the patients suffering from bipolar disorder type I
Methods: 15 patients suffering from bipolar disorder (I) participated in this study, clinically stabilised. Psycho education consisted of a course / week for 16 weeks. Quality of life was assessed before and 3 months afterwards psychoéducation with the aid of SF-36
Results: The total medium scores to SF 36 were 63 before PE pointing out an impairment of QDV. The increase of medium scores by dimension to SF 36 after PE varied from 2.2 to 17.6 certifying a significant improvement of quality of life (P=0.01) for dimensions: physical activity, life and relations with others and limitations of in the psychical state and tendencies towards a functioning improved for other dimensions
Conclusions: Although preliminary, our results show that psycho education therapy is linked to better quality of life at the bipolar patients, both as regards general satisfaction and levels of physical functioning.

P-13-015
Monotherapy with olanzapine of acute manic episode

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Objectives: To determine the improvement of clinical status and to evaluate the adverse reactions incidence in manic episodes with or without psychotic features treated with olanzapine im or velotab, using an active comparator – haloperidol im.

Methods: An open-label study included 21 patients, 13 male and 8 female, mean age 42.8, admitted in our clinic for acute manic episode, with or without psychotic features (DSM-IV-TR). Patients were hospitalised and 5 to 15 mg flexible daily doses of olanzapine im (n=8), olanzapine velotab (n=7) or haloperidol im (n=6) were administered. We assessed our patients using Abnormal Involuntary Movement Scale (AIMS), Extrapyramidal Symptom Rating Scale (ESRS), Young Mania Rating Scale (YMRS), Hamilton Depression Rating scale (HAM-D) – 21 items and a subscale derived from Brief Psychiatric Rating Scale (BPRS) that includes 5 items: tension, hostility, suspiciousness, uncooperativeness, excitement – at 6, 12, 24 and 48 hours of treatment.
Results: The intent-to-treat (ITT) and last-observation-carried-forward (LOCF) analysis showed a statistically significant difference in movement impairments at 48 hours between olanzapine formulations and haloperidol. The BPRS subscale registered also a constant decline in all groups after 6 hours (-7.8±1.3 to baseline), 12 hours (-8.2±0.5) and 48 hours (-9.2±0.9). There were no significant variations at endpoint in HAM-D score between groups or to the baseline.
Conclusions: Olanzapine im and velotab are formulations that allow a good control over manic episodes with psychotic features and are better tolerated than haloperidol. While the im formula allows a smooth transition to the oral treatment with the same drug, the velotab formula has the advantage of initiating and continuing the treatment with the same drug, in the same way of administration.

P-13-016
ADHD and bipolar disorder: Prevalence of misdiagnosis?

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P-13-017
Total agenesis of the corpus aallosum in a patient with a polymorphic clinical presentation

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Objectives: The authors describe a case of a 33-year-old Caucasian woman with a complete Agenesis of the Corpus Callosum. She has a moderate mental retardation and since her eight years old she began psychotic symptoms with bizarre characteristics without mood switches. Contrarily in the last four years she demonstrated periods of mania with psychotic symptoms and a recent depressive episode with a suicide attempt. She is being medicated with olanzapine that she takes irregularly because her poor insight.
Conclusions: The appearance of mood fluctuations and the polymorphism of symptoms, in the absence of corpus callosum, corroborate the actual scientific data regarding the abnormalities in interhemispheric communication in the Bipolar Disorders (BD). Many studies indicate that callosal areas are reduced in BD and suggest that a failure to integrate information across the hemispheres may contribute to the pathophysiology of the disorder and maybe to the variability of the disease spectrum.

P-13-018
Lamotrigine associated rash in adult patients with bipolar i disorder: A multicenter, prospective, naturalistic, open-label trial

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Objectives: The goal of this study was to assess the rate of lamotrigine associated rash in patients with bipolar I disorder in real world setting.
Methods: During 12-week open-label trial, lamotrigine was added to current therapy for DSM-IV bipolar I patients. We assessed rash and other adverse event incidence. The primary outcome measure was the incidence of rash developing from any medication.
Results: A total of 237 patients were included this study and 173 patients (73.0%) completed the study. Thirty patients (12.7%) developed a rash. There was no patients who developed to Stevens-Johnson syndrome or toxic epidermal necrolysis. Demographic variables and clinical variables such as age, gender, medical comorbidity, lamotrigine start dose or concomitant medications were not related to rash incidence. Median time of rash onset was 16 day.
Conclusions: Our findings suggest that the incidence of serious rash associated with lamotrigine was very low. Thus the prescription of lamotrigine should be undertaken with appropriate consideration of the potential risk of adverse events including rash to the patient in relation to potential benefit of improvement of bipolar depression.

P-13-019
The efficacy of quetiapine in patients with bipolar depression: A multi-center, prospective, open-label, observational study (queen study)

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Objectives: Bipolar depression has a disabling course and its treatment represents a major challenge to clinician. Recently, a randomized controlled trial (RCT) with quetiapine monotherapy in patients with bipolar depression reported significant reduction in depressive symptomatology. The purpose of this study was, at the real clinical setting, to evaluate the clinical efficacy of quetiapine in bipolar depression.
Methods: This study was multi-center, prospective, open-label, observational, 8-week evaluation of the efficacy of quetiapine in patients with bipolar depression. In this study, patients with DSM-IV-TR diagnosis of bipolar depression (bipolar I disorder, most recent episode depressed and bipolar II disorder, most recent episode depressed) were included and treated with quetiapine. The dosage of quetiapine was flexible and concomitant mediations were permitted by clinical judgements. Clinical improvements were rated by Clinical Global Impression-Bipolar version (CGI-BP), Montgomery-Asberg Depression Rating Scale (MADRS) at baseline, week 4 and week 8.
Results: Total 1,193 patients were recruited and 46 (3.9%) patients were dropped out from this study. The mean initial dose of quetiapine was 192.3±181.9mg/day and mean dose at week 4 and week 8 were 315.2±229.7mg/day and 337.1±229.9mg/day, respectively. CGI-BP and MADRS were significantly improved at week 4 and 8 as compared to baseline. And improvements at week 8 were greater than at week 4. Subjectively, 75% of patients were reported therapeutic compliance above 75% at week 4 and 8. Seven (0.6%) and four (0.3%) patients showed manic/hypomanic episode at week 4 and 8, respectively.
Conclusions: This study suggest that quetiapine has approving effects on depressive symptoms with minimal incidence of manic switching in bipolar depression. We propose that quetiapine could be a effective and safe modality in treating bipolar depression.

P-13-020
Body Mass Index (BMI) correlates of bipolar disorder: Can BMI help predict prognosis and outcome?

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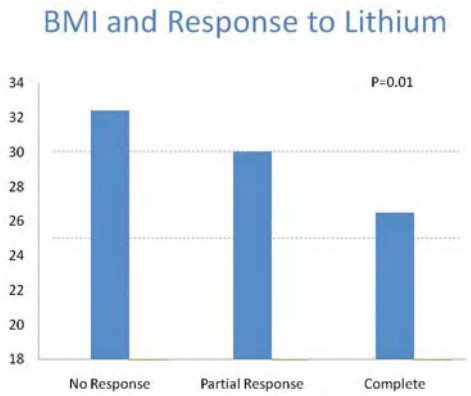
Objectives: Several studies have reported higher prevalence of obesity in patients suffering from bipolar disorder (BD). The possible links between these two conditions include treatment, lifestyle, co-morbid binge eating, neuroendocrine and neurotransmitter dysfunctions, co-morbid metabolic syndrome, and genetic predisposition. To study the relation of elevated body mass index (BMI) in patients with BD more closely, we investigated differences in socio-demographic, clinical and medical characteristics with respect to BMI, with the hypothesis that BMI is related to prognosis and outcome.

Methods: We measured BMI of 276 subjects of a tertiary care sample from the Maritime Bipolar Registry. Subjects were 16 to 83 years old, with psychiatric diagnoses of BD I (n = 186), BD II (n = 85), and BD not otherwise specified (n = 5). The registry included basic demographic data and details of the clinical presentation. We first examined the variables showing a significant association with BMI; subsequently we modeled the relationship between BMI and psychiatric outcome using structural equation analysis.
Results: The prevalence of obesity in our sample was 39.1% (n = 108). We found higher BMI in subjects with a chronic course of BD ($p < 0.001$), longer duration of illness ($p = 0.02$), lower scores on the Global Assessment of Functioning Scale ($p = 0.02$), and on disability due to BD ($p = 0.002$). Overweight patients also had more co-morbid subthreshold social ($p = 0.02$) and generalized anxiety disorders ($p = 0.05$), diabetes mellitus type II ($p < 0.001$), and hypertension ($p = 0.001$). Subjects who achieved complete remission of symptoms on lithium, showed significantly lower BMI ($p = 0.01$), compared to those reporting no therapeutic effects.
Conclusions: Our findings suggest that BMI is relevant to the prognosis and outcome of BD.



P-22
Affective Disorders (Bipolar/Unipolar)

P-22-001
Social perception and emotion regulation in bipolar disorder and schizophrenia

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Objectives: Impaired social information processing in bipolar disorder and schizophrenia may contribute to maladaptive emotion regulation, with negative implications for interpersonal and social functioning. We examined associations between complex social perceptual skills and the employment of particular emotion regulation strategies in bipolar disorder and schizophrenia.
Methods: Preliminary data are reported for eight patients with bipolar disorder (Mean age = 43.75yrs, SD=9.96), thirteen schizophrenia patients (Mean age = 46.46yrs, SD = 9.96), and eleven healthy control participants (Mean age = 35.46yrs, SD=15.48). All participants completed The Awareness of Social Inference Test (TASIT), incorporating the assessment of affect perception and mental state inference from short vignettes of sincere and sarcastic social exchanges. Clinical participants also completed the Cognitive Emotion Regulation Questionnaire to assess the use of cognitive strategies to regulate emotional responses to negative life events.
Results: Patients with schizophrenia demonstrated poor affect perception on the TASIT, and impaired ability to infer the intentions of others in sarcastic social exchanges, compared to healthy control participants. In contrast, patients with bipolar disorder demonstrated intact affect perception, alongside impairments in the perception of simple sarcasm and deception that were not significantly different to those observed in schizophrenia. In bipolar disorder, aberrant detection of sarcasm was associated with increased tendency for 'rumination', decreased 'acceptance', and increased 'self blame'.
In schizophrenia, the ability to perceive affect was associated with increased 'self blame', and the ability to perceive sarcasm was negatively associated with the use of 'cognitive reappraisal' and 'refocus on planning'.
Conclusions: Deficits in affect perception and mental state inference may be more widespread in schizophrenia as compared to bipolar disorder, and appear to be differentially associated with the use of particular cognitive strategies for emotion regulation. Further research to determine the clinical significance of these findings for both disorders, and the potential contribution to social functioning impairments is warranted.

P-22-002
The prevalence of metabolic syndrome in Tunisian patients with bipolar I disorder

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Objectives: This study aims at investigating the risk to develop metabolic syndrome in patients with bipolar I disorder.
Methods: It was a case-control study carried out on 130 with bipolar I disorder (45 women and 85 men, mean age: 37.9 ± 12.1 years) recruited in the psychiatry department in the University Hospital of Monastir and 130 voluntary subjects (46 women and 84 men, mean age: 37.26 ± 13.1 years) with no psychiatric or endocrinological disturbances, matched for age and sex with bipolar patients. Triglycerides, c-HDL and uric acid were determined by enzymatic colorimetric method on Konélab 30™. Insulin was determined by chemiluminescence (Elecsys 2010TM Roche diagnostics). Metabolic syndrome was defined according to NCEP ATP III. Statistic analysis was performed using SPSS version 11.0.
Results: 26% of bipolar patients have metabolic syndrome versus 8.5% of controls. Patients with bipolar disorder have approximately 4-fold higher risk to develop metabolic syndrome than healthy subjects (Odds Ratio = 3.83, 95% CI: [1.84-7.96]). For all criteria defining metabolic syndrome, the prevalence in bipolar patients were higher than in control group, for HDL: 79.4% Vs 72.7 %, for hypertriglyceridemia: 94.1% Vs 81.8 %, for obesity: 73.5% Vs 45.4%, for high fasting glucose: 47% Vs 54.4%, for hypertension: 23.5% Vs 54.5 %. Metabolic syndrome in bipolar patients was significantly associated with high plasma uric acid level ($p = 7.10\text{-}3$) but no association in control group.
Conclusions: Bipolar disorders increase the prevalence of metabolic syndrome and consequently cardiovascular disease.

P-22-003
Vagus nerve stimulation in treatment-resistant depression: An Italian case-series

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Objectives: Treatment options for resistant depression include pharmacological and brain stimulation augmentations such as Vagus Nerve Stimulation (VNS). VNS provides a widespread continuous stimulation of different brain areas through an electrode attached to the left VN and connected to an implanted pulse generator. Recently, VNS showed to be effective in treatment-resistant rapid-cycling bipolar disorder. This case-series reports 12-month results of the first 3 consecutive patients treated with VNS at the IRCCS Policlinico of Milan.
Methods: The first subject was a 38 year-old man with Bipolar Disorder type I, comorbid GAD and current chronic Major Depressive Episode. Over the previous 2 years, he had been treated with different SRIs without showing any response. The other patients were two 45 and 62 year-old women, with the same diagnosis of rapid cycling Bipolar Disorder, who, during the previous 2 years, had been treated with antidepressants, mood stabilizers and antipsychotics without a sustained response. Patients' mean baseline total scores were 18.6 at the HDRS, 22.6 at the MADRS, 13 at the HARS, and 4.6 at the CGI-s. During the VNS trial, patients were maintained on their current pharmacological treatment.

Results: All patients completed the first year of stimulation showing the following mean total scores: 11.6 at the HDRS, 12.3 at the MADRS, 7 at the HARS and 3 at the CGI-s with a global improvement between 35% and 50% compared to baseline. There was a significant improvement on HDRS (t=4.49, p=0.046), MADRS (t=5.09, p=0.03), CGIs (t=5.00, p=0.03). Side effects including hoarseness and cough were present in the first 3 months of stimulation and gradually subsided.
Conclusions: Augmentative VNS was safe and effective in a small case-series of patients with resistant depression, including Bipolar rapid cycling depression. Confidence in the results is limited by the small sample and the lack of a control.

P-22-004
Gender differences in relation to comorbidity patterns and abuse in bipolar disorder

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Objectives: Several data indicate that presentation, course and comorbidity profile of Bipolar Disorder (BD) may differ between women and men (1). The aim of this study was to detect gender differences in relation to comorbidity patterns in a large sample of bipolar patients (BPs).
Methods: Study sample included 508 BPs, subdivided according to gender (224 males and 284 females). All patients were selected from those treated and followed up at the outpatient Mood Disorders Clinic of the University Department of Psychiatry of Milan. Patients with complete clinical charts were included in the study, after giving their informed written consent for being interviewed and for having reviewed the clinical information included in their charts and derived by the diagnostic interview. Diagnoses of Bipolar Disorder were obtained by the administration of a semi-structured interview based on DSM-IV criteria (SCID-I). Clinical variables, in particular psychiatric comorbidity and substance abuse, were compared between groups using chi-square tests. In addition a logistic regression was performed to evaluate whether gender was predictive of substance polyabuse or diagnostic subtype (BD type 1 or 2).
Results: The two groups were homogenous for psychiatric comorbidity ($\chi 2$=10.49, df=9, p=0.305), while they were different for the type of diagnosis with males more frequently diagnosed with BD type I and females BD type II ($\chi 2$=6.38, df=1, p=0.012). Men were more frequent abusers compared to women ($\chi 2$=15.71, df=1, p<0.0001) with a preference for alcohol ($\chi 2$=33.42, df=8, p<0.0001). Male gender results to be predictive of substance abuse (O.R.=2.198, p<0.0001) and a diagnosis of BD type 1 (O.R.=0.632, p=0.012)
Conclusions: In our sample of BPs, male gender seemed to be predictive of comorbid substance abuse and of a diagnosis of BD type 1. References 1. Arnold LM. Gender differences in bipolar disorder. Psychiatr Clin North Am, 2003; 26(3): 595-620.

P-22-005
Eating disorder and bipolar disorder: A hard to treat comorbidity

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Objectives: To review the literature regarding treatment of comorbid eating disorder and bipolar disorder.
Methods: Description of a case study taken from the eating disorders consultation. Sistematic review of medical and psychiatric databases regarding treatment of both conditions.
Results: Although previous research has suggested a link bipolar disorder and eating disorders, the association is poorly understood. Pharmacologic treatment approaches to patients with bipolar disorder and a co-occurring eating disorder require examination of the possible adverse effects of the treatment of each syndrome on the other and attempts to manage both syndromes with agents that might be beneficial to both.
Conclusions: There are high rates of comorbidity among these illnesses. Treatment must be carefully planned for both disorders.

P-22-006
Risk of cancer and HIV infection in patients with bipolar disorder: A systematic review

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Objectives: To synthesize the available knowledge on the prevalence of cancer and HIV infection in patients with bipolar disorder (BD).
Methods: Relevant studies were identified by a MEDLINE search from 1966 to January 2008, and supplemented by a manual review of reference lists of the articles identified and previous review articles. We included studies with any design, in patients with BD as diagnosed by any criteria, with sample size ≥30 patients, and reporting any measure of frequency or association about comorbidities. Priority was given to comparative studies.
Results: We identified 3 comparative studies providing information on the risk of malignancies (1 nested case-control study, 1 retrospective cohort study and 1 cross-sectional study) and 4 comparative studies presenting data on the prevalence of HIV infection (2 retrospective cohort studies and 2 cross-sectional studies). The nested case-control study showed that patients with BD had a similar cancer risk as people without either BD or schizophrenia; the other two comparative studies showed that some cancers were less common in patients with BD than in patients without psychiatric disorders (i.e. lymphoma or metastatic cancer) or than in the general population (i.e. prostate and lung cancer). As compared with the general population, two studies reported a higher prevalence of HIV infection among patients with BD (0.8-9.1% vs 0.3-0.5%) and one study reported a similar prevalence (1% vs 0.5%); in another study, the prevalence of HIV infection in patients with BD was higher than in patients without a psychiatric diagnosis (0.1% vs 0%).
Conclusions: Available data do not support that patients with BD have an increased risk of cancer. Although the information is limited, it suggests that BD might be associated with an increased frequency of HIV infection.

P-22-007
Treatment with escitalopram of patients with depressive disorders admitted in a general hospital

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Objectives: The study primary objective was to evaluate the effectiveness of the treatment with escitalopram on depressive symptoms of hospital admitted patients due to organic conditions. Secondary objectives were to evaluate the incidence and characteristics of adverse reactions occurred during antidepressant treatment, as well as their clinical management.
Methods: Methods: This was an observational post-marketing study with escitalopram, in which a total of 44 patients experiencing depressive symptoms during their admission in a general hospital, and fulfilling inclusion criteria (over 18 years of age, being admitted due to a non-psychiatric reason, and fulfilling diagnostic criteria for depressive disorder according to DSM.IV) were included. Clinical effectiveness of treatment was evaluated using the Hamilton scale, HAM-17, and the Clinical Global Impression-severity and - IMPROVEMENT scales.
Results: Results: A total of 44 patients, 25 females and 15 men, were treated with escitalopram, 4 (10%) of which withdrew form the study. All patients initiated treatment with a 10 mg /day dose. The mean maintenance dose was 12.9 mg./day during the first week and 12.3 mg /day during the second week. At hospital discharge, the mean administered dose was 12.1 mg /day. At the end of follow-up, decreases of 10.5 points in the Hamilton scale, and 2.6 points in the CGI severity scale were observed relative to baseline values. At final visit, 63.4% of patients stated they were feeling "much better" according to the CGI-improvement scale. A total of 4 withdrawals (10%) were recorded during the study, all of them due to adverse events and none due to a lack of efficacy. The most frequent adverse events were nausea, insomnia, and diarrhea.
Conclusions: Conclusions: Escitalopram seems to be a good treatment option for patients admitted in a general hospital due to organic reasons, and experiencing depressive symptoms during their admission, both for its therapeutic effectiveness and its good tolerability profile.

P-22-008
Prevalence of mixed episode in Korean bipolar patients

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Objectives: The prevalence of mixed episode in patients with bipolar disorder is 5 to 70 percents. Mixed episode satisfied with DSM-IV criteria is not frequent but the coexistence of manic symptoms and depressive symptoms in one episode is not uncommon. The purpose of this study was to investigate the diagnosis of mixed episode in clinical situation and estimate its prevalence in bipolar disorders.
Methods: Fifty one patients with bipolar disorder were enrolled in this study. Various cut-off points of Young Mania Rating Scale(YMRS) and Hamilton Rating Scale for Depression(HAM-D) were used to decide the current episode of a patient, compared with the clinical diagnosis.
Results: Forty eight out of 52 were diagnosed as bipolar I disorder by clinician, 3 were bipolar II disorder. Clinically 44 of 48 bipolar I patients were in manic episode, 4 were in depressive episode. All 3 bipolar II patients were diagnosed as depressive episode. In 44 manic patients, 18(40.9%) were diagnosed as euphoric, 5(11.4%) mixed or dysphoric, and 21(47.7%) psychotic. However, the patients with 6 or more in HAM-D were 23(52.3%) out of 44 manic patient, 6(33.3%) of 18 euphoric mania, and 12(57.1%) of 21 psychotic mania. And 9(20.5%) out of 44 mania, 2(11.1%) of 18 euphoric mania, and 3(14.3%) of 21 psychotic mania had 9 or more in HAM-D. All 5 mixed or dysphoric patients had 6 or more in HAM-D, and 4 of them had 9 or more. Three(6.8%) of 44 manic patients had 20 or more in YMRS and 15 or more in HAM-D.
Conclusions: Depressive symptoms were not uncommon in bipolar patients who were diagnosed as mania. Some patients with dysphoric mania were seemed to be misdiagnosed as euphoric mania. So clinicians have to ask about the presence of depressive symptoms even in manic patients.

P-22-009
Neural oscillatory activity to speech sounds in bipolar disorder

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Objectives: The synchronous activity of neurons mediated by oscillations in the Gamma band has been hypothesized to play an important role in the integration of perceptual features. Recently, abnormal auditory evoked neural oscillatory activity has been reported in patients with bipolar disorder. It was suggested that different magnetoencephalography (MEG) patterns of the evoked oscillatory activity (eOA) in 20-45 Hz to speech and non-speech sounds were an evidence of a fast mechanism for the representation and identification of speech sounds in humans. The current study investigated eOA to speech and non-speech sounds in patients with bipolar disorder.
Methods: Eleven patients and 24 normal control subjects participated in this study. MEG responses to speech and non-speech sounds were recorded and phaselockings in 20-45 Hz were analyzed.
Results: Patients showed significant later peaks of the eOA phaselocking to speech sounds in both hemispheres but no significant differences to non-speech sounds.
Conclusions: These results indicated that patients with bipolar disorder may be characterized by the delayed eOA phaselocking to speech sounds in both hemispheres.

P-22-010
Affective disorders as risk factors for delirium after cardiac surgery

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Objectives: Delirium is a known adverse outcome of cardiac surgery and research has supported an association with depression. The objective of this study was to determine the association between incident delirium after cardiac surgery and preoperative affective disorders, and also Type-D personality.
Methods: Ninety nine cardiac surgery patients free from delirium were assessed preoperatively for mood and anxiety disorders using structured diagnostic interview, and patients completed a Type-D scale. Patients were re-examined for new onset delirium in the postoperative period, and results were analyzed using Fisher's exact tests.
Results: Postoperative assessment showed that 22 (22.2%) patients met criteria for delirium. The prevalence of affective disorders at baseline was 12.1% for current major depression, 8.1% for panic disorder and 4% for generalized anxiety disorder (GAD). Delirium was associated with major depression (5.2% vs. 36.4%), $p < .001$, panic disorder (2.6% vs. 27.3%), $p < .001$ and GAD (1.3% vs. 18.2%), $p < .01$. Social phobia was not associated with incident delirium (1.3% vs. 9.1%), $p = .12$. Delirium was associated with high negative affect without social inhibition (23.4% vs. 45.5%), $p = .06$, but not in combination with social inhibition (i.e. Type-D personality) where a trend was observed (11.7% vs. 27.3%), $p = .10$.
Conclusions: This preliminary study highlights an association between affective disorders and incident delirium following cardiac surgery, while support was also shown for negative affect in isolation without social inhibition. This suggests that current distress rather than distressed personality style is associated with incident delirium. Possible pathophysiological pathways that underlie both the affective disorders and delirium may include activation of the sympathetic nervous system and the limbic-hypothalamic pituitary adrenal axis. Liaison psychiatrists should consider affective disorders as associated with incident delirium in hospital settings.

P-22-011
Columbia University Lithium Archives Project: Bridging the gap from laboratory evidence to clinical findings

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Objectives: Lithium has been used in the successful treatment of bipolar disorders since the 1950's. There is agreement among the experts that for these illnesses it remains the most researched and effective treatment to date. Advancements in basic neuroscience show that it has neuro-protective properties suggesting a possible efficacy in stroke, Alzheimer's and dementia. There is also evidence showing lithium protection of neurologic injury by changing GSK-3 inhibition in animals. This laboratory research has not been applied to humans other than the clinical trial of lithium in Alzheimer's disease currently being sponsored by the Medical Research Council in England. As of 2005, cerebrovascular disease, including stroke, is the third leading cause of death in the United States and Alzheimer's disease ranks seventh.
Methods: The Lithium Archives Project is based on systematic chart reviews of 8000 patients with mood disorders treated at the New York State Psychiatric Institute/Columbia University mood disorder clinic and its Foundation for Mood Disorders affiliate over the past 40 years. Data analysis of over 700 of these patients indicates that patients treated with lithium had a lower incidence of stroke, seizures and other cerebrovascular incidents compared to the general population and patients who did not receive lithium. This is a retrospective naturalistic study carried out by a trained psychiatric researcher extracting data of over 100 variables per chart followed by computer entry into SPSS.
Results: Given the significant level of 5% ($p = 0.05$), the patients receiving lithium had a significantly lower proportion of seizure disorders ($p = 0.012$), cerebrovascular disease ($p = .033$), and multi-infarct dementia ($p = .006$) than those without lithium treatment and general population.
Conclusions: Considering the neuroprotective and neuroregenerative properties of lithium and other psychotropic drugs, further exploration of these properties (i.e. clinical trials) should be conducted on patients with multiple stroke, Alzheimer's, and other cerebrovascular diseases.

P-22-012
Bipolar Disorders (BPD) in Emergency Departments (ED) in Latin-America: Prevalence and associated comorbidity

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Objectives: This study presents prevalence rates of BPD and associated comorbidity in ED in Latin American countries.
Methods: To identify patients with BPD, we used a combination of DSM IV- criteria interview and a questionnaire screen including the Mood Disorder Questionnaire (MDQ). We analyzed data from consecutive patients from hospitals in Argentina, Brazil, Chile, Colombia, and Mexico and described the demographic and comorbidity between BPD and non-BPD patients.
Results: Prevalence of BPD ranges from 3.8-6.0%. The estimate was based on a total of 1,535 patients, mean age 37 years, with response rates of 83.0%. Compared to non-BPD patients, BPD patients were more likely to be obese (39.7% vs. 26.9%) and to report a diagnosis of asthma (16.7% vs. 9%), thyroid problems (12.8% vs. 5.8%) and seizures (23.1% vs. 3.0%), all $p \leq 0.05$. BPD patients versus those without bipolar disorder were also differentiated in their psychiatric comorbidity as follows: higher rate of alcohol abuse (30.8% vs. 10.0%), ADHD (50.0% vs. 12%), depression (81.6% vs. 45.7%), OCD (20.1% vs. 3.0%), panic disorders (23.1% vs. 12.3%) and other anxiety disorders (82.1 %vs. 41.8%). Compared to non-BPD, suicidal plans and attempts were also significant higher in the bipolar group (11.5% vs. 2.8% and 10.3% vs. 1.8% respectively). Multivariate analysis identified ADHD, anxiety, depression, alcohol abuse, and last month suicide plan and attempts to be independently associated with BPD.
Conclusions: Our data suggest that the prevalence of BPD is elevated among ED patients in Latin American countries. BPD patients in ED are likely to have complex psychiatric, and medical histories, which will be necessary to take into account when evaluate and design ED-initiated interventions.

P-22-013
Chronic musculoskeletal pain: Depression, anxiety and altered cytokine levels

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Objectives: Chronic musculoskeletal pain is a disorder of poorly understood pathophysiology and is often associated with depression. In recent years, a pathogenic role of altered cytokine profiles has been implicated in depression and in chronic pain disorders.
Methods: 45 patients with chronic musculoskeletal pain - 25 with fibromyalgia syndrome (FMS) and 20 patients with non-specific findings (chronic muscle pain, CMP) - were enrolled in this study. The control group consisted of healthy volunteers. Depression and anxiety states were detected with ADS and HADS-D questionnaires. Messenger RNA (mRNA) of the pro-inflammatory cytokines interleukin (IL)-6 amd IL-1beta and of the anti-inflammatory cytokines IL-4 and IL-10 in peripheral blood cells was analysed using quantitative real-time polymerase chain reaction.
Results: About 2/3 of all patients showed increased depression values and about 1/3 showed increased anxiety scores. FMS patients had a higher likelihood of increased ADS and HADS scores than CMP patients. All control subjects had normal outcomes in both questionnaires. mRNA levels of IL-1beta and IL-6 were significantly higher in patients' blood than in healthy controls. The mRNA levels of IL-4 were significantly decreased in CMP patients and those of IL-10 were significantly decreased in FMS patients. Patients with a critically high anxiety-score, had increased IL-1beta and decreased IL-4 and IL-10 levels. Patients with elevated depression-values showed increased IL-6 and decreased IL-10 levels.
Conclusions: Patients with chronic musculoskeletal pain, especially FMS patients, had a higher likelihood to suffer from depression and anxiety states than healthy controls. They had pro-inflammatory cytokine profiles with reduced anti-inflammatory cytokine production, which may be involved in the pathogenesis of pain. The presence of depression and anxiety also seems to influence the cytokine profiles.

P-22-014
Effect of Melatonin on the serotonergic neural activity across the light-dark cycle

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Objectives: Melatonin (MLT) and serotonin (5-HT) are two biosynthetically related compounds that have been implicated in the etiology of seasonal affective disorder (SAD). However, their reciprocal interaction has not yet been characterized. In this study we explored the 5-HT neuronal activity of the dorsal raphe nucleus (DR) across the light-dark cycle and after MLT pharmacological and experimental manipulations.
Methods: Rats kept under a constant 12hr light-dark cycle (lights on at 7hr) were used to perform in vivo DR single unit extracellular recordings. We assessed the firing rate of 5-HT neurons at 4 different time periods of the light-dark cycle (2 periods for each phase). Recordings were done at basal conditions (CTRL) to compare with the responses after a single intravenous injection of MLT (1mg/kg), and after pinealectomy (Px) without and with MLT restitution.
Results: Under basal conditions, the firing rate of 5-HT neurons tends to decrease at the dark phase of the cycle (7-12hr: 0.9±0.08Hz; 13-18hr: 0.82±0.08Hz; 19-24hr: 0.69±0.11Hz; 1-6hr: 0.67±0.08Hz). MLT significantly decreased the 5-HT firing rate during the light phase and the second period of the dark phase (7-12hr: 0.63±0.07Hz; 13-18hr: 0.44±0.05Hz; 19-24hr: 0.59±0.06Hz; 1-6hr: 0.42±0.03Hz, $p \leq 0.05$). Meanwhile, Px significantly increased the firing rate on the second period of the light phase and during the dark phase (7-12hr: 0.8±0.10Hz; 13-18hr: 1.06±0.10Hz; 19-24hr: 1.0±0.11Hz; 1-6hr: 1.05±0.13Hz, $p<0.05$). In Px rats, MLT administration (1mg/kg) reinstates the firing rate to basal levels (CTRL: 0.67±0.09Hz; Px: 1.01±0.08Hz; Px+MLT: 0.49±0.09Hz, $p<0.01$).
Conclusions: These data suggest that MLT exerts a tonic inhibition over the 5-HT system and provide a new perspective in understanding the etiology of SAD.

P-22-015
Lithium effects on the chronobiological model of affective disorder

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Objectives: The present study was designed to examine the lithium effects on chronobiological models of affective disorder in experiment.
Methods: The studies were carried on adult male rats, weighting 220-240 g, with bipolar electrolytic lesion of locus coeruleus or middle brain raphe or suprachiazmatic nucleus (1.5 mA, 20 s with change polar). The control groups were intact and sham operated animals. The behavioral activity in «open field» and the rectal temperature was measured each 4 hours for 3 light:dark cycles (72 h) after preliminary animal's adaptation to condition of experiment. Rats were maintained in cages into groups with 7-9 animals. Standard diet was available ad libitum. The spectral and "Cosinor" methods were carried out. The studies were fulfilled during winter and summer solstices and also in constant light (LL24, 120 Lx, 10 days) and in constant total darkness (DD24, 10 days). Lithium hydroxybutirate (10 mg/kg, 8 days) was done in the beginning light or dark phase to the rats with destruction.
Results: In our experiments was defined that lithium hydroxybutirate phase delayed by activation of noradrenergic pathway to evening oscillator of rhythm activity. Lithium hydroxybutirate improved the light entrainment of circadian rhythms by lower of central serotoninergic functional activity. Lithium hydroxybutirate improved internal synchronization by activation of noradrenergic and serotoninergic pathways to "morning" oscillators of rhythms of body temperature and behavioral activity.
Conclusions: Chronopharmacological methodology will allowed formulate of monoaminergic conception of circadian phase dependence neurotropic and rhythmomodul Lithium effects; to integrate chronobiological and monoaminergic hypothesis of affective disorder and Lithium normothimic mechanisms.

P-22-016
The Redundant Signal Effect as index of abnormal interhemispheric integration in schizophrenic and bipolar patients

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Objectives: From the study of scientific literature it can be learnt that in schizophrenic patients there are abnormalities in interhemispheric interactions. A reliable behavioral measure of the interhemispheric integration of visual stimuli is the Redundant Signal Effect (RSE), that is, the speeding of responses of double stimuli presented across the vertical meridian as compared to single stimuli in one hemifield.
Methods: In a first experiment 34 medicated patients and 30 matched controls had to press as quickly as possible the space-bar of a PC keyboard with the index-finger, following presentation of small single or double visual stimuli. The latter appeared simultaneously one in the right and in the left visual hemifield. In a second experiment a different group of 18 patients and 18 controls performed the same task with the difference that not only simultaneous but also asynchronous double stimuli (ISI: 17,51 and 68 ms) were presented.
Results: In exp. 1 we found a reliably larger RSE for control (19 ms) than for schizophrenic subjects (25 ms). In the second experiment this effect was confirmed (19 ms for controls and 24 ms for schizophrenic). However, in schizophrenic patients the RSE practically disapperead (1 ms) at the ISI of 17 ms, while it was still present in normal subjects (4 ms).
Conclusions: Schizophrenic patients have an enlarged RSE in comparison to controls and this is in keeping with what has been found in patients with a total callosal section. This suggests an impairment of callosal interhemispheric integration in schizophrenics. Moreover, the duration of the visible persistence of the stimuli seems to be smaller in schizophrenic than in controls. We are testing a similar group of bipolar patients. The work is still in progress.

P-22-017
Auditory sensory gating deficit to voices in patients with psychotic bipolar disorder: A MEG study

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Objectives: P50 auditory gating is typically assessed by P50 suppression to the second auditory stimulus with a conditioning-testing paradigm via EEG. It has been reported that P50 suppression is often absent or reduced in patients with schizophrenia. Additionally, it was reported that bipolar patients with psychotic symptoms showed P50 sensory gating deficits. Magnetoencephalography (MEG) is superior for localization and analysis of lateralized cortical auditory responses. Previously, our group has reported that schizophrenia patients showed left-lateralized auditory gating deficits to human voices. The present study investigated auditory sensory gating to human voices using MEG in patients with psychotic bipolar disorder.
Methods: Auditory evoked MEG responses to human voices with a conditioning-testing paradigm were recorded in 16 patients with psychotic bipolar disorder and 26 age-, gender-, handedness-, and parental socioeconomic status-matched healthy control subjects. Auditory gating ratios were measured responses to the second stimulus divided those to the first stimulus (S2/S1).
Results: Patients with psychotic bipolar disorder showed significantly larger P50m gating ratios in the left (p=0.03) and the right (p=0.03) hemispheres, suggesting bilateral auditory gating deficits to human voices.
Conclusions: These results indicated that patients with psychotic bipolar disorder may be characterized by bilateral auditory gating deficits to human voices.

P-22-018
Depression and coagulation of blood

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Objectives: From case reports it has become clear that selective serotonin reuptake inhibitors (SSRIs) can cause bleeding disorders. J. D. Lewis et all. reported that use of any moderate or high affinity serotonin reuptake inhibitor is associated with an increased risk of hospitalization for upper gastrointestinal toxity (Lewis, 2008). Serotonin realease from platelets is important for regulating haemostasis. But D. Hougardy and all show that there was no significant difference between the SS, SL, LL genotypes of the serotonin transporter and the platelet function analyzer (PFA) closure time in 43 patients on >4 weeks of paroxetine therapy. The aim of the study was the evaluation of the blood coagulation in men with depression before the drug treatment.
Methods: In the current study 35 men between 20 and 40 years had been investigated. All of them had no antidepressive therapy in more than 6 month before the including to the study. Using the BDI's results we were divided the patients into 3 groups; 1) men without depression (n=18); 2) people with depression without directly need to prescribe the drugs (n=12); 3) severe depression in witch antidepresive drugs are strongly recommended (n=5).
Results: The protrombin's time which characterized the activity of so-called "protrombin's complex" (V, VII, X and II factors of blood coagulability) is increased in all groups. In second group we have seen the low level of protrombin's index. It's mean that there is an increased risk of bleeding in this people in comparing with healthy subjects. Man with severe depression have a normal blood coagulability.
Conclusions: People from second group may be in risk group of spontaneous bleeding without using any antidepressive drugs. From another side, when we use SSRI and reduce the level of depression lower than 24 (BDI) we have to worry about the hemorrhagic complications.

P-22-019
Headache and personal disorders in local wars participants

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Objectives: Recent literature shows an interest in the relationship between psychiatric disorders and headache. Many studies confirming high rates of comorbidity between depression, anxiety and migraine and tension-type of headache (TTH). J. C. Erickson (2008) said that migraine patients which had been previously deployed to a combat theater and have PTSD tend to experience more frequent headaches and more likely to have chronic headache. The aim of the current research was to study how the chronic pain syndrome (headache) influence to personality in local wars participants.
Methods: 162 patients (only men) had been investigated. They are divided into two groups according to age and local war in which they had got taking part: first group – the participants of Afghanistan's war (84 men, middle age 46,3, SD =1,38), and second one – the participants of local war in Chechnya (78 men, middle age 32,7, SD =1,54). We used Leonhard's questionnaire to reveal the character's accentuation and second edition of International headache classification to determine headache type.
Results: It seems that 113 patients suffer from cephalgia. Another 49 was a control. During the investigation of headache syndrome structure we have shown that most often patients suffer from posttraumatic headache (PH) – 61 men, and tension-type of headache (TTH) – 33 men. The number of men having got 18 and more in one or several scales of Leonhard's questionnaire is reliable more in the first group both for PH (85,7% and 69,2%) and TTH (85,7% and 68,9%). There were no differences between headache subgroups. But in patients from control group (without headache) the expression of personality changes did not increase during the age (69,6% in first group, 73,1% in second).
Conclusions: So chronic pain may be a risk factor for decompensation of personality changes.

P-42
Affective Disorders (Bipolar) II

P-42-001
Factors associated with spatial working memory function in euthymic bipolar patients

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Objectives: Patients with bipolar disorder (BD) experience a range of cognitive deficits during remission, impairments of working memory, executive functions and verbal memory have been observed. The reports on visuospatial ability in BD are inconsistent. The aim of the study was to assess spatial working memory function in euthymic bipolar patients on long-term prophylactic lithium treatment and to establish if there is a relationship between clinical variables and neuropsychological performance.
Methods: Sixty out-patients with bipolar disorder in remission lasting for at least four months (25 males, 35 females, mean age 54.1±11.1 years, education level 13.7±3.5) and 77 healthy control subjects (24 males, 53 females, mean age 51.5±14.1, education level 13.2±2.5) were recruited. Spatial working memory was assessed using two tests from the Cambridge Neuropsychological Testing Automated Battery: Spatial Working Memory (SWM) and Spatial Span (SS). They assess maintenance of spatial information (SS) and both the maintenance and manipulation components of visual-spatial working memory (SWM). The subtests were presented on a high resolution monitor with a touch-sensitive screen. Serum brain derived neurotrophic factor (BDNF) levels were estimated by enzyme-linked immunoassay method (ELISA, R&D, USA).
Results: Bipolar patients had significantly worse results in SWM, they made significantly more between search errors and used less effective search strategy than controls. The number of within-search errors (repetition of responses within the same search) did not differ significantly between groups. Patients performed also worse on SSP, but the difference did not reach statistical significance. Spatial working memory tests results were associated with a duration of illness and number of affective episodes. No correlation between BDNF levels and cognitive tests performance was found.
Conclusions: The results suggest that bipolar patients have cognitive deficits associated with a dysfunction of prefrontal cortex and that these deficits are related to progression of illness.

P-42-002
Serum Progesterone in males during euthymic phase of Bipolar Disorder – subtype differences

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Objectives: Aggression is a common problem in bipolar affective disorder occurring in some 30% of patients. Clinical correlates of aggression are thought to be a subsyndrome of bipolar disorder with paranoia and irritability along with impulsivity, suicide attempts and personality traits. Alterations in neurosteroids such as progesterone have been implicated in aggressive behaviour in animals and humans. The aim of this study is to examine the relationship between documented interpersonal violence, relevant clinical and biological correlates of this and the levels of progesterone in males with bipolar disorder during a period of euthymia.
Methods: The first 81 males aged 18-65 enrolled with the St Göran Bipolar Project and classed as Bipolar 1 or 2 according to Concensus of several psychiatrists were rated according to a standardized protocol for clinical features including documented interpersonal aggression. Ratings on the Swedish scales of personality, and on the ASRS were obtained along with CSF monoamine metabolites. Serum progesterone was measured between 08.00 and 09.00 and was analysed with respect to clinical variables of relevance for aggression and controlled for age.
Results: Raised concentrations of progesterone were found in the bipolar group who exhibited euphoric mood during mania or hypomania. Relatively reduced levels of progesterone were found in the subgroup with persecutory delusions, manic irritability and aggression (p=0.003-0.03). Impulsivity as measured by ASRS, trait aggression on the Swedish Scales of Personality and previous suicide attempts did not correlate with progesterone levels.
Conclusions: Serum progesterone is clinically elevated in some bipolar males but in those with the subsyndrome characterised by irritability and persecutory delusions during mania along with increased propensity to interpersonal aggression progesterone is significantly lower.

P-42-003
Quetiapine in the treatment of bipolar depression: Improvements in quality of life and functioning in four randomized, placebo – controlled trials

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Objectives: Patients with bipolar depression experience reduced quality of life (QOL) and functioning during acute episodes. This analysis assessed the effects of 8 weeks of quetiapine treatment on QOL and functioning in patients with bipolar depression.
Methods: Data from 4 double-blind, randomized, placebo-controlled trials (BOLDER I and II and EMBOLDEN I and II) that evaluated the efficacy and safety of quetiapine monotherapy (300 and 600 mg/d) in bipolar depression were combined. The Quality of Life Enjoyment and Satisfaction Questionnaire (Q-LES-Q) -Short Form measured QOL in BOLDER I, II, and EMBOLDEN II and the Sheehan Disability Scale (SDS) measured functioning in BOLDER II and EMBOLDEN I and II.
Results: Least squares mean (LSM) changes (SE) in Q-LES-Q total score from baseline to Day 57 were 9.69 (0.51), 9.95 (0.50), and 6.81 (0.54) with quetiapine 300 mg/d (n=488), quetiapine 600 mg/d (n=495), and placebo (n=405), respectively (ANCOVA; ITT population; P<0.001, both doses vs placebo). LSM changes (SE) in SDS score were -7.23 (0.49), -7.49 (0.49), and -5.91 (0.54) with quetiapine 300 mg/d (n=568), quetiapine 600 mg/d (n=584), and placebo (n=370), respectively (P<0.01). SDS domain scores showed that quetiapine (both doses) was associated with significantly reduced interference in work/school, social life, and family life/home responsibilities versus placebo (ANCOVA; P<0.05). Significant reductions in missed days at school/work and lost productivity due to bipolar symptoms were reported for quetiapine 600 mg/d compared with placebo (P<0.05). Tolerability was consistent with the recognized profile of quetiapine.
Conclusions: Quetiapine treatment (300 and 600 mg/d) for 8 weeks was associated with significant improvements in QOL and functioning compared with placebo in patients with bipolar depression. Supported by funding from AstraZeneca Pharmaceuticals LP.

P-42-004
The efficacy of quetiapine monotherapy in bipolar depression: Combined data from the BOLDER and EMBOLDEN studies

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Objectives: Combined data are presented from 4 placebo-controlled, fixed-dose studies (BOLDER I and II; EMBOLDEN I and II) that evaluated the efficacy of quetiapine in bipolar depression.
Methods: All studies included an 8-week, double-blind treatment phase in which patients were randomly assigned to quetiapine 300 mg/d, 600 mg/d, or placebo. EMBOLDEN studies also included lithium (EMBOLDEN I) or paroxetine (EMBOLDEN II) as active comparators. The primary outcome measure was change from baseline in MADRS total score at Week 8. Secondary outcomes included MADRS response (≥50% reduction in MADRS score) and remission (MADRS score ≤12) rates, and HAM-D and HAM-A scores.
Results: The mean change in MADRS total score at Week 8 was significantly greater in both quetiapine treatment groups versus placebo (-15.99 [n=811] and -16.17 [n=816] vs -11.43 [n=580] for quetiapine 300 mg/d, quetiapine 600 mg/d and placebo]; P<0.001 for both doses). Improvement was evident as early as Week 1 and continued through Week 8. The overall effect size for quetiapine was 0.45 (ITT, LOCF). A significantly greater proportion of quetiapine- than placebo-treated patients met response or remission criteria at Week 8 (response: 64.1%, 64.5% vs 46.4% for quetiapine 300 mg/d, quetiapine 600 mg/d vs placebo [P<0.001 for both doses]; remission: 61.3%, 62.9% vs 42.4%, respectively [P<0.001 for both doses]).

Quetiapine-treated patients showed significant improvement (P<0.001) in HAM-A and HAM-D total scores compared with placebo. Tolerability was consistent with previous reports for quetiapine.
Conclusions: Collectively, the BOLDER and EMBOLDEN trials—4 of the largest placebo-controlled studies of quetiapine monotherapy to date—confirm the efficacy of quetiapine (300 or 600 mg/d) in acute bipolar depression. Quetiapine was generally well tolerated in all studies. Supported by funding from AstraZeneca Pharmaceuticals LP.

P-42-005
The efficacy of quetiapine monotherapy in bipolar II depression: Combined data from the BOLDER and EMBOLDEN studies

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Objectives: Combined data are presented from 4 placebo-controlled studies (BOLDER I and II; EMBOLDEN I and II) that evaluated the efficacy of quetiapine monotherapy for depressive episodes in patients with bipolar II disorder.
Methods: This analysis was conducted in 819 patients (safety population). All studies included an 8-week, double-blind treatment phase in which patients were randomly assigned to quetiapine 300 mg/d, 600 mg/d, or placebo. The EMBOLDEN studies also included a 26- to 52-week continuation phase, in which patients achieving remission continued on the same dose of quetiapine or switched to placebo. Outcome measures included the change from baseline in MADRS total score at Week 8 (all studies) and time to recurrence of any predefined mood event (EMBOLDEN only). MADRS response and remission rates and HAM-D and HAM-A were also assessed.
Results: Improvements in mean MADRS total scores from baseline to Week 8 were significantly greater with quetiapine 300 mg/d and 600 mg/d (-15.58 and -14.88; P<0.001) compared with placebo (-11.61). MADRS effect sizes were 0.44 and 0.47 for quetiapine 300 mg/d and 600 mg/d (P<0.0001 vs placebo). In the EMBOLDEN studies, continued treatment with both doses of quetiapine significantly reduced the risk of recurrence of a mood event versus placebo (hazard ratios of 0.47 [95% CI, 0.25-0.92] and 0.18 [95% CI, 0.07-0.51]; P≤0.05 vs placebo). Common adverse events associated with quetiapine (both doses) included dry mouth, somnolence, sedation, dizziness, and headache. Rates of mania/hypomania were similar for quetiapine and placebo.
Conclusions: Quetiapine monotherapy demonstrated significant efficacy, compared with placebo, in the treatment of bipolar II depression. Quetiapine was generally well tolerated in all 4 studies. Supported by funding from AstraZeneca Pharmaceuticals LP

P-42-006
Effect of Quetiapine on the subjective estimates of sleep in the 8 weeks treatment of acute bipolar depression

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Objectives: Sleep disturbance is a characteristic feature of bipolar depression, and both the quality and quantity of sleep are typically adversely affected during depressive episodes. The purpose of this study was to evaluate the subjective estimate of sleep after quetiapine treatment in bipolar I and II patients.
Methods: Patients with bipolar I or II depression were included. They were treated with quetiapine and other mood stabilizers. The doses of quetiapine and mood stabilizers were flexible according to the clinical judgment. Clinical improvements were rated by severity of illness of Clinical Global Impression-Bipolar version (CGI-BP-S) and Montgomery-Asberg Depression Rating Scale (MADRS). Modified version of Leeds Sleep Evaluation Questionnaire (LSEQ) was used to assess the subjective measures of nighttime sleep and hangover, which included the factors covering four areas: i) getting to sleep (GTS), ii) quality of sleep (QOS), iii) awakening from sleep (AFS), and iv) behavior following wakefulness (BFW) or hangover during the next day. All assessments were done at baseline and week 4 and 8 after treatment.
Results: A total of 877 patients [bipolar I depression; N=577 (65.7%), bipolar II depression; N=301 (34.3%)] were recruited and 44 (5%) patients were dropped out during the study. CGI-BP-S and MADRS were significantly improved at week 4 and 8 compared with baseline. Clinical improvements were not differed between bipolar I and II patients. The nighttime sleep parameters (GTS and QOS) were more impaired in bipolar II patients at baseline. But, all sleep parameters of modified LSEQ were improved at week 4 and 8 without impairment of daytime hangover in both bipolar I and II patients and significant differences were not found at week 4 and 8 between two groups.
Conclusions: This result based on LSEQ suggests that quetiapine improved multiple dimensions of subjective estimate of sleep, including sleep quality and sleep duration, without daytime dysfunction.

P-42-007
Preclinical characterization of antidepressant effect of norquetiapine: Role of the norepinephrine transporter in preclinical depression models

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Objectives: Norquetiapine is a major human metabolite of quetiapine. Norepinephrine transporter (NET) inhibition by norquetiapine is a putative mechanism of the antidepressant activity of quetiapine. This preclinical study investigated assays of NET affinity, potency, and antidepressant activity for norquetiapine, quetiapine, reboxetine, and desipramine.
Methods: Binding to hNET was measured using radioligand [3H]-MeNER in HEK membrane. In-vitro potency was quantified by inhibition of fluoro dye uptake at hNET in HEK cells. In-vivo NET occupancy was measured by [3H]-MeNER displacement in rat thalamus. Antidepressant efficacy was investigated in rat and mouse forced swim tests (FST) and the rat learned helplessness test (LHT).
Results: Norquetiapine showed moderate affinity to hNET (Ki 29 nM), versus high affinity for reboxetine and desipramine and low affinity for quetiapine (Ki >4.3 μM). Norquetiapine demonstrated moderate inhibitory potency at hNET (Ki 34 nM), versus high potency for reboxetine and desipramine and low potency for quetiapine (Ki >4.6 μM). Norquetiapine displayed moderate NET occupancy (free plasma EC50=19 nM) compared with reboxetine and desipramine. Norquetiapine (10 and 20 mg/kg, subcutaneously) significantly reduced immobility in the mouse but not rat FST; desipramine and reboxetine were active in both, whereas quetiapine was not. Norquetiapine (5 mg/kg) significantly reduced escape failures in the LHT.
Conclusions: Norquetiapine has moderate affinity and potency at NET, unlike quetiapine. NET binding translates into in-vivo occupancy at behaviorally relevant doses. Norquetiapine is generally active in antidepressant models. These results support the hypothesis that NET inhibition mediates the antidepressant activity of norquetiapine. Supported by funding from AstraZeneca Pharmaceuticals LP.

P-42-008
Association study of brain-derived neurotrophic factor (BDNF) gene and bipolar disorder in Korea

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Objectives: Brain-derived neurotrophic factor (BDNF) plays an important role in cell survival, differentiation, and cell death as well as in neural plasticity. Recent studies have suggested that BDNF plays a role in the pathogenesis of bipolar disorder. The aim of this study was to investigate the association of the genetic variations of the BDNF gene with bipolar disorder in Korea. We also studied the possible association of these genetic variants with clinical features.
Methods: Val66Met polymorphism of the BDNF gene were analysed using a polymerase chain reaction (PCR)-based method in 166 bipolar patients and 214 controls.

Results: No significant difference was found between bipolar patients and controls in the genotype and allele frequencies for the investigated BDNF polymorphism. Also no significant difference in the clinical features such as age of onset, onset type, family history, and suicidal history was observed between the two groups.
Conclusions: Our results suggest that the investigated polymorphisms of BDNF gene are not major risk factors responsible for predisposition to bipolar disorder or its clinical features. However, replication studies with large samples are needed.

P-42-009
Nutritional, metabolic and endocrine disorders in patients with bipolar disorder: A systematic review

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Objectives: To evaluate the frequency of nutritional, metabolic and endocrine disorders in patients with bipolar disorder (BD).
Methods: A Medline search (up to January 2008) and manual review of reference lists of primary articles and review articles. All studies in Spanish or English, all study designs, BD diagnosis by any criteria, with a sample size of ≥ 30 patients, and which reported any measure of frequency or association. When available, priority was given to comparative studies.
Results: Thirty studies were identified: 18 (60%) cross-sectional and 12 (40%) retrospective cohort; 2 (6.7%) population-based; and 2 (6.7%) random sampling. The frequency of obesity in patients with BD was higher than that of the general population (n=4, 19-53% vs 9-14%), of other medical populations (n=1, 4.6% vs 1.1%) and of patients with schizophrenia (n=1, 11.6% vs 9.9%). The frequency of diabetes in patients with BD was higher than (n=5, 6 26% vs 2-16%) or similar to (n=2, 3.5-4.3% vs 3.4-4.8%) that of the general population; higher than that of other medical samples (n=2, 1.8-4.4% vs 0.6-2.2%) and similar to that of patients with schizophrenia (n=1, 17.7% vs 17.6%). The frequency of dyslipidaemia was higher than that found in a medical sample (n=1, 0.9% vs 0.3%) and in patients with schizophrenia (n=1, 27% vs 23%). The frequency of hypothyroidism was higher than that of a medical sample (n=1, 10% vs 3%).
Conclusions: BD appears to be associated with an increased rate of obesity. It may also be associated with increased rates of dyslipidaemia and hypothyroidism. Data on the association between BD and diabetes are inconclusive.

P-42-010
The clinical approach to bipolar disorder diagnosis

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Objectives: The importance of premorbid personality and past history is essential in correct diagnosis of Bipolar Mood Disorders, of which depressive episodes are often only one phase.
Methods: An observational study of the diagnosis of 300 consecutive new patients in a period of four years led to the main observation of an unusual high percentage of bipolar spectrum diagnosis. The diagnostic method follows the proposal for the classification of bipolar spectrum disorders into sub-types, based on an analysis of clinical interviews, personal history of the illness and familial anamnesis.
Results: It appears clear that significantly more patients within the series appear to have a soft bipolar illness than a major unipolar depressive episode.
Conclusions: Bipolar disorders (included subthreshold forms) are much more prevalent than previously believed; the inappropriate use of antidepressants in bipolar spectrum illness may lead to complications (induction of mania, mixed states or cycling).

P-42-011
A cyclical thought-action-mood-model of mixed bipolar disorders: From Kraepelin's "Fig.228" to Askland's biaxial model?

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Objectives: We can only handle 4 dimensions easily and need models like W. Weygandt´s T-A-M-model (1899). To understand "bipolarity" in 2006 Kathleen Askland (JAD 94:15-33,35-66) proposed a biaxial interaction between neurochemical capacity ("range") and neuroelectrical modulation ("tonicity") driven by genes for transmitter systems and ion-channels respectively.
Methods: The 3+1-TAM-cube spans Thought, Action and Mood. At its corners Depression and Mania both have three mixed states with one "inverted" score. It clarifies the lagged triple sinus curves of Fig.228 (S.1289). A loop is inserted made out of an approach wave closed to form a perception-action loop: default mode => need => appetitive planning (Thought) => ecological encounter (Action) => consumption => "Mood". In mechanics such figures of Lissajou model sinusoidal loading with damping: strain (analogous to "Action") lags behind stress ("Thought"). This cube models mixed states, anxiety disorders and basic emotions.
Results: Using this cyclical 3+1-D-model it is argued by the structure of SH-oscillators that neurochemical capacity "corresponds" to the T-axis (representing 4D-"Thoughts" knowing that) and neuroelectrical modulation to the psychomotoric A-axis (summarizing higher-D "Action" knowing how).
Conclusions: The model predicts that the "parietal motor brain" (A) systems (Rizzolatti 2004) perform High-D-operations and are influenced more by ion-channels. 4-D "symbolic search systems" (T) are dominated more by transmitters. Deformed loops depict temperaments. Cholerics use clear fast frugal models (T-) which rapidly lead to "Action". Sanguinics with a stiff "T-spring" search for truthful, but too slow models. A graphical synopsis of the model and its psychobiological evidence are shown.

P-42-012
French validation of the BAC-A (brief assessment of cognition in affective disorders): A pilot study

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Objectives: Study cognition in bipolar disorders is an essential topic to first improve knowledges about the etiopathology of the disease (search of specific endophenotypes) and then to target better treatments (specific pharmacology and remediation therapy). The objective of this study is to do a transcultural validation of the BAC-A (Version A) (Keefe and al., 1999) in a French sample bipolar disorders patients
Methods: 1-Proceed to the French translation of the BAC-A; 2-Assess a sample of bipolar disorders with the BAC-A to a matched sample of controls on sex, age, taking account of the level education. We used first bivariate analysis then we proceeded a linear regression using the significant variables. The level of significancy is $\alpha < 0, 05$.
Results: We assessed 17 stabilized bipolar disorders according to DSM-IV criteria and their controls with the French translation of the BAC-A (approved by Duke University), recruited from the Clermont de l'Oise psychiatric hospital (Picardie area, France). Bivariate tests show significant results regarding: 1- motricity ($p = 0, 001$); 2- attention and speed of processing ($P = 0, 008$) with bipolar disorders. Then linear regression show significant **results:** 1- motricity with bipolar disorders ($p = 0, 025$); 2- non affective interference with bipolar disorders ($p = 0, 025$). There also some trends significative and non significative results and some significative results linked with sex and level of education.
Conclusions: Bipolar disorders perform worse than controls in some cognition domains: motricity, affective interference and probably attention and speed of processing. These results must be confirm in a larger sample in order to go on the validation of this new instrument. The BAC-A appears to be useful to assess cognition in affective disorders.

P-42-013
Bipolarity in adolescent populations

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Objectives: Bipolar Disorder among adolescent represents a new major challenge to Psychiatry. Its identification among adolescent is more recent than among adults. The present article aims to revisit 1/the history of the emergence of adolescent BPD as a psychopathological entity; 2/ its diagnostic criteria; 3/ its evolution, risk factors and associated co morbidity; 4/ its differences from and links to ADDH; 5/ treatment in both its acute and maintenance phases.
Methods: Review of the literature in Medline – Psycinfo – Psycarticles
Results: Over the past ten years, researchers have been attempting to test, among adolescents, the knowledge that has already been validated among adults through reproducing and analyzing the effects of the adults' treatment guidelines among adolescents. Moreover, others have used various brain imagery anatomic analyses in order to compare structural abnormalities among adolescents and adults. As they have found, the specific aspects of adolescent BPD become manifest in some screening modalities and difficulties. Criteria such as BPD phenotype --or having a first degree relative with BPD—are associated with the probability of its emergence. Diagnostic symptoms such as grandiosity, flight of ideas, decreased need for sleep, and hyper sexuality seem to discriminate BPD from ADDH. Finally, anti social behaviors, drug consumption, and suicidal risks often complicate the clinical description. Lithium, Anticonvulsive and atypical neuroleptic drugs remain the molecules of choice for treatment.
Conclusions: Although diagnostic tools are still being developed, numerous studies suggest that the adolescent form of BPD still remains insufficiently identified. However, early diagnosis seems essential to improve its prognosis

P-42-014
Asenapine efficacy in patient subpopulations experiencing manic or mixed episodes of bipolar disorder: A pooled analysis

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Objectives: Asenapine is being developed for bipolar disorder and schizophrenia. We describe the efficacy of asenapine in treating acute mania or mixed states in patients with bipolar I disorder using pooled data from two pivotal trials.
Methods: In two similarly designed 3-week trials (Ares 7501004 and 7501005), patients were randomized to sublingual asenapine (10 mg BID on day 1, flexible 5 or 10 mg BID thereafter; n=379), oral olanzapine (given to verify assay sensitivity; 15 mg QD on day 1, flexible 5–20 mg QD thereafter; n=395), or placebo (n=202). Change from baseline to day 21 on the Young Mania Rating Scale (YMRS) and the Clinical Global Impression for Bipolar Disorder severity score (CGI-BP-S) was assessed versus placebo in patient subpopulations diagnosed with either manic or mixed episodes (exploratory post hoc ANCOVA with LOCF, using pooled data from both trials).
Results: After pooling the data (N=976), twice as many patients were diagnosed with a manic episode (69.1%) vs a mixed episode (30.9%). Mean ± SD changes from baseline to day 21 in YMRS total score were greater with asenapine (manic: –11.4±11.3, n=265; P<0.0001; mixed: –10.4±11.1, n=107; P<0.071) and olanzapine (manic: –14.3±10.8, n=269; P<0.0001; mixed: –12.3±8.2, n=122; P<0.003) than with placebo (manic: –6.1±11.5, n=131; mixed: –7.7±10.2, n=66). Mean ± SD changes from baseline to day 21 in CGI-BP-S score were also greater with asenapine (manic: –1.2±1.5, P=0.0009; mixed: –1.4±1.5, P=0.009) and olanzapine (manic: –1.5±1.3, P<0.0001; mixed: –1.3±1.1, P=0.003) than with placebo (manic: –0.8±1.4; mixed: –0.8±1.1).
Conclusions: This exploratory analysis indicates that asenapine and olanzapine reduce the severity of acute manic symptoms in patient subpopulations with bipolar I disorder diagnosed with either manic or mixed episodes. This research was supported by Schering-Plough and Pfizer Inc.

P-42-015
A study to evaluate the efficacy, safety and tolerability of atipical antipcychotics in subjects with bipolar disorder Type 1

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Objectives: Bipolar disorder is a chronic disease, which need treatment of maintenance for long term to prevent any recurrence. Atypical antipsychotics proved their efficacy not only in schizophrenia, but also in many other psychiatric disorders, like affective disorder. In our study we evaluated the efficacy and safety of administration of atypical antipsychotics to prevent recurrence of any affective episode in patients with bipolar disorder type I.
Methods: The patients were randomized in 4 therapeutic groups: Olanzapine, Quetiapine, Risperidone, Valproat. Valproat was used to assure the sensitivity of the study and to evaluate the balance risqué-benefit of atypical antipsychotic versus classical moodstabilizators like Valproat. We enrolled 120 patients for University Hospital of Psychiatry Socola Iasi with a diagnosis of bipolar disorder type I, current manic or mixte episode, age between 18 to 65 years old. For validation of diagnosis we used criterion for DSM IV and SCID interview. The study had 4 phases: acute, continuation, maintenance and follow-up. The instruments of assessments were YMRS for manic symptoms, MADRS for depressive symptoms, CGI severity and improvement for bipolar disorder, GAF to evaluate functioning of the patient, SSI for suicidal thoughts and BARS, SAS, AIMS to evaluate the safety of administration of the drugs. We also evaluate the costs of therapy.
Results: Atypical antipsychotic had a very good tolerability and they determined decreasing number of recurrence and a good compliance for treatment. We also observed an incresed quality of life for this patients, wich had a good functioning.
Conclusions: Monotherapy proved a huge benefit in therapy of maintenance for long-term in bipolar disorder. That's why atypical antipsychotics represent the future of maintenance therapy in bipolar disorder type I.

P-42-016
Cannabis use and bipolar disorder: Search for association and causality through a review of literature

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Objectives: It has been established that cannabis use is involved in the emergence and evolution of psychotic disorders. Although cannabis use is very frequent in bipolar disorders, there has been a considerable debate about the association observed between these two disorders. This review aims to clarify the relation between cannabis use and bipolar disorder, in order to unveil a possible causality and find the effect of cannabis on the prognosis and expression of bipolarity.
Methods: The review used MedLine database using the keywords "cannabis" or "marijuana" and "bipolar" or "mania" or "depression". This search found 158 publications related to these topics. From these, 36 articles were found clinically relevant to subject and were included and discussed in this review.
Results: The first studies discussing the link between cannabis use and psychotic disorders reveal manic features in the substance abuse group, hence suggesting a possible association between cannabis use and bipolar disorder, in favor of triggering a manic episode. According to the studies, between 25% and 64% of bipolar patients are cannabis users, and the prevalence is higher in younger and male patients. The risk of developing a mood disorder is higher among cannabis user compared to the general population. This substance abuse in bipolar disorders would increase the frequency and duration of manic episodes without changing the total duration of mood episodes. In a first episode of bipolar disorder, the use of cannabis would increase the rate of relapses, of manic episodes and worsen the prognosis of the disorder.
Conclusions: The frequency of substance abuse in bipolar disorders is higher than the prevalence in the general population, and cannabis is one of the most used illegal substances in the worldwide. Hence, the association between cannabis use and bipolar disorders is frequent.

P-42-017
Family history, obstetric complications and age of onset in bipolar patients

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Objectives: A number of studies have suggested that exposure to obstetric complications increases the risk of bipolar disorder and may account for some of the structural brain abnormalities reported in some patients with bipolar disorder. However, little research has examined the relationship between obstetric complications, age at illness onset and genetic predisposition to bipolar disorder. The aim of this study was to test the hypothesis that bipolar disorder in general and early onset disorder in particular are associated with higher frequency of pregnancy and birth complications. The study also examined the relationship between obstetric complications, genetic risk and age of illness onset.
Methods: Thirty DSMIV bipolar I patients in remission and twenty seven healthy controls were investigated using structured interview, life chart and pregnancy and birth complications questionnaire. Family history, pregnancy and birth complications and age of illness onset were verified and rated. Comparisons were made between patients and age and gender matched controls and between two patient groups with age of illness onset above and before 21 years cut-off point.
Results: There was no significant difference between bipolar patients and healthy controls in the reported obstetric complications. Early and late onset patient groups did not differ significantly in the rates of familial affective disorder and obstetric complications.
Conclusions: The findings of this study suggest that bipolar disorder, irrespective of family history or age of onset is not associated with increased risk of obstetric complications. Further research is needed to explore this issue in larger cohorts of bipolar patients.

P-42-018
Mixed states with or without psychotic symptoms: 24-month outcomes of the European Cohort Emblem

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Objectives: Few data are available regarding prevalence and course of mixed states (MS) with psychotic symptoms (PS). This analysis aimed to describe MS with PS and compare patient characteristics and outcomes to MS without PS at baseline and after 24 months in an observational study.
Methods: EMBLEM (European Mania in Bipolar Longitudinal Evaluation of Medication) is a 2-year prospective, observational study of outcomes following a manic/mixed episode. Adult in/outpatients with bipolar disorder were enrolled within the standard course of care if they initiated or changed oral medication for acute mania.
Results: Prevalence of MS at baseline was 23.8% (572) and of these, 45.3% (259) had PS. Baseline socio-demographics, psychiatric history and social and functional characteristics were comparable in MS with or without PS except for the number of depressive episodes in the past year. MS with PS were more severe at baseline (CGI-BP: Overall, mania, hallucination/delusion, YMRS score, $p<0.001$), in the past year (CGI-BP Overall, $p=0.049$) and more were inpatients (48.4% vs 30.7%, $p<0.001$). Baseline patterns of prescription were different, with more atypical antipsychotic (APA) and antimanic combinations prescribed to MS with PS (respectively 81.5% vs.56.5%, $p<0.001$, 61.8% vs. 53.4%, $p=0.043$) and less antidepressant (32.4% vs. 48.2%, $p<0.0001$). More switches to depression in MS without PS (38.5% vs. 17.1%, $p<0.001$) and conversely more switches to mania in MS with PS (84.8% vs. 64.2%, $p<0.001$) were observed. During follow-up, no differences were observed in rates of recurrence, relapse and recovery.
Conclusions: Presence of PS in MS is associated with baseline severity but there is no evidence of an impact on the course of MS in this population. This may be due to specific pattern of prescription, in particular a higher proportion of APA and combination therapy prescribed in MS with PS.

P-42-019
Spanish consensus on physical health in patients with bipolar disorder

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Objectives: Bipolar disorder is a serious mental illness which may affect between 2% and 5% of the population. These patients present much higher morbidity and mortality rates than the general population. In addition to a higher mortality rate from suicide, they also have a higher prevalence of other physical disorders. The purpose of this consensus is to establish recommendations for diagnostic procedures and clinical interventions in order to control the risk factors which have repercussions on the physical health of the patients.
Methods: After carrying out a systematic review of medical co-morbidity and mortality rates in bipolar disorder, two multidisciplinary consensus meetings were held in which 31 psychiatrists and 11 experts from other medical specialities participated. Working groups were formed for each speciality for the purposes of adapting the guidelines applied in the general population to these patients.
Results: The bibliographical review revealed an increased risk of hypertension, obesity, smoking, pulmonary diseases, migraine and HIV infection. There is evidence of higher mortality rates from cardiovascular and respiratory diseases and infections, as well as from suicide. The expert group reached consensus on a series of basic measures for detecting medical co-morbidity. The resulting recommendations will be validated by Spanish Psychiatry and General Medicine Associations.
Conclusions: The physical health of patients with bipolar disorder could be improved. It is hoped that the publication of this consensus will have an impact in terms of better psychosocial functioning, quality of life and life expectancy for these patients in Spain.

P-02
Affective Disorders (Unipolar) I

P-02-001
Executive control of emotion in depression

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Objectives: Depression is associated with impaired neuropsychological function that may contribute to emotion dysregulation. In particular, frontal executive processes and inhibitory mechanisms implicated in adaptive emotion regulation are disrupted in depression. In this study, we investigated associations between executive and inhibitory processes and emotion regulation in depressed subjects.
Methods: Twenty-four depressed subjects (10 female; mean age = 41.83 yrs, SD = 10.89 yrs) completed neuropsychological tests to assess inhibition and sustained attention (Rapid Visual Processing; RVP), emotional inhibition (Affective Go/No-go; AGN), set shifting and mental flexibility (Intra-Dimensional/Extra-Dimensional Shift; ID/ED), and working memory (digit-span). The use of cognitive emotion regulation strategies in response to negative life events was assessed using the self-report Cognitive Emotion Regulation Questionnaire.
Results: Better digit span performance was associated with adaptive cognitive emotion regulation strategies of ‚refocus on planning' and ‚positive refocusing' as well as the inclination to ‚blame others'. Errors in set-shifting on the ID/ED task, and failure to respond to positive emotions on the AGN task were negatively associated with the tendency to 'refocus on planning'. In addition, erroneous responses to neutral stimuli as emotional on the AGN task were negatively associated with 'positive refocusing'. Finally, failure to inhibit responses to emotional stimuli on the AGN task, and false alarm errors reflecting poor inhibition on the RVP were associated with reduced use of 'positive reappraisal'.
Conclusions: The tendency to employ adaptive cognitive emotion regulation strategies may be compromised in depression due to known impairments in cognitive flexibility, working memory, and inhibition of emotional material.

P-02-002
Selective response of dopamine in the presence of ascorbic acid at carbon nanotubes paste modified electrode

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Objectives: Selective detection of dopamine in the presence of ascorbic acid at carbon nanotube paste modified electrode. Determination of the concentration of this neurochemical is important and plays a very important role in the function of the central nervous, renal, hormonal and cardiovascular system, which is a symptom of several diseases such as schizophrenia and Parkinson ism and to the HIV infection.
Methods: Electrochemical approach is used to detect dopamine. The catalytic activity of ferophthalocyanine towards different neurotransmitters was compared with that of CoPhC complex. The chemically modified electrodes based on carbon nanotube paste electrode (CNTPE) have been tested for the capacity to electrochemically detect dopamine and serotonin (5-HT).
Results: Electrochemical approach is used to detect dopamine at low applied potential. The present study proposes an easy-to-make and low-cost sensor construction for the selective determination of dopamine. The chemically-modified carbon nanotube paste electrode is capable of enhanced electrochemical monitoring of dopamine due to the properties of the electrode material and metallophthalocyanines used as mediators.
Conclusions: Interference of ascorbic acid in the carbon nanotube paste modified electrodes response was eliminated.

P-02-003
An association between physical activities and depression in working population

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Objectives: An association of symptoms of depression with routine and leisure physical activities was evaluated in working population.
Methods: 136 inhabitants of Palanga having a permanent job, 48 men (35%) and 88 women (65%), ranging from 35 to 58 years of age, participated in the study. WHO Wellbeing Index was used to assess depressive mood. Participants filled in forms with information on their leisure physical and sport activities (raiding a bike, attending aerobics, attending gym, running, swimming, playing basketball or volleyball, riding a horse etc.), exercising at least 30 min. a day, and how long it takes walking to the job and back home.
Results: An association between symptoms of depression and different forms of routine physical activities, such as exercise ($p<0.01$); walking to the job ($p<0.01$); or sport activities in leisure time ($p<0.05$) was found. Symptoms of depression were more prevalent among those with lower incomes ($p<0.05$). Marital status and education had no impact on the presence of symptoms of depression.
Conclusions: Routine physical activities independently from their form are related with the lower presence of symptoms of depression in working population.

P-02-004
The increase in Serotonin Transporter occupancy from single to multiple dosing is associated with treatment outcome in major depressive disorder

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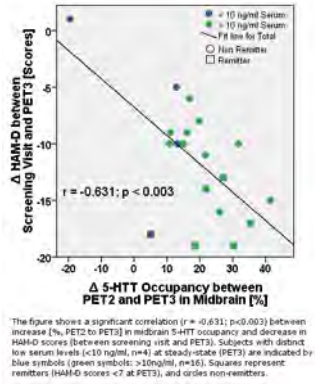
Objectives: The serotonin transporter (5-HTT) occupancy of SSRIs can be quantified by PET and the radioligand [11C]DASB [1,2]. Here we investigated the relationship between treatment outcome and the 5-HTT occupancy in patients with major depressive disorder (MDD) treated with escitalopram or citalopram.
Methods: 20 medication-free (≥3 months) outpatients (DSM-IV, HAM-D≥16; mean age ± SD: 41.95±8.8 years; 12 women) were analyzed in this double-blind, randomized PET study. Treatment doses were 10mg/d escitalopram or 20mg/d citalopram, i.e., equal doses of the S-enantiomer. Each patient underwent 3 PET scans (ID 354.1±93.6 MBq), PET1 at baseline before medication, PET2 6h after first administration, and PET3 after 24.7±3.3 days of treatment. The Hamilton Depression Rating Scale (HAM-D, 17-item) was assessed at screening visit and before each PET scan. 5-HTT occupancy was calculated via the Logan graphical analysis (reference cerebellum) in the midbrain, thalamus, nucleus caudatus, putamen.
Results: There was a significant increase in S-citalopram plasma levels ($p<0.001$; 6.91±2.2ng/ml to 14.55±5.9ng/ml; mean ± SD) and midbrain 5-HTT occupancy ($p<0.001$; 63.41±9.5% to 78.42±9.5%) between single and multiple doses, and a significant decrease in HAM-D scores ($p<0.001$; 20.75±3.2 to 9.35±4.4). We found no significant correlation between 5-HTT occupancy at steady state (PET3) and HAM-D scores. However, the increase in midbrain 5-HTT occupancy between single (PET2) and multiple doses (PET3) were correlated ($r=-0.631$; $p<0.003$; $n=20$) with the improvement in HAM-D scores between screening visit and PET3 (see figure). The correlation in the thalamus ($r=-0.519$; $p=0.019$) and other areas investigated did not survive adjustment for multiple comparisons. There was no significant correlation between absolute values or increase in plasma levels and change in HAM-D scores.

Conclusions: In contrast to plasma levels, the increase in 5-HTT occupancy during treatment with escitalopram and citalopram is associated with clinical improvement within the first 3 weeks elucidating the biological changes which take place during amelioration of psychopathology with specific acting treatments. References: [1] Meyer JH, Wilson AA, Ginovart N, Goulding V, Hussey D, Hood K, Houle S, Occupancy of serotonin transporters by paroxetine and citalopram during treatment of depression: a [(11)C]DASB PET imaging study, American Journal of Psychiatry, 2001 Nov;158(11):1843-9 [2] Reimold M, Batra A, Knobel A, Smolka MN, Zimmer A, Mann K, Solbach C, Reischl G, Schwärzler F, Gründer G, Machulla HJ, Bares R, Heinz A. (2008), Anxiety is associated with reduced central serotonin transporter availability in unmedicated patients with unipolar major depression: a [11C]DASB PET study, Molecular Psychiatry, vol. 13, no. 6, pp. 606-13



The figure shows a significant correlation (r = -0.631; p<0.003) between increase [%, PET2 to PET3] in midbrain 5-HTT occupancy and decrease in HAM-D scores (between screening visit and PET3). Subjects with distinct low serum levels (<10 ng/ml, n=4) at steady-state (PET3) are indicated by blue symbols (green symbols: >10ng/ml, n=16). Squares represent remitters (HAM-D scores <7 at PET3), and circles non-remitters.

P-02-007

Modafinil reduces microsleep during partial sleep deprivation and improves antidepressant treatment response

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Objectives: Sleep deprivation (SD) can induce a prompt decrease in depressive symptoms within 24 hours. Following the recovery night, however, a relapse into depression occurs in most patients. Recovery sleep, naps and even very short episodes of sleep [termed, microsleep (MS)] during SD have been shown to provoke a rapid relapse into depression. This study tested the hypothesis that modafinil reduces MS during SD and augments antidepressant treatment response.

Methods: 28 patients with a major depressive episode (13 men, 15 women) age 45.1 ± 12.1 years (mean ± SD) were investigated using a double blind placebo controlled study design. All patients were treated with a stable mirtazapine monotherapy. A partial SD (PSD) was performed after one week. Additional morning treatment with modafinil vs. placebo started during PSD and was maintained over two weeks. Sleep EEG and MS episodes were recorded with a portable EEG. Depression severity was assessed using the Hamilton Depression Rating Scale during and after PSD and at follow-ups after one and two weeks.

Results: Modafinil treated patients showed significantly reduced microsleep during PSD (11.63 ± 15.99 min) compared to the placebo group (47.77 ± 65.31 min). This suppression of MS did not enhance the immediate antidepressive effect of PSD. After two weeks of treatment, the modafinil group showed a significant reduction in REM density, accompanied by a descriptively 3-fold increase in the antidepressive response rate.

Conclusions: Modafinil reduces MS during PSD. Furthermore, modafinil augments the antidepressant treatment response to mirtazapine. We conclude from this study, that the augmenting effect of modafinil is not mediated by the suppression of microsleep that is thought to detriment the antidepressive effects of PSD. We assume that modafinil exhibits its augmenting effects on antidepressant treatment via modulation of monoaminergic as well as cholinergic neurotransmission as indicated by the decrease in REM density.

P-02-008

No predictors of antidepressant response to Milnacipran was obtained using the Three Factor Structures of the Montgomery and Åsberg Depression Rating Scale in Japanese patients with major depressive disorders

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Objectives: Milnacipran, a new specific serotonin and noradrenaline reuptake inhibitor, is as effective as tricyclic antidepressants. Symptomatological predictors of antidepressant response to milnacipran have not been studied until now.

Methods: This study included 101 Japanese patients who fulfilled the DSM-IV criteria for the diagnosis of major depressive disorders and whose score on the Montgomery and Åsberg Depression Rating Scale (MADRS) was 21 or higher. Eighty-three patients were finally included. Patients with a pretreatment MADRS score of ≥ 31 points were defined as "severe" (n = 28), and the rest, "non-severe" (n = 55). The three-factor model of MADRS was used for analysis; the first factor was defined by 3 items, the second factor was defined by 4 items and the third factor was defined by 3 items representing dysphoria, retardation, and vegetative symptoms, respectively. Milnacipran was administered twice daily for 6 weeks. The initial dose was 50 mg/day; after a week it was increased to 100 mg/day.

Results: No significant difference was observed in the mean score of first factor, second factor and third factor at pretreatment time between responders and non-responders in both "severe" and "non-severe" patients.

Conclusions: No predictor of antidepressant response to milnacipran was obtained using the three-factor structures of the MADRS in Japanese patients with major depressive disorders.

P-02-009

Predictors of antidepressant response to Fluvoxamine Obtained using the Three-Factor Structures of the Montgomery and Åsberg Depression Rating Scale for major depressive disorders in Japanese patients

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Objectives: Fluvoxamine, a selective serotonin reuptake inhibitor, is widely used to treat major depression. However, the symptomatological predictors of the response to fluvoxamine have not been studied.

Methods: This study included 100 Japanese patients who fulfilled the Diagnostic and Statistical Manual of Mental Disorders (DSM)-IV criteria for the diagnosis of major depressive disorders and whose score on the Montgomery and Åsberg Depression Rating Scale (MADRS) was 21 or higher. Eighty-one patients were finally included. Patients with a pretreatment MADRS score of ≥31 were defined as "severe" (n = 32) and the rest, "non-severe" (n = 49). The three-factor model of MADRS was used for analysis: the first factor was defined by 3 items, the second factor was defined by 4 items, and the third factor was defined by 3 items representing dysphoria, retardation, and vegetative symptoms, respectively. Fluvoxamine (100~200 mg/day) was administered twice daily for 6 weeks.

Results: In the non-severe patients, the mean factor 3 score of the non-responders at pretreatment was significantly higher than that of the responders. However, a significant difference was observed in the mean factor 3 scores from 1 week onwards between the non-severe responders and non-responders. Further, the fluvoxamine response rate in the severe patients was 75% and higher than that of the non-severe patients (65.3%).

Conclusions: This study suggested that a low factor 3 score at pretreatment was a good predictor of the response to fluvoxamine in non-severe patients. The marked efficacy of fluvoxamine in the treatment of severe patients was also confirmed.

P-02-010
Neuropsychological impairment and high prevalence of depression in patients with chronic Hepatitis C virus

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Objectives: WHO estimates that globally 170 million people are infected with chronic hepatitis C virus (HCV). Approximately 75% of these people have contracted the disease by intravenous substance abuse. Impaired cognitive function is commonly found in patients infected with HCV. This may be due to a toxic effect of the virus or by neuroinflammatory processes having a damaging cerebral effect. The cognitive deficits appear in the pre-cirrhotic stage of the disease and impair in combination with a high prevalence of depression, chronic fatigue and reduced quality of life the patient's level of functioning. Furthermore, the antiviral treatment with interferon induces depression in approximately 30% of the patients. Very little is known about the causal relationship of HCV infection, psychiatric disorders and neuropsychological deficits, but evidence has shown that these symptoms cannot solely be accounted for by a history of substance abuse. In the present study we wish to thoroughly examine cognitive impairment and psychiatric symptomatology in HCV patients in order to explore the causal relationship. Furthermore, it is sought to identify specific personality traits and lifetime prevalence of psychiatric disorders in the group of HCV patients developing interferon induced depression.
Methods: 60 HCV patients about to commence antiviral treatment will be examined with an extensive neuropsychological assessment battery and diagnosed according to the diagnostic interview Schedules for Clinical Assessment in Neuropsychiatry (SCAN). NEO-P-IR measuring personality traits will also be administered. In the 8th treatment week the patients will again undergo SCAN. 40 HCV patients not about to commence treatment and 30 healthy participants will serve as controls. An extensive MRI protocol will be administered on the same study group in another study (S. Hjerrild).
Results: Preliminary results will be presented delineating the cognitive function and psychiatric symptomatology of HCV patients as well as characteristics of the group developing interferon induced depression.
Conclusions: Preliminary conclusions will be presented.

P-02-011
Depression severity: Is it influenced by chronotypes?

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Objectives: Rhythm disturbances are a frequent clinical manifestation of depression. In recent years a possible relationship among depression and chronotypes has emerged. Specifically eveningness has been proposed as vulnerability factor. The aim of this study was to describe the sleep features of depressed patients according to the chronotypes of the Morningness-Eveningess Questionnaire (MEQ) and to explore possible associations with the clinical features of depressive episodes.
Methods: 100 patients diagnosed with Major Depressive Disorder (MDD) according to the Mini International Neuropsychiatric Interview (MINI) were included (age: 34±11.74, range: 18-60 years; female/male: 79/21). At admission the Hamilton Rating Scale for Depression (HRSD) was administered. Patients were also administered the Morningness-Eveningness Questionnaire (MEQ), Epworth Sleepiness Scale (ESS), Athens Insomnia Scale (AIS) and the Pittsburgh Sleep Quality Index (PSQI).
Results: According to MEQ scores the patients were classified in three groups: a) eveningness (n=18), b) neither (n=61) and c) morningness type (n=21). The age was different among chronotypes, being morningness-type patients older. The eveningness-type group showed higher scores in suicidal thoughts, more impaired work and activities, more severe depressive episodes, higher scores on the anxiety cluster (HRSD) and higher proportion of melancholic symptoms. We did not find association between sleep parameters and specific chronotypes, except for more diurnal dysfunction in eveningness patients.
Conclusions: Our data suggest the idea that chronotypes have an impact on depressive episodes features, with higher severity for the eveningness-type.

P-02-012
Administration of cannabinoid CB2 receptor antagonist AM630 decreased emotional-like behaviours after acute and chronic depressive stimuli

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Objectives: The purpose of this study was to examine the role of the CB2r in the regulation of depressive-like behaviours. To this aim, the effects of cannabinoid CB2 receptor antagonist AM630 were analysed by using different types of experimental paradigms to evaluate its response to depressive-like behaviours in mice overexpressing the CB2 receptor (CB2xP, develop in our laboratory) and in wild-type mice.
Methods: To this aim, the effects of AM630 (1 mg/kg or 3 mg/kg, i.p.) were evaluated by using tail-suspension test and in the weekly unpredictable chronic mild stress (CMS) regime for 6 weeks. The depressive-like behaviours (tail suspension test) of non-stressed and stressed groups were evaluated. The anhedonia experienced (sucrose intake) was measured at the end of the CMS. BDNF expression was measured by Rt-PCR and immunohystochemistry in the hippocampus of mice exposed to the CMS.
Results: In WT mice, the administration of AM630 (1 mg/kg, 3 mg/kg, i.p.) significantly reduced the time of immobility in TST compared to the vehicle-treated group whereas in CB2xP mice was without effects. CMS significantly increased the time of immobility in stressed-WT vehicle group. In contrast, CMS failed to alter these measurements in stressed-WT AM630 group. The sucrose intake decreased significantly in stressed-WT vehicle group but did not change in stressed-WT treated with AM630. CMS significantly reduced the expression of BDNF in stressed-WT vehicle group. However, no alterations were found in the expression of BDNF in stressed-WT AM630 group.
Conclusions: The results of this study revealed that the antagonist AM630 presented antidepressant activity in the behavioural paradigms. Further studies are needed to evaluate its usefulness as a new target in the treatment of depressive-like behaviours.

P-02-013
Overexpression of cannabinoid CB2 receptors results in decreased response to acute and chronic depressive stimuli

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Objectives: The purpose of this study was to examine the role of the cannabinoid CB2r in the regulation of depressive-like behaviours. To this aim, transgenic mice overexpressing the CB2r (CB2xP; developed in our laboratory) were challenged against different types of experimental paradigms to evaluate its response to depressive-like behaviours.
Methods: CB2r gene expression in CB2xP and wild-type (WT) mice was assessed by Rt-PCR and immunohystochemistry in microdissected brain nuclei. The response of CB2r to depression stimuli was evaluated by using different behavioural tests (tail-suspension test (TST), novelty suppressed feeding test (NSFT)). CB2xP and WT mice were exposed to the weekly chronic mild stress (CMS) regime for 6 weeks. Once every week, the anxiolytic (light dark box and elevated plus-maze test) and depressive-like behaviours (tail suspension test) of non-stressed and stressed groups were evaluated. The sucrose intake was measured at the end of the CMS. BDNF was studied by Rt-PCR and immunohystochemistry in the hippocampus of mice exposed to the CMS.
Results: Mice CB2xP significantly reduced the time of immobility compared to WT in the TST. The time of latency to initiate consumption is lower and the amount of consumption is significantly higher in CB2xP compared to WT mice in the NSFT. CMS procedure significantly decreases the time spent in the lighted box, the time visiting the open arms and the time of immobility in WT mice. In contrast, CMS failed to alter these measurements in CB2xP mice. The sucrose intake decreased significantly in WT mice after CMS but did not change in CB2xP mice. CMS significantly reduced the expression of BDNF in the hippocampus of WT mice. In contrast, no change in the expression of BDNF was found in CB2xP mice.

Conclusions: The results revealed that overexpression of CB2r induced a depressive-resistant behavioural phenotype. These results point out the cannabinoid CB2r as a potential target in the treatment of depression related disorders.

P-02-014
A specific memory profile in depression remitters following electroconvulsive therapy: Preliminary findings

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Objectives: Remitted depression is frequently associated with persistent memory dysfunction in pharmacologically treated patients. Anterograde, retrograde and semantic memory deficits following electroconvulsive therapy (ECT) are also consistently reported. However, the memory profile of depression remitters after ECT has not been specifically studied. We aimed to compare memory function in remitters and nonremitters from depression after ECT. Secondly, we explored possible relationships between variables where specific memory impairments were identified.
Methods: This prospective study was conducted in patients with Major Depressive Disorder (DSM-IV) treated with bilateral or high-dose right unilateral ECT. Depressive symptoms were assessed with the 24-item Hamilton Rating Scale for Depression (HRSD). Remission was defined as HRSDscore of 10 or less. Memory function was assessed at both baseline and following end of ECT with Buschke Selective Reminding Test (BSRT), Autobiographical Memory Interview (AMI-SF), Impersonal Public Events Questionnaire (IPEQ), and Semantic fluency. Remitters were compared to nonremitters on all memory variables by t-tests with Bonferroni corrections for multiple comparisons. Exploratory correlation analyses were conducted to investigate possible relationships between memory variables.
Results: Remitters (n=8) and nonremitters (n=9) showed comparable age and baseline HRSD score. Remitters performed significantly better than nonremitters on Semantic fluency at baseline ($p=0.012$) and on AMI-SF after ECT ($p=0.03$). No other significant difference was observed between the two groups. After ECT, positive correlations were found between IPEQ-previous-year scores and BSRT learning ($p<0.05$), while Semantic fluency correlated positively with IPEQ-5-previous-years ($p<0.01$), IPEQ-10-previous-years ($p<0.05$) and AMI-SF ($p<0.05$).
Conclusions: At both baseline and end of ECT, remitters and nonremitters showed comparable levels of functioning with regards to anterograde memory and retrograde memory for impersonal events. However, remitters showed better baseline semantic memory and their autobiographical memory was less affected by ECT. Retrograde memory function appeared related to semantic memory, but not to learning abilities in depressive patients treated with ECT.

P-02-015
Prevalence of perinatal depression in Portuguese women preliminary results

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Objectives: To determine the prevalence of depressive disorders in a community-based sample of pregnant and postpartum Portuguese women.
Methods: To date 446 women in their third trimester of pregnancy (M=32.57 weeks of gestation; SD=3.470), mean age 29.78 years (SD=4.498) and 464 three months postpartum women (M=13.07 weeks post-partum; SD=1.808), mean age=30.52 (SD=4.176), were evaluated. Women who were waiting for their prenatal/postnatal medical appointment at their Local Health Medical Centres were invited to participate. After their written consent, all women were interviewed (face-to-face) using the Diagnostic Interview for Genetic Studies/ Mood Disorders Section which assesses the presence of signs and symptoms according to a number of different diagnostic systems. Operational Criteria Checklist for Psychotic Illness (OPCRIT) was completed and data from this checklist were entered in the software system to generate diagnoses according to DSM-IV and ICD-10 criteria.
Results: In pregnancy the prevalence of major depression/DSM-IV was 1.3% and the prevalence of depression/ICD-10 was 3.1% (mild depression, .7%; moderate depression, .7%; mild depression with somatic syndrome, .4%; moderate depression with somatic syndrome, 1.1%; severe depression without psychotic symptoms, .2%). In the postpartum these percentages were 3.9% and 4.7%, respectively (mild depression, 1.9%; moderate depression, .2%; mild depression with somatic syndrome, .2%; moderate depression with somatic syndrome, 1.7%; severe depression without psychotic symptoms, .6%).
Conclusions: In Portuguese perinatal women the prevalence of depressive disorders was lower than the figures recently found in a rigorous meta-analysis (Gaynes et al., 2005). To our knowledge, this is the first study presenting prevalence rates of perinatal depression using a polydiagnostic approach. *Data for this study were drawn from a research project on Postpartum Depression and Sleep, funded by FCT (POCI/SAU-ESP/57068/2004).

P-02-016
Efficacy and Safety of Desvenlafaxine 50 and 100 mg/d in the Treatment of Major Depressive Disorder: Results From 2 Placebo-Controlled Studies

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Objectives: To assess the efficacy and safety of 50- and 100-mg/d doses of the serotonin-norepinephrine reuptake inhibitor (SNRI) desvenlafaxine (administered as desvenlafaxine succinate) in the treatment of major depressive disorder (MDD).
Methods: Two identically designed, multicenter, randomized, double-blind, placebo-controlled studies were conducted. One study took place in the United States (US) and the other was international (INT; European Union and South Africa). Participants were ≥18 years of age and met criteria for MDD per the Diagnostic and Statistical Manual of Mental Disorders, Fourth Edition, with a 17-item Hamilton Rating Scale for Depression (HAM-D17) total score ≥20 at screening and baseline. Patients were randomly assigned to treatment groups, which included desvenlafaxine 50 mg/d, desvenlafaxine 100 mg/d, or placebo. Treatment was administered for 8 weeks (including a 1-week, 50-mg/d titration period for the 100-mg/d group). The primary efficacy variable was change from baseline on the HAM-D17 at the final on-therapy evaluation. Analysis of covariance model was used for the efficacy analysis.
Results: In the US study (n=447), compared with placebo, a significant difference was observed in the adjusted mean change from baseline on the HAM-D17 in the 50-mg/d group (–11.5 vs –9.5; P=0.018), although no significant difference was observed in the 100-mg/d group. In the INT study (n=483), there was a significantly greater improvement on this same measure for both desvenlafaxine groups (50 mg: –13.2; P=0.002; 100 mg: –13.7; P<0.001) compared with placebo (–10.7). Each dose of desvenlafaxine was generally well tolerated and adverse events were consistent with the SNRI class.
Conclusions: These results demonstrate the efficacy of desvenlafaxine 50 and 100 mg/d in the treatment of MDD.

P-02-017
Analysing depression using DASS-21 scale among diabetes in Malaysia

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Objectives: The study was aimed to verify the correlation and relationship that exist between depression and diabetes, through analysing demographic and disease related variables that may predict depression symptoms among diabetes patients.

Methods: Diabetes patients (n=153) aged above 25 years old participated and were required to answer structured questionnaires about socio-demographic traits and the awareness of depression. DASS-21 questionnaires which consist of twenty-one questions examined on three scales; depression, anxiety and stress were used to evaluate depressive symptoms among the subjects. Pearson's correlation and multiple regression analysis were performed to assess the association of depressive symptoms with socio-demographic factors of age, gender, race, marital status, level of education and employment status. Habits and behaviours assessments containing six questions were also tested using the same method of analysis.
Results: Socio-demographic traits showed significant correlation with the depression level among diabetes patients. Distribution of the patients according to gender showed not much difference in terms of percentage, whereby 51% were females and 49% were males. 6.53% of participants agreed to discuss their problems with depression with physicians.
Conclusions: There was significant relationship between diabetes and depression. The underlying causes of depression might vary, thus, further studies should examine other factors that could contribute to depression.

P-02-018
Depression and rheumatoid arthritis – case report

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Objectives: There are 127 forms of arthritis, where disorders range from relatively minor, to the serious inhibitions such as rheumatoid arthritis (RA), where 37% of patients experience reduced work ability. Creed and Ash (1992) have concluded that RA major depression prevalence ranges 17-27%, based on the studies using structured diagnostic interviews.A female patient case report: T. J., age 49, merchant, divorced, has one child. RA patient for 20 years, with visible joint deformations of feet and hands, total working disability for 12 years, the period when she was tied to wheel-chair. Nineteen years earlier she was cured of TBC pulmonum, and first depression symptoms date from the march 2008.
Methods: The standard psychiatric interviews are done along with Hamilton Depression Rating Scale (HAMD).At the same time, anamnestic data are collected on RA and TBC pulmonum illness and took the existing deformities photographs, along with the appropriate medical documentation.
Results: T.J. have had all medical treatments outside the hospital utility, that is, in her flat. At first interview, HAMD scale scored 24.It is diagnostically recognized as F 32.2 (Depressive episode),and in therapy included escitalopram 5mg and alprazolam 0,5mg/daily, besides the RA medicaments. The next interview, two weeks later gave HAMD score 12; escitalopram raised to 10mg, alprazolam raised also to 0.75mg/day.The third interview made 6 weeks after the first one, gave HAMD score of 6, so previous therapy is continued without corrections.
Conclusions: Early recognizing of the correct diagnose of the RA depression ,as well as adequate therapy, effect in great extent to the patient wellness and his life quality. In this case, a late depression appearance is reported (depressive exhaustion) at RA, and showed that the introduction of therapy resulted in reduced pain and elimination of analgetic.

P-02-019
The study of the relationship between depression and trust in god among undergraudate students

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P-02-020
Revealing of psychological problems at women

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Marina Zhiltsova

P-14
Affective Disorders (Unipolar) II

P-14-001
Depression and body mass index in primary care patients: Impact of gender

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Objectives: To evaluate an impact of symptoms of depression and symptoms of anxiety on the Body Mass Index (BMI) in primary care patients in relation to gender.
Methods: Five-hundred and four consecutive primary care patients were invited to the study and 496 patients, 136 (27%) men and 360 (73%) women, completed the study. Mean age of the study patients was 52 (range from 18 to 83) years. All patients were screened for symptoms of depression and for symptoms of anxiety using the Hospital Anxiety and Depression Scale (HADS). The BMI was evaluated using standard procedure.
Results: Fifty-six (11%) patients had symptoms of depression and 125 (25%) patients had symptoms of anxiety. BMI was significantly higher in patients with symptoms of depression when compared to patients without symptoms of depression (27.4±5.3 and 25.4±4.9, respectively, p=0.005). In men without symptoms of depression the BMI was higher compared to men with symptoms of depression, but the difference was not statistically significant (23.9±4.4 and 26.3±4.5, respectively, p=0.2). In contrast to men, in women without symptoms of depression the BMI was lower compared to women with symptoms of depression and the difference was statistically significant (25.0±4.9 and 27.8±5.3, respectively, p<0.001). Presence or absence of symptoms of anxiety did not have impact on the BMI in men and in women together and separately.
Conclusions: In primary care patients symptoms of depression are associated with higher BMI in women, but not in men. Symptoms of anxiety do not have effect on the BMI neither in men nor in women.

P-14-002
Association between major depressive disorder and anxiety disorder and heart rate variability in the Netherlands Study of Depression and Anxiety (NESDA)

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Objectives: Psychopathology is associated with lower heart rate variability which may play an important role in the increased risk of cardiovascular disease among individuals with psychopathology.This paper investigates whether patients with major depressive disorder (MDD) and anxiety disorder (AD) have lower heart rate variability compared to healthy controls in a sample that was sufficiently powered to examine the effects of lifestyle and antidepressants.
Methods: The standard deviation of the normal-to-normal intervals (SDNN) and respiratory sinus arrhythmia (RSA) were measured in 2802 individuals (age 41.7 years, 66.5% female) participating in the Netherlands Study of Depression and Anxiety (NESDA). Based on the DSM-IV based CIDI interview for each participant the presence or absence of current or remitted MDD and current or remitted anxiety was ascertained. In this way, 618 participants were classified as healthy controls, 344 individuals had an AD, 605 patients had a MDD diagnosis and 1235 subjects had both an AD and MDD diagnosis.

Results: Depressed subjects had lower SDNN (-3.3ms) and RSA (-6.7) compared with controls. Individuals without depression but with a current AD had a lower SDNN (-3.6ms) and RSA (-4.8ms). Finally, SDNN and RSA were significantly lower in individuals comorbid for MDD and AD (-3.5 and -4.7ms, respectively) than in controls. The association of MDD and AD with SDNN/RSA fully survived adjustment for lifestyle. However, additional adjustment for antidepressant use reduced all associations to non-significant or only borderline significance. All anxious and/or depressed subjects who used a TCA, SSRI, or other antidepressants showed significantly lower SDNN (-18.9, -4.3 and -9.6ms respectively) and RSA (-17.8, -8.7 and -12.6ms respectively) compared to controls and non-medicated AD, MDD, or comorbid patients.
Conclusions: This study shows that both MDD and AD are associated with significantly lower heart rate variability, but the associations appear to be largely driven by the effects of antidepressants.

P-14-003
Evidence for sustained improvement in memory deficits following computer assisted cognitive remediation in patients with mood disorders

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Objectives: Major depressive disorder (MDD) and bipolar disorder (BD) are characterized by impairments in cognitive performance across multiple domains. These deficits can persist into the euthymic state (Paradiso et al., 1997; Ferrier et al., 1999), and a large percentage of remitted patients fail to achieve pre-morbid levels of functioning (Fagiolini et al., 2005). Cognitive remediation therapies have been successfully implemented for patients with schizophrenia, however only one study has explored their efficacy for patients with MDD (Elgamal et al., 2007). We are extending these preliminary findings to investigate the efficacy of a computer-assisted cognitive remediation (CACR) program for mood disorder populations. We expect patients to show improved cognitive performance immediately following the 10-week program, and we expect gains to be maintained after 3-months.
Methods: Patients with MDD or BD completed a 10-week CACR program. This intervention involved administration of five software packages aimed at improving performance across four domains: attention, memory, psychomotor speed, and executive function. Cognitive functioning was assessed with a battery of standardized neuropsychological tests at baseline, at completion, and at 3-months follow-up.
Results: This study is in progress; results are preliminary. Repeated-measure ANOVAs and paired-sample t tests showed sustained improvement on memory tasks in patients (n = 9) relative to controls (n = 7), including delayed verbal recall, verbal retention, working memory, and implicit learning.
Conclusions: Findings from this study will help establish the utility of cognitive remediation programs for patients with a mood disorder. Implementation of such programs may eventually translate into decreased medical-related disability and better functional outcome for patients with illness-related cognitive impairment.

P-14-004
Is "male-type" depression specific for females, too?

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Objectives: According to recent studies there is an evidence for a "male depressive syndrome" in patients with major depressie disorder (Rutz,1999; Winkler et al, 2005).Males are markedly overrepresented among suicide victims and the opposite is true for suicide attempters. We wanted to know if suicidal females also have "male type" depression.
Methods: Therefore we investigated the rate and global severity of Gotland Male Depression as measured by the Gotland Male Depression scale (Rutz, 1999, Möller-Leimkühler et al, 2007) in 86 suicide victims (74 males), 86 suicide attempters (21 males) with current DSM-IV major depressive episode and in 144 normal controls (116 males). The rate of Gotland "Male" Depression (total score of 13 or more) was significantly higher in depressed suicide victims (98%) and in depressed suicide attempters (93%) than in normal controls (2%, p=0.00001).
Results: Among depressed suicide victims 100% of males and 83% of females have had Gotland "Male" Depression (p=0.02), while the same figures among the depressed suicide attempters were 91% and 94%, respectively (not significant). The total Gotland Male Depression scores were significantly higher in depressive suicide victims (22.26) and in depressive suicide attempters (23.23), than in normal controls (4.01, p=0.00001 and p=0.0001, respectively), with significant gender differences only among depressed suicide victims (males: 22.85, females: 18.58, p=0.009) and normal controls (males: 4.33, females: 2.71, p=0.05).
Conclusions: However, since male and female depressed inpatients do not show clinically significant difference in their mean total scores on Gotland scale symptoms (11.99 vs 12.04, Möller-Leimkühler et al, 2004), it would be premature to conclude from our present findings that compared to nonsuicidal female depressives, suicidal female depressives have male-type depression profile.

P-14-005
Psychopathological and neuropsychological profiles of primary major depression and post – traumatic brain injury major depression

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Objectives: Major Depression Disorder (MDD) is the most frequent psychiatric complication after traumatic brain injury (TBI), with a prevalence of 14-77%. Nevertheless clear clinical and neuropsychological differences between Primary MDD and Post-TBI MDD aren't still assessed. This study aims to analyse the psychiatric sequelae of TBI and to identify the neuropsychological and psychopathological correlates of Post-TBI MDD, highlighting the differences between Post-TBI MDD and Primary MDD.
Methods: The study was performed by according to a longitudinal, prospectic, case-control design. The study group consisted in 16 patients (10 M, 6 F; age 18-65, mean 40,44), with closed brain injury and a lesion visible by Computerized Tomography (CT), who were evaluated at 1 (T1), 3 (T3), and 6 (T6) months after discharge from the Neurosurgery Department. 6 patients with MDD (without TBI) were included as control group. DSM-IV diagnoses were made using SCID-I and psychiatric symptomatology was evaluated by mean BPRS, HRSD, BDI, HRSA,GAF, IADL. Neuropsychological test consisted in Coloured Matrices of Raven (PM48), Visual Search Test, Trail Making Test, Test of Prose Memory, Digit Span, Corsi's Span, Verbal fluency Test, Token Test, Wisconsin Card Sorting Test, Tower of London Test. CT scan was obtained for all the patients with TBI immediately after trauma.
Results: At T1 MDD was observed in 10 (62,5%) patients at T1, resulting the most frequent diagnosis. Furthermore 12,5 % of subjects exhibited a Maniac Episode and 6,5% showed a Post-Traumatic Stress Disorder. MDD was diagnosed in 8 (50%) and 6 (37,5%) cases at T3 and T6 respectively. Post-TBI MDD patients showed less severe depressive symptomatology and increasing social isolation and hostility comparing with MDD.
Conclusions: MDD is a frequent complication of TBI. Post-TBI MDD presents a specific psychopathological profile and a neuropsychological pattern significantly associated with a greater deficits in cognitive functions compared to Primary MDD.

P-14-006
Clinical caracteristics of female depression patients in East – South Serbia

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Objectives: Depression syndrom is to form part of clinical combination of psychological, psychomotoric and somatic symptoms. His manifestations are differents, from not difficult to psychotic forms.
Methods: The aim of this research was to investigate clinical caracteristics of female depression patients on Admission Department of 'Special Psychiatric Hospital'-one among the five biggest psychiatric hospitals in Serbia. Duration of in hospital treatment was analyzed in 33 female patients who were consecutively admitted to the department within 2007. and 2008. Obtained results show type and severity of disease. Factors that analized are diagnosis, type and severity of disease, the beginning, suicidity, comorbidity, psychological profil. The measurement of depression's intensity was Hamilton scale.
Results: Results gained were discussed in detail during the research.

P-14-007
New options in monitoring the course of depressive disorders: Development and validation of a short screening for depression (DESC) using Rasch analysis

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Objectives: Meanwhile, a multitude of instruments for the assessment of depression is available, but several studies demonstrated substantial psychometric shortcomings, for example multidimensionality or dependence on sample characteristics. Here, modern test theories, e.g. Rasch Analysis, offer new directions of assessments. Still, although some effort has been made to apply Rasch analysis to the evaluation of diagnostic tools for depression, neither a concise instrument is available consequently using Rasch methodology nor an integration of Rasch analysis and Structural Equation Modelling (SEM) has been realised in the development of a new questionnaire, yet.
Methods: To further improve this situation, two parallel 10 item depression questionnaires of Depression Screening Version (DESC) were developed by combining Rasch analysis and SEM. Both scales were developed on the basis of a previously established Rasch homogeneous item bank for depression (N=367) and proved one-dimensionality according to Rasch and SEM analyses, justifying total score interpretation of the DESC. The new data of 333 patients (mean age 43.6 years; 46.2% females) suffering from psychic disorders including depression as well as different somatic disorders were included for a first psychometric evaluation.
Results: Both DESC versions feature different but highly correlated item sets. Cut-off scores with good sensitivity (0.82, 0.81) and specificity (0.78, 0.77) for the diagnosis of an affective disorder were developed with ROC analyses. No serious Differential Item Functioning in Rasch analyses for both scales was found.
Conclusions: The newly developed DESC represents a short screening instrument for depressive symptoms in two parallel versions with very sufficient psychometric quality. Particularly clinicians, who aim at screening diverse samples patients within a strongly limited amount of time and repeatedly during the course of their diseases, will benefit from this new screening instrument.

P-14-008
Experimental challenge studies of central monoamine systems in humans: Comparison of methodology and neurophysiological effects

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Objectives: Monoaminergic challenge tests allow investigating central nervous changes in humans under acute depletion of specific neurotransmitters (5-HT, DA, NE). In the design of these studies, several biochemical and methodological aspects have to be taken into account as well as the assumed monoaminergic vulnerability of specific human samples.
Methods: Along with studies using alpha-methyl-para-tyrosine test (AMPT) and phenylalanine/tyrosine depletion test (APTD), the tryptophan depletion test (TDT) represents the currently most established human challenge tool for the assessment of brain serotonin functioning and alterations in various psychiatric disorders.
Results: Results of different monoamine challenges APTD, AMPT and TDT depletion tools in the various neurophysiological studies (i.e. electroencephalography, magnetoencephalography, polysomnography, evoked potentials) will be evaluated. Still, despite strong depletion test situations, the assumed differential monoaminergic effects are not always observable. With respect to one proposed electrophysiological marker of the serotonergic system, the stimulus intensity of auditory evoked potentials (i.e. loudness dependence), TDT in animal and clinical studies suggests an inverse influence on the 5-HT neurotransmission. However, similar effects of TDT in healthy humans remained mostly inconclusive including own studies. Regarding auditory sensory gating and processing, TDT led to reduced acoustic startle amplitudes, but no change of prepulse inhibition. As opposed to other selective pharmacological challenges (e.g. SSRI, NRI) possible causes may be lack of receptor specificity with rather global manipulation in challenge tests (e.g. 5HT-system in ATD) or interactions with other neurotransmitters systems (e.g. priority of DA system in APTD). [Norra 2007, Norra et al. 2008, 2008, in prep.]
Conclusions: Current research using human experimental challenge tests suggests that predominantly individuals with assumed monoaminergic vulnerability or neuropsychiatric disorders are sensitive to the acute changes of depletion tests as opposed to studies in healthy subjects. Altogether, depletion techniques offer a potential non-invasive and reliable neurobiological marker of human monoaminergic dysfunction to investigate changes of neurophysiological parameters.

P-14-009
Adrenal and thyroid axis activity and FT4 / FT3 ratio in depression

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Objectives: The aim of this study was to investigate the relationships between chronobiological hypothalamic-pituitary-adrenal (HPA) and thyroid (HTP) axis activity and the (FT4)/triiodothyronine (FT3) ratio in depression.
Methods: Circadian rhythm of cortisol and TSH and 8 AM FT4/FT3 were determined in 78 drug-free DSM-IV major depressed inpatients, and 25 healthy hospitalized controls.
Results: Compared to controls, patients showed higher mesor and amplitude of cortisol ($p<0.001$ and $p<0.01$ respectively) and lower mesor and amplitude of TSH ($p<0.001$ and $p<0.01$ respectively). In patients, 8 AM FT4/FT3 ratios were negatively correlated with mesor ($r=-0.39$; $p<0.001$) and amplitude of TSH ($r=-0.30$; $p<0.01$), and positively correlated with mesor ($r=0.34$; $p<0.001$) and amplitude ($r=0.22$; $p<0.05$) of cortisol.
Conclusions: Our results suggest that an increased HPA axis activity and a decreased TSH secretion characterize depression. Given the inhibitory effects of thyroid hormones on cortisol secretion, the positive relationship found between cortisol and FT4/FT3 ratio might reflect a compensatory mechanism in order to counteract HPA hyperactivity.

P-14-010
Chronobiological HPA axis dysfunction in depression

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Objectives: The aim of this study was to evaluate the chronobiological hypothalamic-pituitary-adrenal (HPA) axis activity in depression.
Methods: Circadian rhythm of cortisol and cortisol response to dexamethasone suppression test (DST) were determined in 145 drug-free DSM-IV major depressed inpatients, and 25 healthy hospitalized controls
Results: Circadian secretion of cortisol showed a significant rhythm in controls and patients; however, mesor and post-DST cortisol values were significantly higher in patients ($p<0.01$ and $p<0.05$ respectively). In patients, mesor and post-DST cortisol values were positively correlated (Δ=0.63; $p<0.00001$). According to their DST responses, patients were classified into suppressors (n=105; 73%) and nonsuppressors (n=40; 27%). Both DST nonsuppressors and suppressors exhibited higher mesor than controls ($p<0.001$ and $p<0.01$ respectively), while DST nonsuppressors showed higher mesor than DST suppressors ($p<0.001$).
Conclusions: Our results, obtained in a large sample of patients, confirm increased nyctohemeral cortisol secretion in depression. Since both types of glucocorticoid receptors (i.e. type I mineralocorticoid [MR] and type II glucocorticoid [GR]) play a role in HPA axis regulation, one may hypothesize that DST nonsuppression associated with hypercortisolemia reflects impaired negative feedback at the level of the pituitary corticotroph (i.e. decreased GR function), while hypercortisolemia associated with DST suppression might involve altered MR function.

P-14-011
Dopamine function and cortisol secretion in depression

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Objectives: Several lines of evidence suggest that hypothalamic-pituitary adrenal (HPA) axis hormones stimulate the activity of dopamine (DA) systems. The aim of this study was to investigate the relationship between HPA axis and DA activity in depressed patients.
Methods: Cortisol and adrenocorticotropic hormone (ACTH) reponse to apomorphine (APO, a dopamine receptor agonist), circadian rhythm of cortisol and cortisol response to dexamethasone suppression test (DST) were determined in 107 drug-free DSM-IV major depressed inpatients, and 21 healthy hospitalized controls.
Results: Mesor and post-DST cortisol values were significantly higher in patients ($p<0.02$ and $p<0.03$ respectively) than in controls, while ACTH responses to APO (delta ACTH), but not cortisol, were significantly reduced ($p<0.01$). In patients, mesor and post-DST cortisol values were positively correlated ($r=0.58$; $p<0.00001$). DST nonsuppressors (n=31) showed 1) higher mesor and amplitude of cortisol values ($p<0.00001$ and $p<0.05$ respectively), and 2) lower delta ACTH values ($p<0.006$) than DST suppressors (n=76).
Conclusions: Our results suggest that blunted ACTH response to APO (which may reflect decreased D2-receptor-like function at the hypothalamic level secondary to increased DA release) is associated with chronic elevation of cortisol in depressed patients. However, further studies are needed to determine the influence of other factors such as CRH receptor desensitization of corticotropes (secondary to chronic CRH hypersecretion), altered processing and storage of ACTH precursors, and alternative processing of propiomelanocortin in the blunting of ACTH response to APO in depressed patients.

P-14-012
Investigating the impact of spiritual therapy in treatment of depression (with emphasis on the Islamic Tradition)

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Objectives: The main purpose of this of this research was to investigate the impact spiritual therapy in the scope of Islamic tradition in treatment of depression.
Methods: Investigators selected fourteen cases with major depression (ages 20-40) on the basis of clinical interviews, DSM-IV diagnostic criteria. The intervention package was implemented on them. In this investigation implementation package was consisted of spiritual therapy that was based primarily on Islamic tradition.
Results: Results indicated that selected therapy was effective in reducing aggressive symptoms of all fourteen cases with various backgrounds in demographic data, and environmental stressors. (Client's demographic data that varied across fourteen subjects included age, intensity of depression, educational levels, marital status, cooperation of their spouses with process of treatment, having or lack of sexual disorder, religiosity of clients, and level of adaptation of clients with the rest of family members.)
Conclusions: Analysis of data revealed that in the short form of Beck Depression Inventory overall mean of depression in pretest was 20.7, and in posttest (after invention) it was 3.6 ($t = 11.68$, $p< 0.01$).

P-14-013
Depression and Omega-3 fatty acids in the general population of Greece: A preliminary study

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Objectives: The role of essential fatty acids in the human body and especially the decreased levels of in patients with depression is a domain of interest for many researchers. The aim of the present study was to investigate the correlation between consumption of food rich in omega-3 fatty acids and depressive symptoms, in the general population of the area of Larissa, central Greece.
Methods: The sample consisted of 300 individuals (mean age 41, 0133) man 137 (46%) and woman 163 (54%), randomly selected by the method of stratified multistage sampling. The Food Frequency Questionnaire (FFQ) and the Beck Depression Inventory-II (BDI-II) were used in order to investigate the correlation between food consumption and depression. An inventory concerning socio-demographic factors was also completed by the sample. The Pearson's Correlation Test was used for the statistic analysis.
Results: A statistically significant negative correlation was detected between fish consumption, seafood consumption and score at the BDI-II (-0.451 $p<0.01$, -0.164 $p<0.01$ respectively). As concern the kind of fish consumed by our sample, statistically significant negative correlation was also detected by Pearson's Correlation Test. Individuals with increased consumption of fatty fish (rich in omega-3 fatty acids) have reduced scores at the BDI-II (Pearson's Correlation Test -0.453 $p<0.01$). The same statistically difference was found among the combined consumption of fish, seafood and food supplements (containing omega-3 fatty acids) and BDI-II score (-0.480 $p<0.01$). Finally, the combined consumption of fruit, vegetables and nuts was negatively correlated with BDI-II score (-0.260 $p<0.01$).
Conclusions: The results of the present study indicate that depressed mood in our sample is negatively associated with dietary intakes of food rich in omega-3 fatty acids. It is also clear that omega-3 fatty acids should be delivered in a dietary framework that includes and other important nutrients contained in fruits, vegetables and in nuts.

P-14-014
Efficacy and tolerability of once-daily extended release quetiapine fumarate (quetiapine XR) monotherapy in elderly patients with major depressive disorder (MDD)

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Objectives: Assess efficacy and tolerability of quetiapine XR (QTP-XR) monotherapy in elderly patients with MDD.

Methods: 11-week (9-week randomised; 2-week post-treatment), double-blind, placebo-controlled study (D1448C00014; Sapphire). Patients (DSMIV diagnosis MDD; >=66 years) randomised to QTP-XR (flexible dosing 50-300mg/day) or placebo. Primary endpoint: MADRS total score change from randomisation to Week 9. Secondary endpoints: MADRS total score change from randomisation to each assessment; MADRS response (>=50% decrease in total score) and remission (total score =<8) at Week 9; change from randomisation in HAM-D, HAM-A, CGI-I and QLESQ % maximum total scores; AEs recorded throughout.
Results: 338 patients randomised (mean age 71.3 years): 166 QTP-XR (mean 159.9mg/day); 172 placebo. Week 9: QTP-XR significantly reduced MADRS total score from randomisation versus placebo (-16.33 versus -8.79; p<0.001). Week 1: MADRS total score significantly reduced with QTP-XR versus placebo (-4.65 versus -2.56; p<0.001). For QTP-XR versus placebo, MADRS response rate (64.0% versus 30.4%; p<0.001) and remission rate (45.1% versus 17.0%; p<0.001) were significantly improved. Week 9 HAM-D total and item 1 scores significantly reduced with QTP-XR versus placebo (-15.66 and -1.84 versus -8.62 and 1.13; both p<0.001). At Week 9, QTP-XR significantly reduced HAM-A total scores versus placebo (-10.51 versus -5.20; p<0.001) and significantly improved QLESQ % maximum total score (16.86 versus 9.17; p<0.001); 71.3% (p<0.001) patients had a CGI-I score =<2 with QTP-XR vs placebo (39.2%). Most common AEs (>10% any group): somnolence, headache, dry mouth, dizziness.
Conclusions: In elderly patients with MDD, QTP-XR monotherapy (50-300mg/day flexibly dosed) is effective, with symptom improvement observed as early as Week 1. AEs were consistent with known profile of quetiapine.

P-14-015
Fluvoxamine induces the phosphorylation of Akt – 1 in PC12 cells

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Objectives: The expression of brain-derived neurotrophic factor (BDNF) may be a downstream target of a variety of antidepressant treatments, and the selective serotonin reuptake inhibitors (SSRIs) are representative antidepressants. BDNF binds to and activates receptor tyrosine kinases (TrkB) to exert their effects. TrkB activated by ligand stimulates phosphatedylinositol 3-kinase (PI 3-K). The downstream target of PI 3-K is Akt-1, a serine-threonine kinase, which is also referred to as protein kinase B.
Methods: We examined the effect of one of the SSRIs, fluvoxamine (FLV), on the serine-threonine kinase Akt-1 by means of immunoblotting in PC12 cells.
Results: The treatment of PC12 cells with 100 μM FLV was found to stimulate 3.8-fold maximal increases in the level of Ser473-phosphorylated Akt-1 at 40 min. The treatment with 50 ng/ml BDNF was found to be similar to FLV, and the Ser473 -phosphorylated Akt-1 maximally increased by 2.6-fold at 5 min. In addition, the phosphorylation induced by FLV and BDNF were blocked by LY294002, a selective inhibitor of PI 3-K.
Conclusions: The phosphorylation of Akt-1 induced by both FLV and BDNF is mediated by the PI 3-K pathway.

P-14-016
Attentional impairments in depression: Impact of depression subtype and severity

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Objectives: Clinically significant depression is characterised by impairments in information processing, and it is possible that the extent of such impairment is dependent on depression sub-type and severity. The primary aim of this study was to determine the impact of depression subtype (melancholic and non-melancholic) on event-related potentials (ERPs) associated with a well-validated auditory oddball, selective attention task.
Methods: 127 unmedicated clinically depressed patients (including 67 melancholics and 55 non-melancholics) and 116 healthy controls participated in this study. Oddball targets represent significant sensory change, and elicit the N100/P200 (80-270ms) and N200/P300 (180-550ms) ERP complexes, while non-targets elicit only the N100/P200 complex.
Results: The key findings were an exaggeration of the P200 to both targets and non-targets in depression versus controls and a reduction in the P300 to targets. In addition, the N200/P300 complex was slowed in latency corresponding to the slowed behavioural responses to targets in depression. The profile of larger P200 with reduced P300 was most pronounced in melancholic, followed by non-melancholic patients and controls. The larger P200 indicates that depressed patients may need to 'dwell' on sensory input more than is normal.
Conclusions: The combined disruption of early sensory processing (P200) and subsequent context processing (P300) may be a 'signature' for depression, particularly for melancholic and severe depression.

P-14-017
Depressive comorbidity in patients candidates to epileptic surgery

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Objectives: To investigate the link between depressive disorders and the refractory epilepsy in candidates to epileptic surgery.
Methods: Psychiatric evaluation of patients candidates to epileptic surgery. Affective disorders where classified according to the DSM-IV criteria. Psychopatological assessment: HDRS and BPRS.
Results: 104 subjects were included (average 37,42 ± 11,18 years old, 59% women), long evolution of epilepsy (average 24,05 ± 12,77 years), all of them are under anti-epileptic drugs. A psychiatric diagnosis of affective pathology was done by the first time at the evaluation in 28,8% of the subjects. "Major" Depression was found in 27,88% of the 104 subjects (HDRS>16 in 92,86%, BPRS medium score 39,81). Adjustment disorder with depressive mood was found in 19,23 % of the 104 subjects (HDRS >16: 18,75%, HDRS between 10 and 16: 43,75%, HDRS < 10: 37,50%, BPRS medium score 27,71). 27,59 % of patients with depressive symptoms where on more than 2 anti-epileptic drugs compared with 20% of non depressive patients.
Conclusions: Depressive symptoms and "Major" Depression are common in this population and the subjects are underdiagnosed. Depressive symptoms are more common in polypharmacy in Epilepsy. Psychiatric evaluation and intervention must be integrated interdisciplinary in the presurgical workup.

P-14-018
QEEG prediction of response to rTMS and/or venlafaxine in patients with depressive disorder. A double-blind, single-centre, randomized study

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Objectives: Previous studies of patients with unipolar depression have shown that early decreases of prefrontal EEG cordance in theta band predict treatment response/remission to various antidepressant drugs. The aim of the present study was to examine whether the reduction of theta prefrontal QEEG cordance value after 1 week of treatment is associated with MADRS reduction independent of treatment group (1Hz repetitive Transcranial Magnetic Stimulation-rTMS or venlafaxine ER).
Methods: This single-centre study involved a two-arm double-blind, randomized trial. A total of 53 inpatients with depressive disorder (DSM-IV criteria), who previously did not respond to at least one antidepressant treatment, were randomly assigned to rTMS applied over the right dorsolateral prefrontal cortex and placebo or to venlafaxine ER with sham rTMS for 4 weeks. EEG data were monitored at baseline and after 1 week of treatment. QEEG cordance was computed at 3 frontal electrodes in theta frequency band. Depressive symptoms and clinical status were assessed using Montgomery-Åsberg Depression Rating Scale (MADRS).

Results: Three linear regression models were calculated using improvement in MADRS as the dependent variable. The 1 week theta cordance change was the significant predictor (beta = 0.433, t=3.363, p=0.002, adjusted R2 = 0.171) in pooled data set. A greater theta cordance reduction was associated with better response. When these models were calculated separately for the 2 treatment groups, theta cordance change predicted MADRS reduction for venlafaxine ER (beta=0.495, t=2.79, p=0.01, r=0.495, adjusted R2=0.213) as well as for 1Hz rTMS (beta=0.447, t=2.40, p=0.025, r=0.447, adjusted R2=0.165).
Conclusions: Our data support the hypothesis that prefrontal cordance reduction in theta band predict clinical response not only to antidepressive drugs but also to rTMS. Those data indicate that 1Hz rTMS have similar mechanism of action as treatment with antidepressants. Acknowledgements: Supported by projects 1M0517 (MSMT CR) and NR9330 (IGA MZ CR).

P-14-019
Brain-derived neurotrophic factor plasma level is reduced in antidepressant-free patients with late-onset depression

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Objectives: To investigate the BDNF plasma levels in older depressed patients as compared to matched controls. We further assess the effect of age of the first depressive episode onset (late-onset vs. early-onset) on the BNDF plasma levels.
Methods: Twenty-nine elderly subjects with depression (15 with late-onset depression and 14 with early-onset depression) and 42 healthy elderly controls were enrolled in this study. All depressed patients were antidepressant-free at the time of clinical and laboratorial assessment. BDNF plasma levels were determined with sandwich ELISA.
Results: BDNF levels were lower in depressed patients as compared to controls (p=0.034). Elderly with LOD had the lowest BDNF level (median 478.5, interquartile range 373.5 – 740.9 pg/mL) as compared to elderly with EOD (median 620.7, interquartile range 366.1 – 971.9 pg/mL) and healthy controls (median 711.3, interquartile range 534.7 – 1181.0 pg/mL) (p 0.03). BDNF levels were negatively correlated with the severity of the depressive episode (rho= -0.266, p=0.025).
Conclusions: The present results suggest that reduced BDNF levels is a state marker of depression in non-medicated elderly patients and that the lack of neurotrophic support may play an important role in the physiopathology of geriatric depression. Furthermore, the more prominent reduction of BDNF levels in LOD as compared to EOD suggests that distinct features are involved in pathogenesis of these disorders.

P-14-020
Recovery from trauma-related major depression and bipolar disorder

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Objectives: During the last few years, most cases of major depression encountered by the author in his private practice proved to be issues of psychological trauma. Among the incriminated traumatic causes, very few were potentially life-threatening events, and some were various forms of sexual abuse; however, most were seemingly trivial experiences that had had deleterious effect on the subject's narcissism or perceived social recognition. It appeared that in all cases where previous psychotherapy or psychiatric treatment had been performed, such trauma had been ignored or overlooked. Amazingly, careful and exhaustive trauma-targeted psychotherapy brought about exceptional relief and eventually recovery from the mood disorder. More amazingly, five cases of apparent bipolar disorder proved to be traumatic disorders. One of these presented with a very typical first manic episode; the other four had been diagnosed with this condition in a psychiatric hospital, they had a documented bipolar history and had received mood-stabilisers or atypical neuroleptics with satisfying results. Here too, careful trauma-centered psychotherapy achieved complete recovery and allowed to stop chemical treatment. Four and a half year follow-up (the longest among these five cases) showed no relapse in any of the five patients, despite the lack of any chemical treatment. Significant case reports will be discussed.

P-14-021
Deviant stress responses in girls at risk for familial depression. The TRAILS Study

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Objectives: Depression is generally considered a stress-related disorder. It runs in families, and having a parent with a history of depression is a strong predictor for depressive problems in offspring (Pilowsky et al., 2006; Weissman, 2006). Sensitivity of the psychophysiological stress-system may be a determining factor of the development of mental health problems after exposure to stressful events. In an earlier study, we reported that adolescents at risk for familial depression had an increased sensitivity to stress (Bouma et al., 2008). This might be a consequence of transmitted vulnerability genes (Sullivan et al., 2000) and/or increased family stress (Goodman and Gotlib, 1999). In this study, the cortisol response to a laboratory stressor was examined in adolescent boys and girls at risk for familial depression.
Methods: The data were collected as part of the third assessment wave of the TRAILS (TRacking Adolescents' Individual Lives Survey), a large prospective population study of Dutch adolescents, and concern 344 adolescents (age 15-17 years) who participated in a laboratory session including a performance-related social stress task (public speaking and mental arithmetic). Four cortisol samples were collected before, during and after the task. Risk for familial depression (FD) was assessed by self-reports on lifetime depression by both biological parents.
Results: We found a blunted cortisol response to a social stress task in adolescent girls at risk for FD ($F(1,144) = 3.10$, $p = .05$) but not in adolescent boys at risk for FD ($1,195) = 0.79$, $p = .37$).
Conclusions: Blunted cortisol responses to similar stress paradigms are associated with stressful experiences in the past. Our results suggest that girls are more sensitive to stress associated with the depression of the parent than boys are.

P-33
Affective Disorders (Unipolar) III

P-33-001
Preeclampsia in pregnant women depression

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Objectives: Depression is a mental health disorder which affects daily physical activities and can be a factor for hypertension. Hypertension can cause serious pregnancy complications, including a dangerous condition called preeclampsia. Preeclampsia is a disorder that occurs only during pregnancy and the postpartum period and affects both the mother and the unborn baby. A research was planed to find out the number of preeclampsia in people who have different physical activities.
Methods: Two year medical records including seven hundred and eighty files of pregnant subjects were studied. A list of occupations and preeclampsia was obtained.
Results: The results show seventy seven pregnant ladies were suffered from preeclampsia and most subjects were housewives.
Conclusions: In result, despite the earlier studies that preeclampsia is the effect of out door activities because of the stressful environment, in our present study, the physical activity as outdoor activities may be a factor to prevent Depression and in result hypertension in pregnancy. The possible reasons are the mental and psychological factors in this regard which will be discussed in detail in full paper.

P-33-002
Depression post myocardial infarction: A cross sectional study in University Malaya Medical Center

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Objectives: The World Health Organization (WHO) predicted that both depression and myocardial infarct (MI) will be the top-5 leading causes of disability by the year 2020. For Malaysia this is worrying as we plan to achieve developed nation status by then. Literature has revealed that undiagnosed and subsequently untreated depression may lead to worsening heart condition thus resulting in increased mortality and also morbidity. This study aims to look into the prevalence of depression in subjects with myocardial infarct.
Methods: This is a cross –sectional study conducted in the outpatient Department of Cardiology University Malaya Medical Center (UMMC). Subjects who met the inclusion and exclusion criteria were interviewed with a clinician based questionnaire, Mini International Neuropsychiatric Interview (MINI). Socio-demographic data was obtained from a questionnaire designed by the research team. Ethical approval to conduct the study was obtained from the UMMC Ethics Committee 596.3.
Results: A total of 141 subjects were recruited. The prevalence of depression post-MI using the MINI in our study was 31%. Majority of subjects were male (85%), Non – Malays (66.4%), married (97.9%) and had secondary level education (62.1%). Mean age was 57 years old S.D. 8. Our study revealed associations with race, ability to work post infarct, being the main earner of the household, employment and having hypertension.
Conclusions: Our study is the first that we are aware in Malaysia to record prevalence of depression post-MI using a valid and reliable diagnostic instrument. A prevalence of 31% is 3 times the national average of 11%. Interestingly, being Non-Malay in Malay majority Malaysia increases the risk of depression 4 times. Associations with work related variables may be the result of the Asian culture which values physical health and employment status. These findings albeit preliminary, will hopefully provide more data towards this important yet under researched area of medicine and psychiatry in particular.

P-33-003
Associations between cyclothymic temperament and bipolarity factors in recurrent depressive patients

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Objectives: Recent studies have suggested that clinicians may underdiagnose bipolarity in substantial proportion of depressive patients, and proposed the existence of "pseudo-unipolar" depression. The objectives of this study were to assess the cyclothymic temperament in patients with recurrent depressive disorders and to explore its associations with clinical features of depressive disorders.
Methods: 91 patients (40 men and 51 women, age = 46.85 ± 10.14 years), followed for recurrent depressive disorders according to DSM-IV criteria were recruited during partial or total recovery interval. The mean age of first depressive episode was 34.9 ± 11.1 years and the mean number of previous depressive episodes was 4.8 ± 2.9. Cyclothymic temperament was assessed using the Arabic version of the TEMPS-A cyclothymic subscale (21 items). Recurrent depressive patients were divided on the basis of cyclothymic temperament scores: those with high scores of cyclothymic temperament (≥ 10) and those with low scores of cyclothymic temperament (<10). We compared clinical features of depressive disorders between the two groups using khi2 and Student "t" tests.
Results: The mean score of cyclothymic temperament was 5.9 ± 5.8. Twenty-five (27.5%) of patients had a cyclothymic temperament scores ≥10. These patients with high cyclothymic temperament scores had significantly more psychotic features (p<0.001) and suicide ideas and attempts (p<0.01) during the last depressive episode compared to patients with low cyclothymic temperament scores. Moreover, an association was found between the postpartum onset of the first depressive episode and the cyclothymic temperament score (7.4±6.9 versus 3.3±3.6; p=0.04). However, age of first episode, number of previous depressive episodes and atypical or seasonal features did not differ between the two groups.
Conclusions: The high cyclothymic temperament scores would be associated with some clinical predictor factors of bipolarity. These results suggested the relevance of the cyclothymic temperament screening in recurrent depressive patients.

P-33-004
Cognitive inhibition and working memory in unipolar depression

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Objectives: Over the past decade, evidence has accumulated to suggest that people suffering from Major Depressive Disorder (MDD) present impairment in attention, working memory, executive function, including cognitive inhibition, problem- and task-planning. The aim of the current study was to assess inhibitory mechanisms within working memory with emotionally neutral material in a group of patients suffering from MDD. We hypothesized that impairment in cognitive inhibition is global and not only due to the emotional valence of the stimuli employed for the tasks.
Methods: Twenty patients with MDD (DSM-IV) and 20 healthy controls were recruited. To assess cognitive inhibition, we used neutral material, in the form of the Prose Distraction Task (PDT) (Connelly SL, 1991), Trail Making Test (TMT), Modified Card Sorting Test (MCST), Rule Shift Cards (RSC), Stroop test and Hayling Sentence Completion test (HSC). The Modified 6 elements test, the Brixton Spatial Anticipation test, the dual task performance and the verbal fluencies test were also used to assess other executive function such as flexibility, planning tasks and memory.
Results: Individuals with depression showed impairment in cognitive inhibition. They made more errors on the PDT, alongside slower response times. Slower response times were also observed on the Stroop, TMT and RSC. The MDD group made more errors in HSC and performed worse than controls in the semantic part of verbal fluency and Modified 6 elements tasks. The impairment of access function was significantly associated with the level of depression.
Conclusions: Depressed patients showed inability to inhibit neutral information access to working memory, restrain and delete irrelevant information. This impairment in cognitive inhibition could underlie cognitive slowness and attentional deficits in depression.

P-33-006
Disfunctional cognitive schemes in depressed patients

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Objectives: to evaluate disfunctional cognitive schemes in depressed patients, according to various aspects of clinical and to identify the most important and most common cognitive scheme.
Methods: in the study were included 50 depressed inpatients, from Psychiatry Clinic No I Tirgu Mures, in the period July 2007 - October 2008. Clinical diagnosis was established on the basis of the DSM-IV TR. The control group was composed of 50 persons, without psychiatric history. For evaluation we used the Hamilton Scale for Depression (21 items) and The Disfunctional Attitudes Scale (DAS - Beck and Weissman)
Results: DAS score and the presence of various disfunctional schemes shows a linear increase toghether with the severity of depression (Hamilton Score). DAS score results show that depressed patients may be characterized by the following disfunctionalities: the need for recognition (60% of depressed patients and 28% in the control group) need to be loved (59% to group patients and 29% in control group), perfectionism (58% of depressed patients and 26% in the control group); expectations (55% of depressed patients and 25% in the control group). Disfunctional schemes have different characteristics depending on age, group and type of depression
Conclusions: Study results show the existence of disfunctional attitudes, specific, depending on the diagnosis (bipolar disorder, major depressive disorder), gender and age group, which motivates the needing of new therapeutical methods, which integrates drugs and psychotherapy and works on disfunctional attitudes, depending on gender, age and diagnosis.

P-33-007

Outcome prediction of the Hamilton depression rating scale (HAM-D 17 item) in patients with moderate depression – an artificial neural network (ANN) approach combined with wavelet decomposition

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Objectives: Outcome prediction of antidepressant treatment by easy to obtain pre-treatment or early treatment variables would be of great practical interest in searching for the best therapy for a patient. It was the aim of this study to improve the nonlinear approximation ability of ANN by a wavelet transformation of the input data.
Methods: We re-investigated a 24 week double-blind, randomized, multi-center study comparing Hypericum extract STW3 and Sertraline in patients with moderate depression. A feed-forward backpropagation network (4-10-1 structure) with one step secant training algorithm was trained to predict treatment success (HAM-D score < 8, "yes"-"no") after 12 weeks therapy. Input variables were age, sex, baseline HAM-D score and HAM-D score after 2 weeks treatment. The data were first transformed by a Daubechies 1 level 3 wavelet to provide the ANN with more relevant information as wavelets are localized in time and scale (Matlab software tools).
Results: Of the 235 patients in this study the data of 176 were used for training and validation of the neural network. 59 patients were reserved for the test of the ANN i.e. these data were new for the neural network. In a comparison of the simulated and real treatment success of this test group a correct prediction of the treatment success was made in nearly 78 % of the patients.
Conclusions: Compared to relatively poor results in the literature to predict therapy outcomes with multiple regression models or ANN using few input variables the results obtained in this approach combining ANN and advanced mathematical transformation of the data seem promising. Perhaps it may be possible to obtain better results by using more data and more predicting variables.

P-33-008

High - dose St. John´s wort extract STW 3 - VI is a safe and effective treatment option in mild depression – results of a revaluation

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Objectives: The post-marketing surveillance study presented here included 4188 patients treated with St. John´s wort extract (STW 3-VI). The patients suffered mainly from mild to moderate depression and dysthymia according to ICD 10 and were treated with 900 mg of the extract (1x1 tablet daily) for 12 weeks. Objective of this revaluation was to test whether treatment in patients with mild depression was as effective as in patients with moderate depression, by assessing the change of the HAMD-scores over time according to the 3 main ICD-10 disease classes.
Methods: An analysis of variance (ANOVA) for repeated measures (SPSS 15.0) was conducted with age, body mass index and sex as covariates. Only patients with completed data for all measurements (baseline, after 4 weeks and after 12 weeks) were revaluated.
Results: 1701 patients with mild depression, 1433 patients with moderate depression and 194 patients with dysthymia were revaluated (913 male, 2415 female patients). The 3 main ICD-10 disease classes showed a significant and comparable change of the HAMD-scores over time with very similar scores in moderate depression and dysthymia (mild depression: 13.5 at baseline vs. 3.3 after 12 weeks; moderate depression: 18.2 at baseline vs. 5.5 after 12 weeks). The same was the case in the subgroup of the older patients (>= 65 years), which was investigated separately.
Conclusions: This revaluation indicates that there is no influence of the disease classification (i.e. mild to moderate depressive disorders) to the time course of the treatment outcome in patients treated with St. John´s wort extract (STW 3-VI). It therefore provides evidence that this extract is efficacious in patients with mild depression. It underlines the very good tolerability and efficacy of St. John´s wort extract in comparison to chemically defined antidepressants, which have already been shown also in several randomized placebo-controlled studies.

P-33-009

Investigating models of affect: Comparison of regional brain asymmetry in MDD and PTSD

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Objectives: The approach-withdrawal (Davidson, 1992) and the valence-arousal (Heller, 1993) models highlight that specific brain laterality profiles may distinguish depression and anxiety, which may be characterised by reduced approach and hypoarousal, and increased withdrawal and hyperarousal respectively. However, studies remain to be conducted in clinical populations that directly test this hypothesis.
Methods: The current study compared resting state electroencephalographic data in patients with major depressive disorder (MDD) (N=15) and post-traumatic stress disorder (PTSD) (N=15) relative to healthy controls (N=15) to examine the specificity of brain laterality in these disorders. Planned pair-wise comparisons were carried out to test the hypotheses in both the frontal and parieto-temporal regions.
Results: Key findings included 1) reduced left frontal activity (indicative of reduced approach) in MDD, 2) a positive correlation between PTSD severity and right frontal lateralization (increased withdrawal with increasing PTSD severity), and 3) discrimination of clinical groupings within the right parietotemporal region, such that PTSD subjects displayed greater activity relative to MDD (indicative of increased arousal in PTSD relative to MDD).
Conclusions: This study shows that the approach-withdrawal and valence-arousal models are able to account for a number of key emotional disturbances characterising MDD. Although PTSD participants were not found to differ from controls, PTSD severity was positively associated with the degree of activation within the right prefrontal region, highlighting disorder severity as a crucial variable with respects to withdrawal behaviour. In addition, activation within the right-parieto-temporal region differentiated clinical groupings in the direction predicted by the valence-arousal model. This finding highlights the advantage of directly comparing disorders in addition to conducting comparisons with healthy controls. The various findings in regards to PTSD and MDD provide an important validation of the approach-withdrawal and valence-arousal models.

P-33-010

VEGF serum levels in depressed patients during SSRI antidepressant treatment

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Objectives: Recent evidence indicates that the vascular endothelial growth factor (VEGF) may be involved in the neuronal mechanisms underlying both the depression aetiology and the response to pharmacological and non pharmacological antidepressant treatments. The aim of this study was to investigate putative alterations in VEGF serum levels in MD patients as compared to control subjects. A second aim was the assessment of longitudinal changes in VEGF serum content, hypothesized to be induced by a 12-week long antidepressant treatment with escitalopram.
Methods: We analyzed the serum VEGF concentrations in 25 subjects affected by major depression (MD) before (T0) and after 8 (T8) and 12 (T12) weeks of escitalopram treatment. VEGF levels were measured by an ELISA method using the human VEGF Quantikine kit (R&D system, Minneapolis, USA). The SPSS, version 13.0, software package (http://www.spss.com) was used for all statistical calculations.
Results: No significant alterations in VEGF serum levels were found at T0, even considering possible effects of confounders such as gender and smoking habit (r2=0.227 p=0.74). No changes appeared during the treatment (F(1.83, 43.86) = 0.962; p=0.383) and there was no correlation between percentage VEGF variations at T12 and symptoms improvements (p=0.823).

Conclusions: The present study represents the first report evaluating serum VEGF levels in MD patients and, although no alteration in subjects and no modulation during the treatment has been observed, this factor remains an interesting molecule for further studies, as it is involved in different biological mechanisms. In particular, VEGF might play a role in some subtypes of affective disorders, as late onset depression, since the cardiovascular co-morbidity is more frequent in the elderly. A confirmation of our negative findings in larger samples stratified for clinical characteristics, comorbidities for cardiovascular diseases and confounding factors is required to definitely discard the usefulness of serum VEGF as a biochemical marker in the depression diagnostic assessment.

P-33-011
Cardiovascular disorders in comorbidity with depression

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Objectives: Introduction: Numerous researches show significant presence of cardiovascular disorders in depressed patients that show up several years after first depressive episode. Mortality caused by cardiovascular disorders in depressed patients is 50% higher than in general population. Comorbid depression and cardiovascular disorders is making worse health condition, increasing suffering, making hard treatment, and outcome is not good. **Objectives:** The goal is to confirm presence of cardiovascular disorders in depressed patients as the most common comorbid cardiovascular diseases.
Methods: A retrospective study has been conducted using data from medical history of 274 depressed patients hospitalized and treated at the Psychiatric Clinic, Clinical Center Banjaluka. These parameters were assessed: sex, age, number of hospitalizations, marital and employer status, comorbid disease, BMI, presence of cardiovascular disorders. Data were presented using tables and graphs.
Results: Results obtained in our study were: Cardiovascular disorders in comorbidity with depression we found in 126 patients (45,9%), 96 of them were males and 30 of them were females. Hypertension in comorbidity with depression was diagnosed in 83 patinets (65,8%), while comorbid with cardiac disorders was found in 45 patients (35,7%).
Conclusions: Depression is often accompanied by cardiovascular disorders. It is very important to recognize this comorbidity in order to treat it successfully and to make better treatment's outcome.

P-33-012
Extended release quetiapine fumarate (quetiapine XR) monotherapy for the treatment of patients with major depressive disorder (MDD): A randomised, placebo-controlled clinical trial

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Objectives: Evaluate efficacy and tolerability of once-daily quetiapine XR monotherapy for patients with MDD.
Methods: Multicentre, double-blind, randomised, parallel-group, placebo-controlled study (D1448C00003; Opal) of quetiapine XR monotherapy. Eligible patients (HAM-D total score >=22, item 1 score >=2) received quetiapine XR 150mg/day for 8 weeks. However, at Week 2 inadequate responders (<20% reduction in MADRS total score) had their dose of quetiapine XR increased to 300mg/day for the final 6 weeks. Investigators were blinded to the criteria for defining inadequate response and to any dose increase due to inadequate response. Primary endpoint: change from randomisation to Week 8 in MADRS total score. Secondary endpoints included: change from randomisation to each assessment in MADRS total score; MADRS response (>=50% reduction in total score); change from randomisation to Week 8 in HAM-D total and CGI-S scores; AEs recorded throughout.
Results: 310 patients were randomised to treatment: 154 quetiapine XR, 156 placebo. Week 8 change in MADRS total score was -16.5 with quetiapine XR (p=0.002) vs placebo (-13.1). Week 1 change in MADRS total score was significantly greater for quetiapine XR vs placebo (p=0.01). At Week 2, 17.1% of quetiapine XR and 25.5% of placebo patients had an inadequate response. MADRS response rates were significantly greater at Week 8 for quetiapine XR vs placebo (61.9% vs 48.0%; p=0.016). Change in HAM-D total score at Week 8: -14.8 quetiapine XR vs -12.4 placebo (p=0.012). Change in CGI-S score at Week 8: -1.6 quetiapine XR vs -1.2 placebo (p=0.005). Most common AEs (>10% any group) were dry mouth, sedation, somnolence and headache.
Conclusions: Quetiapine XR monotherapy in a modified fixed-dose regimen (150/300mg/day) was effective for 8 weeks, with symptom improvement as early as Week 1 in patients with MDD. AEs were consistent with the known safety and tolerability profile of quetiapine.

P-33-013
Late-life depression: Differences between early and late onset illness in a melancholic hospitalized sample

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Objectives: Several studies have reported clinical and biological differences between early and late-onset depression that suggest different underlying aetiological processes. The aim of the present study is to examine if there are differences between late and early onset melancholic depressed patients with respect to clinical variables, vascular risk factors and family history of affective disorders or suicide.
Methods: One-hundred twenty-one melancholic patients were split up in three groups: patients with current age and onset earlier than 60 (N=60), patients with current age and onset equal or older than 60 (N=30) and patients with current age equal or older than 60 but with an early onset (N=31). Systematic clinical data were collected with the structured interview ‚The Schedule for Affective Disorders and Schizophrenia'. Symptom ratings at admission and at discharge were assessed by means of the 21-item Hamilton Depression Rating Scale, Hamilton Anxiety Scale and Widlöcher Depression Retardation Scale. Family history of affective disorders or suicide was obtained through the Family History Research Diagnostic Criteria. Vascular risk factors were also recorded.
Results: The only symptoms that differed across the groups were feelings of anger and irritability, which scored lower in the late-onset elderly group. No other significant differences were found on the studied variables.
Conclusions: Our results do not lend support to consider late onset depression as a different depression subtype when melancholic features are present. This study supports that melancholic features are more specific than age when defining depression in the elderly patients.

P-33-014
Platelet serotonergic binding sites in melancholic depression with and without psychotic features: Relationship with clinical and follow-up variables

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Objectives: The aims of the present study are: 1) To determine if there are differences in pre and post platelet serotonergic receptors between melancholic depressed patients (with and without psychotic features) and a control group. 2) To establish if there is an association between platelet serotonergic markers and clinical and lifetime course variables in the patients group.

Methods: [3H]Imipramine, [3H]paroxetine and [3H]ketanserin binding were simultaneously determined in the blood platelet membranes of 42 consecutive hospitalized patients meeting DSM-IV criteria for major depression with melancholia (20 with psychotic features and 22 without psychotic features) and compared to 40 healthy controls. Systematic clinical data were collected with the structured interview ‚The Schedule for Affective Disorders and Schizophrenia'. Symptom ratings at admission, at discharge and at follow-up were assessed with the 21-item Hamilton Depression Rating Scale, Hamilton Anxiety Scale and Widlöcher Depression Retardation Scale.
Results: 3H-Imipramine Bmax (maximum binding) was decreased in both psychotic and non psychotic melancholic depressives compared to controls, without differences between the psychotic and the non psychotic subgroups. In addition, psychotic melancholic depressives showed a significant decrease in 5-HT2 receptors Kd (binding affinity). [3H]Paroxetine binding did not differ neither between depressed patients and normal controls nor between psychotic and non-psychotic subgroups and controls. A different pattern of associations between platelet serotonergic markers and clinical and lifetime course variables was observed within the overall sample, patients with melancholic depression with psychotic features and without psychotic features.
Conclusions: This study provides support for the view that the maximum binding of 3H-imipramine, but not 3H-paroxetine platelet 5-HT uptake sites are reduced in melancholic depression. Furthermore, 5-HT2 binding affinity could allow to differenciate between melancholic depressives with and without psychotic features. The presence/absence of psychotic features should be taken into account when studying the relationship between platelet serotonergic markers and clinical and lifetime course variables in depression.

P-33-015
Circular depressions and factor of seasonality

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Objectives: to study the seasonal influence on circadian rhythm of the indices of spectral analysis of heart rate variability in treatment of depressions.
Methods: 67 patients have been studied (F 31.3 - 31.4, F 32.0 - 32.2, F 33.0 - 33.2). Mean age 46.7±1.4 years. Therapy was carried out with citalopram or mirtazapin. Depending on season the patients have been divided into two groups: group 1 (autumn-winter depression) – 38 patients and group 2 (spring-summer depression) - 29 patients. To assess the variability of the heart rhythm spectral analysis has been used. The patients were examined at 1 a.m., 7 a.m., 1 p.m., 7 p.m. prior to the beginning of treatment, following one week, following three weeks and upon leaving the in-patient department. The control group consisted of 15 mentally healthy people (mean age 44.9±2.4 years).
Results: at the beginning stage the phase shift to an earlier time was more pronounced in spring-summer. Following the first week of treatment features of resynchronization appeared in the day hours (in autumn-winter they weren't). At discharge resynchronization of the rhythms under study was more complete in spring-summer.
Conclusions: in treatment of depressions resynchronization of circadian rhythm of the indices of spectral analysis of heart rate variability is more complete and rapid in spring-summer.

P-33-016
Brain lipid peroxidation enzymes, stress and stress – induced anhedonia in CD1 mice

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Objectives: Identification of reliable biochemical markers of depression and anhedonia in pre-clinical animal models is of high relevance for development of the diagnostics and treatments of psychiatric disorders. Here, we employed a novel advanced mouse model of stress-induced anhedonia with internal control for the effects of stress, not associated with depressive syndrome, in order to assess the peroxidation enzymes' activity in the brain of mice subjected to chronic stress.
Methods: Identification of reliable biochemical markers of depression and anhedonia in pre-clinical animal models is of high relevance for development of the diagnostics and treatments of psychiatric disorders. Here, we employed a novel advanced mouse model of stress-induced anhedonia with internal control for the effects of stress, not associated with depressive syndrome, in order to assess the peroxidation enzymes' activity in the brain of mice subjected to chronic stress.
Results: Comparison of activities of the brain catalase, superoxide dismutase, TBA-reactive substances, glutation peroxidise activity, molondealdehyde in non-stressed, stressed anhedonic and stressed non-anhedonic groups of mice enabled the identification of selective changes in peroxidation activity accompanying anhedonia, but not stress alone. Imipramine, delivered with drinking water (10 mg/ kg) starting 7 days before the onset of stress and during entire stress procedure, significantly reduced percentage of anhedonic animals in a stress group and preserved normal enzymatic activities.
Conclusions: Thus, our model allows once to assess potential effects of new (antidepressant) treatment separately with regard to features of stress and depression that was not possible with other models.

P-33-017
Associations between depression and cardiovascular disease in patients with late onset single episode major depressive disorder

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Objectives: Depression is a risk factor for the development of cardiovascular disease, and there is an increased occurrence of depression in patients with ischemic heart disease (IHD). Furthermore, patients with IHD and depression have a higher rate of major adverse cardiac events, including cardiac death, when compared to non-depressed patients with IHD. Among other mechanisms atherosclerosis is believed to play an important role regarding these notable associations between depression and cardiovascular disease. Patients with late onset major depression have an increased number of small lesions found in the white matter of the brain, commonly named white matter lesions. The main objective of this study is to determine whether these white matter lesions are associated to atherosclerotic disease of the coronary arteries.
Methods: 30 patients of at least 50 years of age with single episode major depressive disorder as defined by ICD-10 and DSM-IV and 30 healthy controls will undergo magnetic resonance imaging of the brain and a coronary artery calcium scan of the coronary arteries of the heart. Data will be analyzed for correlations between coronary artery calcium score and the number and the total volume of white matter lesions.
Results: Recruitment of patients is anticipated to commence during the first quarter of 2009. Preliminary data is expected to be available for presentation at the WFSBP Congress 2009.
Conclusions: No conclusion can be made at this stage.

P-33-018
Subclinical hypothyroidism predicts treatment outcome of inpatients with major depressive disorder

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Objectives: Although thyroid function is implicated to relate with depression, it is still under debate whether it predicts treatment outcome of individuals with depression.
Methods: Participants were inpatients with major depressive disorder according to the diagnostic criteria of DSM-IV, who were hospitalized at the psychiatric ward of Showa University Hospital, Tokyo. Three indices of thyroid function (thyroid stimulating hormone: TSH, free triiodothyronine: fT3 and free thyroxine: fT4) on admission were correlated with demographic features, severity of symptoms, medications and the treatment outcome during hospitalization retrospectively. Patients who were taking any thyroid medications or those with hormonal diseases were excluded.

Multivariate analyses of covariance were conducted with age and Hamilton Depression Scale (HAMD) score on admission as covariates. Spearman's rank correlation and partial correlation controlling for age were performed.
Results: One hundred ninety-one subjects (73 males, mean age 58.4 (Standard Deviation: SD 16.5, range 23-89) years old) were included. HAMD on admission and discharge was 25.3 (SD 7.6) and 10.3 (SD 6.9), respectively. The number of past episodes was 2.3 (SD 1.8), and duration of present hospitalization was 74.9 (SD 53.6) days. Age exhibited significantly positive correlation with TSH (r=0.22, p=0.002), and negative correlation with fT3 (r=-0.32, p<0.001) on admission. Accordingly, age-adjusted analyses were conducted for correlations between data of thyroid function and clinical variables. TSH on admission revealed a significant positive correlation with the HAMD score on discharge (r=-0.331, p=0.007). Non-responders whose HAMD scores on discharge were still above half of those on admission had significantly higher initial TSH than responders (p=0.001).
Conclusions: The present study demonstrated that TSH on admission would have a predictive value for the treatment outcome of individuals with major depressive disorder. A higher level of TSH, which is a marker for subclinical hypothyroidism, may indicate poorer treatment outcome of depression.

P-33-019
Homeopathy versus fluoxetine for moderate to severe depression: Double-blind, randomized non-inferiority trial

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Objectives: To investigate the non-inferiority and safety of individualized homeopathic Q-potencies in adults with acute depression, as compared to fluoxetine, in a prospective, randomized, double-blind double-dummy, parallel, cohort trial.
Methods: Ninety-one outpatients with moderate to severe depression were assigned to receive an individualized homeopathic medicine or fluoxetine 20 mg/day in a prospective, randomized, double-blind double-dummy 8 week trial. Primary efficacy measure was the analysis of the mean change in the MADRS depression scores, using a non-inferiority test with margin of 1.45. Secondary efficacy outcomes were response and remission rates. Safety was assessed with the side effect rating scale of the Scandinavian Society of Psychopharmacology.
Results: Patients receiving homeopathy had lower mean MADRS scores than those treated with fluoxetine. These MADRS differences were not significant at the 4th (p=0.203) and 8th weeks (p=0.057), though at the latter point there was a trend favoring homeopathy. Non-inferiority of homeopathy was indicated because the upper limit of the confidence interval for mean difference in MADRS change was less than the non-inferiority margin. There were no significant differences between the percentages of response or remission rates in both groups. Safety: there were no significant differences between the side effects rates, although a higher percentage of patients treated with fluoxetine (21.4%) than those who received homeopathy (10.7%) reported adverse side effects.
Conclusions: This study illustrates the feasibility of randomized controlled double-blind trials of homeopathy in depression and indicates the non-inferiority of individualized homeopathic Q-potencies as compared to fluoxetine in acute treatment of outpatients with moderate to severe depression. Further studies are needed to confirm these results.

P-33-020
Amygdala volumes in a sample of current depressed and remitted depressed patients and healthy controls

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Objectives: To investigate: (I) whether amygdala alterations constitute either a state or a trait marker of MDD (e.g., being either dynamically related to the course of the illness or a stable marker of MDD vulnerability); (II) the role of laterality in amygdala volumetric alterations in MDD.
Methods: We investigated amygdala volumes in currently depressed patients (cMDD) (n=31), remitted depressed patients (rMDD) (n=31) and healthy controls (HC) (n=33), using 1.5 T Magnetic Resonance Imaging (MRI). The groups were matched for age and gender.
Results: We found a significant group by hemisphere effect on amygdala volume. In detail, left amygdala was enlarged in rMDD patients as compared to healthy controls, while tended to be larger in rMDD patients in comparison with cMDD patients, the latter showing no difference with HC. Right amygdala volumes displayed no alterations. Finally, amygdala volumes did not correlate with clinical features of depression (e.g., age of onset; number of episodes; scores at the BDI, PANAS and MASQ subscales).
Conclusions: Amygdala volumetric alterations appear to be a marker of past MDD in adult patients, possibly reflecting vulnerability for relapse and constituting a neurobiological reaction to the stress related to the past Major Depressive Episode.

P-43
Affective Disorders (Unipolar) IV

P-43-001
Epidemiology of female obesity and depression in different age groups

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Objectives: Despite of the existing problem the epidemiology of obesity and its connection with development of depression is not well-documented. There are a lot of contradictory opinions at this point, but there is convinction about the connection of obesity and depression. The aim of our project was to evaluate the connection of obesity in different age groups and risk of development of depression.
Methods: Methods we examined as the group 200 females at the age from 18 to 60 years with overweight and obesity which was estimated by body-mass index. Depressive sympthoms were assessed using diagnostic interview schedule (DIS) was used to identify major depressive episodes. Statistically the results were estimated via odds ration index.
Results: Results: the most risky groups on development of depression are young women of 18-26 years with overweight and obesity (OR=4 and OR=4,3 accordingly). Women at the age of from 26 to 35 years with overweight has less chances to depression then women with obesity (OR=3,2 and OR=4,8). The age group from 35 to 50 years was exposed to depression less then the younger patients. Females at the age from 50 to 60 years had the same odds ratio (OR=2,3 and OR=5) of depression in spite of the mass index.
Conclusions: Conclusions: this problem is need to be studied but it is obviously that the connection between depression and obesity need to be studied with social status as well as co-morbidity to make the final decision about absence or presence the connection of depression and obesity.

P-43-002
Neurotic hostility explains the association between depressive mood and mortality: Evidence from the French GAZEL cohort study

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Objectives: Depressive mood is associated with mortality. Because personality has been found to be associated with depression and mortality as well, we aimed to test whether depressive mood could predict mortality when adjusting for several measures of personality.
Methods: 20,625 employees of the French national gas and electricity companies gave consent to enter in the GAZEL cohort in 1989. Questionnaires were mailed in 1993 to assess depressive mood, Type A behavior pattern, hostility, and the six personality types proposed by Grossarth-Maticek & Eysenck. Vital status and date of death were obtained annually for all participants. The association between psychological variables and mortality was measured by the Relative Index of Inequality (RII) computed through Cox regression. The RII resembles relative risk in that it compares the mortality at the extremes of the predictor but it is weighted to account for the distribution of the personality scores.
Results: 14,356 (72.8%) members of the GAZEL cohort (10,916 men, mean age: 49 years, 3,965 women, mean age: 46 years) completed the depressive mood scale and at least one personality scale. During a mean follow-up of 14.8 years, 687 participants (581 men, 106 women) had died. Depressive mood predicted mortality, even after adjustment for age, sex, education level, BMI, alcohol consumption, and smoking [RII (95% CI) = 1.56 (1.16-2.11)]. However, this association disappeared (RII reduction: 78.9%) after further adjustment for neurotic hostility [RII (95% CI) = 1.12 (0.80-1.57)]. Neurotic hostility was the only personality measure remaining associated with mortality after adjustment for depressive mood [RII (95% CI) = 1.97 (1.39-2.77)].
Conclusions: Preventive and therapeutic interventions to reduce mortality associated with depressive mood could be refined by considering neurotic hostility as a potential mediating variable.

P-43-004
Patients suffering from major depressive disorder show an altered interaction between cardiac vagal influence and delta sleep EEG

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Objectives: Major depressive disorder (MDD), which is associated with altered neuroplasticity, sleep dysfunction and increased relative cardiac sympathic activity, enhances the risk of cardiovascular pathologies. We tested the hypothesis that interaction between cardiac sympatho-vagal indexes and delta sleep power is altered in MDD.
Methods: Sleep characteristics and cardiac sympatho-vagal indexes of seven patients with single episode MDD were compared to eight healthy male controls across the first three NREM-REM cycles. The interaction between normalized High Frequency (HF) and delta power band was studied using coherence analysis. Comparisons between groups and sleep stages were performed with ANCOVA and post-hoc tests.
Results: Patients showed increased sleep latency but no differences in heart rate variabilities (HRV). Total Power, HF power of HRV and RR-interval duration decreased from NREM to REM sleep and wakefulness in both groups. Gain value between normalized HF and delta power bands was lower in patients while coherence and phase shift were similar between patients and controls. HF power band modifications appear 8 minutes before delta power band modifications.
Conclusions: Depressive patients have: (1) a decreased ratio between amplitudes of cardiac vagal influence and delta sleep signals, as measured by gain; (2) unchanged linkage strength between cardiac vagal influence and delta sleep, as expressed by coherence. Results reveal an altered link between cardiac vagal influence and delta sleep and suggest that in patients with MDD, the neuronal network between brainstem structures employed in sleep and cardiovascular controls is intact, but their interaction is less efficient.

P-43-005
Seasonal distribution of mania in a psychiatric emergency room

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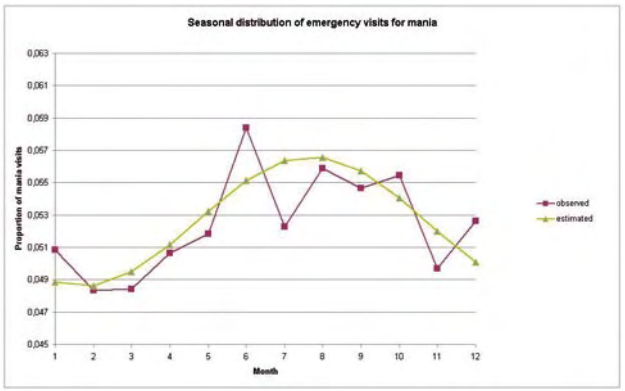
Objectives: Seasonality of affective disorders is an inherited characteristic and bipolar patients are super-sensitive to melatonin suppression by light. Seasonal variations on serotonin metabolism have also been reported. We have recently reported a seasonal distribution of admission for mania in a psychiatric hospital on a tropical region. Late winter/spring peak and summer trough coincided with similar studies around the globe. The present study aims to replicate the research in a different psychiatric emergency setting, correlating visits for mania and climatic conditions.
Methods: Seasonality of emergency department visits at a public psychiatric hospital of Belo Horizonte, Brazil (2000-2007) for manic/hypomanic episodes was analyzed using Cosinor regression. Partial correlations were calculated between mania visits and climatic variables.
Results: In the study period, 4852 emergency visits for mania/hypomania were recorded (out of 82380 total visits). A circannual model was evident and significant, with a February trough and an August peak, even after controlling for total visits. This pattern is similar to that previously reported for psychiatric admissions for mania in other hospital in the same region. The proportion of visits for mania were correlated negatively to temperature (p=0.04) and humidity (p=0.01).
Conclusions: The seasonal distribution of mania in a tropical South-American region has been confirmed by these results. Visits for mania were more frequent in the colder and drier days, corresponding to local winter/spring weather. The neurobiological correlates of this association deserve further consideration.



P-43-006
Premorbid sleep, cognitive and activity circadian profile in depressed patients

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Objectives: Alterations of biological rhythms are well recognized to play a crucial role in the origin and maintenance of depression, but little is known about circadian rhythms profile in premorbid ages of later adult depressed patients. The present study was aimed at investigating the possible association between depressive disorders and modifications of biological and behavioural rhythms both at the time of observation and in ages preceding the clinical onset of depression, in the hypothesis that they could represent an early biological index of vulnerability to the illness.
Methods: 206 patients affected by DSM IV Major Depressive Disorder, Disthymic Disordere or Depressive Disorder NOS were examinated, compared to a group of 206 matched healthy subjects. All the included subjects were asked to fill a retrospective questionnaire about the time of awakening and falling asleep and the time of subjective peak of appetite, energy and cognitive function, during "Adolescence" (12-15 years), "Youth" (16-20 years) and "Present condition" periods.

Results: An advance of the time of awakening of about 20 minutes was found in "Adolescence" in the depressed subjects respect to the controls. This is also significantly (p< 0,02) anticipated of about 39 minutes in "Youth" in depressed patients, while the time of falling asleep at the same age shows in the patients group a delay of 19 minutes. At "Present condition" an anticipation of awakening time (mean 35 minutes) was observed in depressed patients, associated to a delay of the subjective peak of cognitive functioning (95 minutes).
Conclusions: The results are consistent with the hypothesis that early alterations of the general circadian profile can contribute to the origin of adult life Depressive Disorders and play a potential role of marker of biological vulnerability to depression. Sleep profile abnormalities seem to be a central feature of the overall circadian alteration.

P-43-007
Prevalence of sleep disorders among patients with anxiety and depressive symptoms

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Objectives: Sleep disorders have a range of causes and treatments. Some sleep disorders are serious enough to interfere with normal physical, mental and emotional functioning. Authors take into account two major sleep disorders associated with anxiety and depressive disorders: Insomnias and Hypersomnias. Insomnia is a symptom of a sleeping disorder or primary psychiatric disorder characterized by persistent difficulty falling asleep or staying asleep despite the opportunity. It is typically followed by functional impairment while awake. Hypersomnia is characterized by reoccuring episodes of excessive daytime sleepiness or prolonged nighttime sleep.
Methods: Authors ask 84 patients with primary anxiety or depressive disorder admitted during 3 months period into University Hospital of P. J. Safarik in Kosice at 1st Dept. of Psychiatry for completing two self-assessment questionnaires. First questionnaire was pointed to symptoms of insomnia or hyposomnia, together with quality of sleep signs. Epworth sleepiness scale was administered as a second questionaire.
Results: 87 % of patients returned correctly completed questionaries. 27,4 % of patients were diagnosed major depressive disorder, 24, 7 % recurent depressive disorder, 23,3 % mixed depressive-anxiety disorder. 68 % of patients demonstrated symptoms of insomnia or hyposomnia and 18% of patients demonstrated symptoms of insomnia excessive daytime sleepiness.
Conclusions: he quality of sleep, treatment options, length of the sleep and relationship between nocturnal hyposomnia and excessive daytime sleepiness is discussed.

P-43-008
Primary and Secondary Interferon-Alpha induced depression: Cytokine levels and depression ratings

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Objectives: To assess levels of circulating cytokines, and depression ratings in patients with Hepatitis C at baseline and after 8 weeks of treatment with Interferon-alpha. The levels of these cytokines is then compared to patients with a primary depression.
Methods: 7 patients due to start Interferon-alpha treatment were administered the Hamilton Depression Rating scale (HAM-D), and had a blood sample taken at baseline and 8 weeks into treatment. 5 age and sex matched depressed patients also had a blood sample taken and were administered the HAM-D. Blood samples were analysed using the cytokine array biochip for the Randox Investigator.
Results: From baseline to 8 weeks into treatment there was a significant increase in plasma IL-8 (t=-2.4(6),p<0.05), TNF alpha (t=-3.6(6),p<0.05), IL1A (t=2.5(6),p<0.05) and MCP1 (t=-5.3(6),p<0.01). At 8 weeks there was a significant correlation with HAM-D scores and MCP1 (P=0.73, p<0.05). In depressed patients there was no significant difference with IFN patients in levels of IL1A (t=0.8(4),P=0.4) and MCP1 (t=2.2(4),P=.09), but not TNFa (t=4.6(4),p<0.01) or IL-8 (2.6(4),p<0.05). There was no significant correlation between HAM-D scores and MCP1 (P=-0.6, P= 0.1) in depressed patients.
Conclusions: Administration of Interferon alpha leads to an increase in the proinflammatory cytokines IL-8, IL1A and TNF alpha and the chemokine MCP1. MCP1 was also correlated with depression ratings in this population, however, this is not replicated in a primary depressed population. Despite this, levels of MCP1 and IL1A are not significantly different in patients with a primary depression, and those taking Interferon Alpha, which could mean they are important for some, but not all, aspects of depression.

P-43-009
Comorbidity between major depression and arthritis

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Objectives: Negative emotions contribute directly, as well as indirectly to the immune dysregulation by proinflammatory cytokines overproduction. It is considered that major depression (MD) is serious risk factor for development of various chronic medical conditions, including arthritis. Therefore, we aimed to establish prevalence and possible correlation between MD and arthritis.
Methods: In primary health cares setting 212 subjects were randomly selected, where180 successfully completed study. Hopkins Symptom Check List/25 (HSCL-25) validated for observed population and environment was used for MD diagnosis. Diagnosis for arthritis was previously established what was found in medical records. For statistical analysis SPSS package version 13.0 was employed
Results: Total sample was consisted of 180 interviewed subjects (116 women, 64 men), with mean age 47, 57 (SD=12, 48). Estimated prevalence for major depression was 33, 3%, and 28, 5% for arthritis, respectively. Arthritis was more frequent among women (χ2=5,807; p<0, 05) Among patients with arthritis 21(3, 6%) were scored major depression. Moreover, positive correlation was found between MD and arthritis (Pearson coefficient 0, 1783; p< 0.01).
Conclusions: Our findings clearly suggest association between MD and arthritis. Possible biological mechanisms underlying this phenomenon include secretion of proinflammatory cytokines (IL-1, IL-6) which play significant role in development of both MD and arthritis by affecting humoral and cellular immunological response

P-43-010
Decreased aldosterone and renin in suicide attempters with major depressive disorder

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Objectives: Suicidal patients with major depressive disorder (MDD) have specific neurobiological features, partially different from non-suicidal depressive patients. Such features involve disturbances of the hypothalamic-pituitary adrenal (HPA) axis, sometimes with low levels of corticotrophin-releasing hormone in the cerebrospinal fluid (CSF). The aim of the current study was to investigate whether plasma levels of renin and aldosterone, two hormones closely interacting with the HPA-axis, are affected in suicide attempters with MDD.
Methods: A total of 43 patients were enrolled in this study shortly after a suicide attempt. The patients did not receive any antipsychotic or antidepressive medication during a wash-out period after the suicide-attempt. Eighteen non-suicidal patients with MDD and 18 healthy subjects served as controls. Structured interviews were performed using the Comprehensive Psychopathological Rating Scale (CPRS) and the Suicidal Intent Scale (SIS).

Results: Suicide attempters with MDD had significantly lower plasma levels of renin and aldosterone than the two other diagnostic groups of suicide attempters. Moreover, aldosterone was lower in suicide attempters with MDD than in the two non-suicidal control groups, depressed patients and healthy controls.
Conclusions: The neurobiological distinction of suicidal MDD patients involves the renin-angiotensin-aldosterone (RAAS) system. We suggest that plasma aldosterone could be used for biological screening in support of clinical suicide assessments in MDD patients.

P-43-011
Health – related quality of life in depression patients

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Objectives: The aim of the study was to assess the health-related quality of life in depression patients.
Methods: The contingent was 167 depression patients (mean age – 56.3 years, male – 24.6%); the control group was 259 general population subjects (there were randomly selected citizens of Palanga) without depression (mean age – 56.9 years, male – 27.4%). There were no significantly differences between groups according to age and gender. The Medical Outcomes study 36–item Short Form Health survey (SF–36) was used to quantify general health–related quality of life. Psycho emotional status was tested according Hospital Anxiety and Depression Scale.
Results: Health-related quality of life in depression patients between males and females did not differ, except physical functioning domain - male evaluated significantly better than women. Age significantly correlated only with physical functioning ($r=-0.25$, $p<0.01$) and social function ($r=0.15$, $p<0.05$). Health–related quality of life in depression patients was impaired according to severity of depression. More severe depression exerted a profoundly negative effect on health–related quality of life, especially on mental health. Depression patients as compared with general population scored significantly worse all SF–36 domains: physical functioning (60.0 vs. 75.3, $p<0.001$), role-physical problems (23.3 vs. 66.8, $p<0.001$), bodily pain (53.8 vs. 67.8, $p<0.001$), general health perception (34.9 vs. 51.1, $p<0.001$), vitality (35.1 vs. 65.5, $p<0.001$), social function (43.5 vs. 78.6, $p<0.001$), role-emotional problems (20.2 vs. 70.9, $p<0.001$) and mental health (43.3 vs. 70.2, $p<0.001$).
Conclusions: Health–related quality of life in depression patients impaired according to severity of depression. Depression patients scored health–related quality of life significantly worse than general population.

P-43-012
The effect of saffron extract on behavioral changes and depression in male rates

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Jamal Shams

Objectives: Background: Depression currently ranks fourth among the major cause of disability worldwide. Medicinal plants textbook refer to use saffron to treat depression whereas there are few evidence-based document.
Methods: Male rats were placed individually in a cylinder filled with water after 15min rats were removed from water and received three separate i.p injection of N.S Normal Saline, fluoxetin, desipramin and various doses of aqueous extract of saffron 24 hours after the first session rats were retested for 5min and at each 5-S Second interval the predominant behavior was assigned to one of three categories: immobility, swimming and climbing. In this model catecholaminergic agents decrease immobility with a corresponding increase in climbing behavior and 5HT related compound such as fluoxetin also decrease immobility but increase swimming.
Results: Saffron extract reduced immobility and elevated swimming especially in higher (100,150 mg/kg) but in lower doses reduced immobility and elevated climbing (Although not significant)
Conclusions: It was concluded that saffron extract have an antidepressant –like activity mainly via serotonergic system

P-43-013
Increased plasma levels of novel monoamine oxidase, renalase, in patients with major depressive disorder and panic disorder

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Objectives: Monoamine oxidases (MAO) are enzymes that catalyse the oxidation of monoamines, such as noradrenaline, serotonin and dopamine. They are found in neurones and outside the central nervous system bound to the mitochondrial membranes of cells. MAOs play a vital role in the inactivation of neurotransmitters; therefore dysfunction in MAO activity may be important in a number of neuropsychiatric conditions. Recently, a novel soluble monoamine oxidase, renalase, has been identified in the human kidney and heart. It has been shown to be secreted into the bloodstream and is thought to be involved in the degradation of circulating catecholamines in plasma. In the present study we aimed to determine if renalase levels are altered in plasma of patients with major depressive disorder (MDD) and panic disorder (PD).
Methods: Patients with MDD and PD participated in this study. Diagnosis of MDD or PD was made by the consulting psychiatrist following a structured clinical interview. Plasma protein samples were separated by SDS-PAGE and analyzed by western blotting to detect renalase abundance. Plasma noradrenaline levels were determined concurrently to examine the association between renalase and neurotransmitter disposition.
Results: As previously reported, plasma noradrenaline levels in patients with MDD followed a bimodal distribution. Renalase was detectable in all plasma samples. However, the abundance of renalase in plasma samples of patients with MDD and PD was increased when compared to healthy volunteers. Our preliminary data suggest that levels of circulating renalase are not associated with plasma noradrenaline levels. This indicates that renalase expression is centrally regulated.
Conclusions: Our demonstration of elevated levels of novel soluble monoamine oxidase renalase in plasma of MDD and PD patients compared to controls highlights the existence of other pathways regulating neurotransmitter levels. Inhibition of renalase activity may represent a novel target in the design of therapeutics in the treatments of psychiatric disorders.

P-43-014
Tryptophan and Kynurenine metabolism abnormalities in an experimental model of major depressive disorder: The unpredictable chronic mild stress in mice

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Abstract: Tryptophan (TRP) is an essential amino acid playing a key-role in the neurobiology of depressive states, not only by its role as a unique precursor of serotonin, but also as a precursor of kynurenine (KYN). KYN is metabolized in various neuroactive compounds, some of them being active as NMDA receptors ligands, others inducing oxidative stress. Quinolinic acid (QUIN) has an agonistic action on NMDA receptors, whereas kynurenic acid (KYNA) is a NMDA antagonist, counteracting agonists (QUIN) effect. KYN is also metabolized in 3-hydroxykynurenine (3HK) which is a potent generator of free radicals. The KYN pathway is activated in depressive disorders: clinical studies show that KYNA is decreased in the blood of depressed patients. Considering the central role of NMDA receptors in cerebral activity, such an imbalance between KYN metabolites might promote cellular abnormalities in brain of depressed patients. The purpose of this study was to investigate if disturbances of TRP/KYN pathway occurred in an animal model of depressive syndrome. We used the Unpredictable Chronic Mild Stress (UCMS) protocol with Balb/c mice. KYN metabolites were measured by High Performance Liquid Chromatography in cingulate cortex, amygdala, hippocampus and striatum. We showed that TRP/KYN pathway is activated after six weeks of UCMS. NMDA agonist (QUIN) was increased in amygdala, wheras NMDA antagonist (KYNA) was reduced, suggesting a raise of excitatory activity in this structure.

An opposite pattern was observed in cingulate cortex, suggesting that excitatory activity is decreased in this structure. No differences were found in hippocampus. We also found that in amygdala, compounds generating free radicals are increased, suggesting an elevated oxidative stress. An opposite pattern was obtained in cingulate cortex. We will discuss how such alterations are linked to cellular abnormalities observed in the brain of depressed patients.

P-43-015
Depression, relationship and communication

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Helena Vagos

Objectives: This communication will turn on the thematic one of the depression, its diagnosis and treatment. we intend to show how communication inside the couple, can harm or support mental health.
Methods: We will present a case of one depressed lady, which did not answer the individual therapy. So couple therapy was considered, because we feel a dysfunction in the couple, that may be the cause of her depression. The husband acceded to do that, and after 8 sessions, the symptoms that presented initially (Fatigue, loss of the libido, difficulties in sleeping negative thoughts, lack of motivation for the tasks most routine, low auto-esteem) had been disappearing since the conjugal family subsystem initiated a new communicational stage, where both were felt valued more.
Results: With couple therapy the dysfunction relation between husband and wife, has been played and worked in the sessions, so they begin a new stage of communication, in which there were no need to feel sick or to show psychosomatic symptoms'
Conclusions: We want with this case to illustrate the importance of the relationship inside the family in the mental health, especially in depression

P-43-016
Assessment of the respective role of clinical factors – institutionalisation, disease severity and disease duration – on the observed hypovitaminosis D in patients with major depression

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Objectives: Recent studies reported low levels of 25-hydroxyvitamin in patients with minor or major depression when compared to controls. However, it is not known yet whether this hypovitaminosis D is a cause or a consequence of depression.
Methods: To appreciate the effect of three clinical factors – institutionalization length, disease severity and disease duration - on vitamin D status, we measured 25-hydroxyvitamin in a cohort of patients with a wide range of severe psychiatric disorders.
Results: Preliminary results indicate that, when compared to other mental disease diagnosed individuals, patients with moderate to severe major depression i) exhibit very low levels of vitamin D and ii) are more frequently vitamin D deficient.
Conclusions: We are now correlating these outcomes with the three clinical factors mentioned above.

P-43-017
Thyroidal pathology related to induced depressive or anxiety disorders during PegInterferon and Ribavirin therapy in chronic Hepatitis C patients

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Objectives: The purpose of this study was to assess the relationship between baseline thyroid dysfunction and/or the presence of antithyroidal antibodies and depressive or anxiety disorders during PegIFN/RBV therapy in patients with hepatitis C
Methods: A prospective cohort study of 189 HCV patients was follow-up during 24 weeks antiviral treatment. At baseline patients were administered the Patient Health Questionnaire (PHQ) and the Hospital Anxiety and Depression Scale (HADS); serum samples for free tiroxine (T4), TSH, antityroglobulin and antiperoxidase antibodies were collected. Pacients were revaluated with PHQ, HADS, T4, TSH, antithyroglobulin and antiperoxidase antibodies at 4, 12 and 24 weeks of treatment.
Results: Mean (SD) age was 43.04 (11.11), 60% were men. At baseline thyroid dysfunction was found in 16 (8.5%) and thyroidal antibodies in 17 (8.9%). During the treatment the incidence of depression was 70 (37%) and of anxiety disorders 62 (33%). At 4 weeks treatment there were not significant differences between patients with and without induced depression or anxiety and the thyroid hormones. At 12 weeks treatment, patients with induced anxiety disorders had positive baseline antithyroidal antibodies (p=0.019). Similarly, after 24 weeks of treatment patients with depressive or anxiety disorders had most frequently positive baseline antithyroidal antibodies (p=0.026).
Conclusions: Patients with VHC treated with PegIFN/RBV showed a high incidence of depression or anxiety disorders. The psychiatry pathology was related with the alterations of thyroid immunity at baseline. This study has been supported in part by grants from the Instituto de Salud Carlos III (C03/02) and (GO3/184), Fondo de Investigaciones Sanitarias (FIS PI051875) and (FIS PI052565)

P-43-018
Neurobiology of depression: New perspectives for an old disease

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Objectives: Several promising hypotheses of depression and antidepressant action have been formulated recently; still unraveling the pathophysiology of depression is a unique challenge. This study proposes a neurobiological overview of what makes individuals vulnerable or resistant to the syndrome.
Methods: A Medline/PudMed and Cochrane search was performed using 'neurobiology', 'depression', 'biological markers', 'molecular', 'neurotrophic factor' and other pertinent terms.
Results: Not only are depressive syndromes heterogeneous and their etiologies diverse, but symptoms such as guilt and suicidality are impossible to reproduce in animal models. Nevertheless, other symptoms have been accurately modeled, and these, together with clinical data, are providing insight into the neurobiology of depression. Still, enormous gaps in the knowledge of depression and its treatment persist. To improve the still-low remission rates, it will be imperative to look beyond monoamine and neurotrophic mechanisms and expand knowledge about antidepressant pharmacogenetics. Ultimately, one key to solving the mystery of depression lies in genetics; identifying specific genetic variations that confer risk (or resistence) for depression will likely be the essential first step in categorizing depression based on its underlying biology.
Conclusions: Knowledge of the pathophysiology of depression has evolved substantially from Galen's speculations in antiquity about an excess of black bile ('melancholia') to theories focused on 'psychic pain' and 'chemical imbalances', and then to more current hypotheses that incorporate gene–environment interactions, endocrine, immunological and metabolic mediators, and cellular, molecular and epigenetic forms of plasticity. These advances will lead to a second revolution in our approach to depression and to the development of definitive treatments and eventually cures and preventive measures.

P-43-019

A Study of Anger, Alexithymia, and Depression in Korean Patients with Functional Dyspepsia

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Objectives: Functional dyspepsia(FD) is a commonly encountered disturbance of gut function and it has been shown to be associated with psychological disturbance such as depression and anxiety. Of particular importance to clinicians are the relationship between anger, alexithymia, and depression. In this study, we investigated anger, alexithymia, and depression in Korean patients withfunctional dyspepsia.
Methods: The 37 patients who visited Wonkwang University Hospital were diagnosed into functional dyspepsia by gastroenterologist compared to 37 healthy control group. Medical investigation of FD including gastrofiberscopy, esophageal manometry, and ambulatory 24-hours intraesophageal reflux test were negative. All subjects were evaluated for depression, anxiety, anger and anger expression, and alexithymia. The measures included Beck Depression Inventory(BDI), Spielberger State-Trait Anxiety Inventory(STAI), Spielberger State-Trait Anger Expression Scale(STAXI), and Toronto Alexithymia Scale(TAS).
Results: The FD patients reported significantly more symptoms of depression, more difficulty describing feeling to other in TAS, less anger-in and anger-out expression in STAXI than the control subjects. Depressive symptoms in FD were positively correlated with state anxiety, trait anxiety, alexithymia, state anger, trait anger, and anger-in expression. In multiple regression model, state anger and trait anxiety together accounting for 69.1% of the depression in FD.
Conclusions: The FD patients reported more depressive symptoms, and the depressive symptoms were related with anxiety, anger and anger-in, and alexithymia. These finding lend support that FD is a syndrome in which biopsychosocial process and affect dysregulation may play role in features of FD.

P-43-020

Effect of Tramadol on corticosteroid receptor function in patients with major depression

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Objectives: The goal of current study was-to test the influence of the opioid,adrenergic and benzodiazepine drugs on the immunosuppressive levels of leukocyte pyruvat dehydrogenase activity (LPDG) during the DST (dexamethasone suppression test) in patients with Major Depression and Anxiety Disorder.
Methods: Patients: 40 male (mean age,33,1+3,2 years) and 20 premenopausal female (35,1+1,6years) with Primary Major Depressive Episode were studied.All patients were diagnosed by a psychologist and fulfilled DSM-IV criteria for Major Depressive Episode. The DST was conducted to 60 patients with Major Depressive episode and 30 healthy subjects (30 patients with an Anxiety Disorder - comparison subjects). Criteria of the DST estimation included the degree of immunosuppression on LPDG activity after L-Dopa, TRAMADOL (opioid-like drug) and DIASEPAM administration.
Results: The results permitted reliable differentiation between control subjects and patients with Primary Depressive Episode. In cases of Primary Depressive Episode after DEX administration activity of LPDG increased more than 20%. In the cases of Primary Major Depressive Episode in separation with an Anxiety Disorder after Tramadol and Diasepam administration activity of LPDG increased more than 25%. Tramadol of a 50 mg dose and Diasepam of a 10 mg dose had a higher immunosuppressive effect than L-Dopa (0,5 g) on alteration of LPDG activity /more than 5 mmol/l/hour, $p<0,05$/.
Conclusions: Tramadol immunosuppressive action was higher than L-Dopa and Diasepam on LPDG activity in patients with an Anxiety Disorder and Major Depression.). From other side, mechanism of L-Dopa action on corticosteroid receptors stimulated LPDG activity (L-Dopa therapeutic effective dose - 3 g). It means that opiate, adrenergic and benzodiazepine receptors are interacting with each other and influencing on the corticosteroid receptors in different ways during immunosuppression. The current data show that combination of opioid, adrenergic mechanisms could be a new strategy for the development of more potent antidepressive drugs.

P-03
Anxiety I

P-03-001
Sustained attention on Bosnian war veterans with PTSD diagnosis

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Objectives: Aim of our research is to exam sustained attention on Bosnian War Veterans with PTSD diagnosis.
Methods: As a material for construction of this stady we tested 79 war veteranes of Bosnian Army, wich participate in the former war in BIH from 1992 to 1995. From 79 tested war veterans on 45 PTSD has developed, wile 34 stayed without PTSD, and thay are belong to control group. All 79 war veterans are ages from 30 – 50 years; and with the same education level (elementary and secondary school). We tested all of them with sustained attentions to response task – SART. This task includes frequent button pressing on every targeted stimulus and keeping or non-pressing button when targeted stimulus shows. This computerized tests last 4.3 minutes were in this time 225 singular numbers (1-9) shows by accidental order in a center of the computer screen. As a result we got 3 measures: number of faulty positive ones – press / answers on number 3 (maximal error number is 25), number of faulty negative – cases when participants did not press the button but the number which is not 3 appear on the screen (maximal error number is 200) and average reaction time on all answers.
Results: On the tests for the sustained attention to response task SART, patients with PTSD made more errors one and other types (positive and negative errors). Statisticaly significant difference between PTSD group and control group does not exist only at the reaction time measurement at SART test.
Conclusions: Patients with PTSD made more errors what is linked to difficulties of maintaining of vigility over the time. Persons with PTSD has shorter reaction time what is related with the anxiety symptoms on persons with PTSD. Over anxiety can lead to this that persons with PTSD faster react in such tests but with more errors.

P-03-002
Salivary cortisol and emotional arousal in Bosnian refugees with PTSD

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Objectives: We have previously reported PTSD is associated with a specific loss of emotional arousal to pleasant pictures, suggesting that "emotional numbing" in PTSD is selective. The present study was undertaken to determine whether the loss of pleasant arousal we found in PTSD might be related to salivary cortisol level.
Methods: Ten male Bosnian refugees with PTSD were compared to 11 control Bosnian refugees without PTSD for their responses to Lang's "Looking at Pictures" test of emotional responses and for their 8AM salivary cortisol levels on two consecutive days, with 0.5 mg of dexamethasone taken at 11PM of the first day.
Results: PTSD subjects had significantly lower emotional arousal ratings for pleasant pictures. However, there was no significant difference in their 8AM salivary cortisol levels on either day 1 (baseline) or day 2. Both groups did, however, show a significant reduction in cortisol on day 2 after the dexamethasone the night before.
Conclusions: Neither baseline salivary cortisol nor the salivary response to dexamethasone differed between control and PTSD subjects, nor was there any apparent relation between salivary cortisol and emotional arousal.These results are consistent with several other recent studies that failed to find significant differences in salivary cortisol level or responsiveness between control and PTSD subjects.

P-03-003
Application of ASEX-scale for patients with posttraumatic stress disorder by telepsychiatry and psychiatry

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Objectives: This study, by application of telepsychiatry, investigated activity and sexual functioning in patients with PTSD(posttraumatic stress disorder) by sexual dysfunction symptoms(ASEX) scale.
Methods: ASEX scale was administered for 6-10 weeks to 96 sexually active adult outpatients with PTSD (56 by telepsychiatry and 40 direct by classic psychiatry). Sexual functioning was assessed weekly using ASEX scale by telepsychiatry and direct by classic psychiatry. This study investigated to assess the reliability of psychiatric evaluations via telepsychiatry and teleconsultation with ASEX scale.
Results: No any differenties using ASEX scale by telepsychiatry or direct by classic psychiatry.
Conclusions: This study verifies that telepsychiatry is a reliable method of assessing patient conditions. Also, no any significiant differenties using sexual dysfunction symptoms(ASEX) scale by telepsychiatry or direct by classic psychiatry. It may be used to provide much needed mental healthcare services, or any other scale, to patients whose access to them is restricted.

P-03-004
The model of prediction of neurotic, stress-related and somatoform disorders

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Objectives: Study of concentrations of steroid and thyroid hormones for construction of mathematical model of prediction type of neurotic disorders.
Methods: 1 group - patients with dissociative (conversion) disorders (35 persons, F44), 2 group - patients with adjustment disorders (29 patients, F43.2) and control - 27 mentally healthy persons were investigated. Immunoenzime analysis for definition of hormones was carried out. Methods of binary logistical regression and factorial analysis were used for construction of mathematical model.
Results: We have observed a statistically significant increased level of cortizol and thyrotrophin and a lowered maintenance of dehydroepiandrosterone in group 2 as compared with control and group 1 ($p<0,05$). The statistically significant increased level of triiodthyronine and free thyroxine is characteristic for group 1 as compared with control and group 2 ($p<0,05$) With method of binary logistical regression we have identified that thyrotrophin ($b=0,91$; $p=0,0048$) and dehydroepiandrosterone ($b= -0,001$; $p=0,06$) contribute statistically significantly in to formation of neurotic disorders. With method of factorial analysis complex hormonal factors independently influencing display of neurotic disorders have been revealed. Factor 1 combines value of cortizol, dehydroepiandrosterone and thyrotrophin, the weight of this component in group 2 is equal 0,185, in group 1 it makes -0,22. Factor 2 includes triiodthyroninum and free thyroxinum, in group 2 it makes -0,07, in group 1 it is equal 0,085. Thus, factor 1 contribute more significantly in to formation of adjustment disorders, factor 2 is of great value in development of dissociative disorders.
Conclusions: The model of prediction of neurotic disorders has been constructed to predict probability of development of mental disorders and type of neurotic, stress-related and somatoform disorders.

P-03-005

Efficacy and tolerability of extended release quetiapine fumarate (quetiapine XR) monotherapy in elderly patients with Generalised Anxiety Disorder (GAD)

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Objectives: Assess efficacy and tolerability of quetiapine XR (QTP-XR) in elderly patients with GAD.

Methods: 11-week (9-week randomised, 2-week post-treatment), double-blind, placebo-controlled study (D1448C00015; Chromium). Patients (DSMIV diagnosis GAD; >=66 years) randomised to QTP-XR (flexible dosing 50-300mg/day) or placebo. Primary endpoint: HAM-A total score change from randomisation to Week 9. Secondary endpoints: HAM-A total score change at Week 1; Week 9 HAM-A response (>=50% reduction in total score) and remission (total score <=7); change to Week 9 in HAM-A psychic and somatic cluster, PSQI global, pain VAS, QLESQ % maximum total scores and proportion of patients with CGI-I score <=2; AEs recorded throughout.

Results: 450 patients randomised (mean age 70.4 years): 223 QTP-XR (mean 167.6mg/day); 227 placebo. QTP-XR significantly reduced mean HAM-A total score from randomisation vs placebo (Week 9: -14.97 vs -7.21, p<0.001; Week 1: -4.18 vs -2.35; p<0.001). Week 9, QTP-XR vs placebo HAM-A response (68.5% vs 23.9%; p<0.001) and remission (40.1% vs 12.8%; p<0.001) rates were significantly improved. HAM-A psychic and somatic cluster scores were significantly greater with QTP-XR than placebo (psychic: -8.88 vs -3.81, p<0.001; somatic: -6.05 vs -3.37, p<0.001). 73.4% patients had a CGI-I score <=2 with QTP-XR vs placebo (24.3%; p<0.001). QTP-XR significantly improved QLESQ % maximum total (14.82), PSQI global (-6.25) and pain VAS (-17.95) scores vs placebo (4.94, -2.09, -6.18, respectively; p<0.001). Most common AEs (>10% any group): somnolence, dry mouth, dizziness, headache.

Conclusions: In elderly patients with GAD, QTP-XR monotherapy (50-300mg/day flexibly dosed) is effective, with symptom improvement observed as early as Week 1. AEs were consistent with known profile of quetiapine.

P-03-006

Pharmacology of neuropeptides in a mouse model of extremes in anxiety-related behavior

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Objectives: The linkage between learned fear and trait anxiety has been broadly described in terms of neuroanatomical and pharmacological parallels. Moreover, patients diagnosed for anxiety disorders/depression often display faster acquisition and slower extinction of learned fear. To gain further insights into the pathology underlying these phenomena, we used a bidirectional selective breeding approach, based on elevated plus-maze (EPM) behavior, to generate high (HAB), normal (NAB) and low anxiety-related behavior (LAB) mice, respectively. Interestingly, preliminary data show that HAB mice exhibit impaired extinction of conditioned fear in contrast to NAB and LAB animals, resembling the situation in psychiatric patients who are unable to erase traumatic events and to learn novel contexts and cues. Neuropeptide S (NPS) is recently a identified bioactive peptide that has anxiolytic-like properties and facilitates fear extinction in rodents.

Methods: In the present study, we examined the action of intracerebroventricularly (icv) administrated NPS on EPM, forced swimming, and fear conditioning tasks in HAB mice.

Results: Intracerebroventricular (icv) injection of NPS resulted in a clear anxiolytic effect, as reflected by a reduction of general anxiety, independent of hyperlocomotor effects. However, icv injection of NPS failed to impact depression-like behavior in HAB mice. A facilitatory effect of NPS on fear extinction became evident during extinction processes, where NPS-treated animals displayed significantly reduced freezing responses compared to saline-treated controls.

Conclusions: Here, we report that NPS evokes anxiolytic effects and facilitates extinction of conditioned fear responses in HAB mice. These data provide an important confirmation and evidence of NPS effects on anxiety and implicate the NPS system as a target for treatment of fear- and anxiety-related disorders.

P-03-007

Improvement of cognitive functions in anxiety patients treated with psychotherapy and pharmacotherapy

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Objectives: Objectives: The aim of the study was to evaluate the effectiveness of different forms of therapeutic methods on cognitive functions improvement.

Methods: Methods: 60 patients participated in the study. They were divided into 3 groups treated with pharmacotherapy, psychotherapy or both, respectively. Cognitive functioning was assessed with the Vienna Test System (VTS). The study covered patients treated at the Psychiatry and Psychotherapy Clinic of the Medical University of Silesia in Katowice, Poland. Participation in the study was restricted to individuals with a diagnosis of an anxiety disorder (acc. to ICD-10: F-40-F48 excl. F42).

Results: Results: Cognitive functions improvement was found to be correlated with the intensification of the initial disorder. An improvement in concentration and attention was present on average after 6-8 weeks of treatment and was most prominent in patients treated with both forms of therapy.

Conclusions: Conclusions: The above results may be interpreted as a support the hypothesis of neuroplasticity in anxiety disorders.

P-03-008

Efficacy and tolerability of extended release quetiapine fumarate (quetiapine XR) monotherapy for the acute treatment of patients with Generalised Anxiety Disorder (GAD): An analysis of pooled data

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Objectives: Prospectively planned pooled analysis evaluating efficacy and tolerability of once-daily extended release quetiapine fumarate (QTP-XR) monotherapy in GAD.

Methods: Data were analysed from three previously reported, 10-week (8-week treatment; 2-week drug-discontinuation/tapering phase), multicentre, double-blind, randomised, placebo-controlled studies (D1448C00009/D1448C00010/D1448C00011). Patients received QTP-XR 50mg/day, 150mg/day, 300mg/day or placebo. Primary endpoint: Week 8 change from randomisation in Hamilton Anxiety Scale (HAM-A) total score. Data were analysed by subgroup (gender, age, race, disease severity, geographic region). Other assessments: HAM-A response (>=50% reduction in total score); HAM-A remission (total score <=7); adverse event (AE) reporting.

Results: QTP-XR 50 (n=438), 150 (n=654) and 300mg/day (n=425) significantly reduced HAM-A total scores at Week 8 (-13.3, p<0.001; -14.4, p<0.001; -12.5, p<0.05, respectively) vs placebo (-11.3 [n=654]); significant (p<0.001) reductions also seen at Week 1 for all doses. Improvement in HAM-A total scores across patient subgroups was consistent with general pattern of results for QTP-XR in the overall study population. Week 1 HAM-A response rates: 17.9% (p<0.001), 21.7% (p<0.001) and 21.4% (p<0.01) with QTP-XR 50, 150 and 300mg/day vs placebo (12.5%), respectively. Week 8 response rates: 61.4% (p<0.01), 65.0% (p<0.001), 53.9% (p=0.062) with QTP-XR 50, 150 and 300mg/day vs placebo (49.7%), respectively. Week 8 remission rates: 34.2% (p<0.05) QTP-XR 50mg/day; 39.0% (p<0.001) 150mg/day; 28.5% (p=0.722) 300mg/day vs 27.4% (placebo). AEs (>=10% for QTP-XR): dry mouth, somnolence, sedation, dizziness, nausea, constipation, headache and fatigue.

Conclusions: QTP-XR monotherapy (50, 150 and 300mg/day) is effective at reducing anxiety symptoms in patients with GAD, with improvements seen as early as Week 1. AEs were consistent with the known tolerability profile of quetiapine.

P-03-009

Frequency and clinical correlates of adult separation anxiety disorder in a sample of 508 outpatients with mood and anxiety disorders

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Objectives: To evaluate frequency and clinical correlates of adult separation anxiety disorder in a large cohort of patients with mood and anxiety disorders.

Methods: Overall, 508 outpatients with anxiety and mood disorders were assessed for principal diagnosis and comorbidity by the SCID-I. Separation anxiety into adulthood or childhood was evaluated by the Structured Clinical Interview for Separation Anxiety Symptoms (SCI-SAS), the Separation Anxiety Symptoms Inventory (SASI) and the Adult Separation Anxiety Checklist (ASA-CL). Other scales were also used for psychopathology. Level of functional impairment in three inter-related domains, work/school, social and family life was assessed by the Sheehan Disability Scale (SDS).

Results: Of the total cohort of 508 patients with mood and anxiety disorders, 105 (20.7%) were assessed as having adult separation anxiety disorder without a history of childhood separation anxiety; 110 (21.7%) had adult separation anxiety disorder with a history of childhood separation anxiety and 43 (8.5%) reported a history of separation anxiety disorder during childhood only. Analysis of mean age-of-onset of separation anxiety shows that the majority of the respondents classified as adult separation anxiety disorder without a history of childhood separation anxiety cases began in early 20s. Adult separation anxiety cases had higher rates of anxiety comorbidity and a greater number of affective episodes than those without separation anxiety. Multivariate analysis of covariance showed that adult separation anxiety was associated with severe role impairment in work and social relationships after controlling for potential confounding effect of anxiety comorbidity.

Conclusions: Adult separation anxiety disorder is likely to be much more common in adults than previously recognized. It has been found to have a substantial impact on level of functioning after controlling for mood and anxiety comorbidity. Research is needed to better understand the relationships of this condition with other co-occurring affective disorders.

P-03-010

Morphological analyses of neurons in serotonin transporter knockout mice

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Objectives: Dysfunctions of the central serotonergic (5-HT) system are involved in basic pathophysiological mechanisms of anxiety disorders and depression. Thereby different genetic variations of the serotonin transporter (5-HTT, 5-Htt), a principal target for antidepressants, are associated with the development of emotional dysregulation and depression (Lesch et al., 1996). Neuroadaptive mechanisms including morphological changes occur especially after stress exposure. 5-Htt knockout (KO) mice display an anxious phenotype and exaggerated adrenomedullary stress responses. So the overall aim of this project is to analyse structural changes of neurons in the brain of 5-Htt KO and wild type (WT) mice, with and without stress.

Methods: We used male mice of each genotype which had gone through the resident-intruder-paradigm resulting in loser experience. These semi-chronically stressed mice were compared with completely unstressed male mice. In Golgi-Cox-stained sections we could reconstruct neurons and analyse their morphological features with the computer based microscopy system Neurolucida (Microbrightfield, Inc.). Evaluation of reconstructed neurons was performed doing Sholl Analysis with 20 µm radii around the soma as well as whole length comparisons.

Results: We focused our interest on pyramidal neurons of the cingulate cortex (CG), the infralimbic cortex (IL), and the hippocampus to evaluate possible consequences of the disruption of 5-Htt function for corticolimbic neuronal pathways involved in the regulation of anxiety, fear and memory. Sholl Analysis didn't reveal any differences in the approximate structure of pyramidal neurons in CG and hippocampus. But in IL we could find differences between unstressed WT mice and 5-Htt KO mice: Apical dendrites of pyramidal neurons were shortened in 5-Htt KO mice compared to WT mice.

Conclusions: Though morphological changes do not provide direct evidence of functional changes they may correlate to neural substrates underlying the behavioural abnormalities observed in these mice.

P-03-011

Efficacy of alprazolam sub-lingual tablets in the acute phase of panic disorders

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Objectives: Objectives: To compare different parameters of efficacy, between sub-lingual (ALP-SL) and conventional (ALP-CT) tablets of alprazolam in the treatment of acute phase of panic disorder with and without agoraphobia.

Methods: Methods: Comparative, multicenter (6 research sites), double-blind, randomized, fixed-flexible dose study. 190 outpatients with panic disorder with (n=117) and without (n=73) agoraphobia (DSM-IV diagnostic criteria), 36% with psychiatric comorbidity, were treated with ALP-SL or ALP-CT for 12 weeks. Outcome was assessed with: Clinical Global Impressions (CGI), Hamilton Rating Scale for Anxiety (HAM-A), Arizona Sexual Experiences Scale (ASEX), Patient Global Impression (PGI), Psychological General Well-Being Index (PGWBI), Panic Disorder Severity Scale (PDSS), the number, length and intensity of panic attacks and intensity of anticipatory anxiety.

Results: Results: Pharmacological treatment resulted in a clinically and statistically significant improvement in all severity measures. ASEX had no changes during the study. The average dose of alprazolam through 12 weeks was 1.36 ± 0.70 mg/day (1.39 ± 0.77 ALP-CT and 1.33 ± 0.64 ALP-SL). With ALP-SL panic attacks were shorter ($p<0.05$) as the length ($p=0.16$) and intensity of anticipatory anxiety ($p=0.14$). Treatment were well tolerated without differences between both groups.

Conclusions: Conclusions: Alprazolam proved efficacy, safety and good tolerability in the treatment of the acute phase of panic disorder. ALP-SL showed some comparative advantages.

P-03-012

Executive and metacognitive deficit in the social anxiety disorders

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Objectives: Introduction: Social anxious subjects tend to be less flexible especially when the environment is ambiguous or demand set shifting processes and context evaluation. Attention and memory biases, less flexibility in social situations, poor recall of autobiographical memories and use of internal clues to interpret external events which affect their social interactions had all been described in the literature about patients with social anxiety disorders (SAD). Neuropsychological assessment of SAD patients may be a useful strategy to evaluate executive, cognitive and metacognitive skills.

Methods: Ten patients with SAD (DSM IV TR diagnostic criteria) were assessed in an exploratory study with a comprehensive neuropsychological battery that included classic neuropsychological tests like Rey Auditory Learning Test, Rey Osterrieth Complex Figure, Wisconsin Card Sorting Test, Trail Making Test, Stroop Test, among others.
Results: Deficits in executive functions (planning, attention, organizational strategies and cognitive flexibility) were found as well as impairment in the environmental appraisal and reward clues. Metacognitive compensatory strategies to deal with these difficulties were also found.
Conclusions: SAD patients may have executive and metacognitive deficits which affect their possibility to deal with environmental demands. These deficits may be constructed along development and closely related to the symptoms of the disorder and the typical biases classically described by cognitive psychologists. The specific rehabilitation of impaired neuropsychological process may be a supplementary third therapeutic field in addition to psychotherapeutic and psychopharmacological treatments.

P-03-013
Generalized anxiety disorder: The neuropsychological approach

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Objectives: Introduction: Although many anxious patients refer an inadequacy to solve problems and deal with environmental demands, some anxiety disorders like Generalized Anxiety Disorder (GAD) were left behind by neuropsychological research.
Methods: Methods: Ten adult patients with GAD (DSM IV TR diagnostic criteria) and five children with overanxious disorder (OAD, the childhood version of GAD prior to DSM IV), were assessed with a complex neuropsychological battery that included Rey Auditory Learning Test, Rey Osterrieth Complex Figure, Wisconsin Card Sorting Test, Trail Making Test, Stroop Test, Verbal Fluency, Non Verbal Fluency (Ruff) and Benton Visual Memory Test among others.
Results: Results: Preliminary results suggest that GAD patients show a distinct executive incompetence (DEI); difficulties in conceptualization, nonverbal reasoning, planning and strategy, decision making and problem solving were found with attention and working memory preserved.
Conclusions: Conclusions: some kind of inadequacy to dealing with real life events, solving problems and making decisions, named distinct executive incompetence, might be the key feature in neuropsychology of GAD. Cognitive biases, exaggerated worry and anticipatory anxiety could be compensatory strategies to deal with this DEI. Therefore this should be an interesting point of research in the immediate future. DEI may be related to an abnormal development of executive functions; in fact children with OAD evidence similar executive deficits as well. The specific rehabilitation of impaired neuropsychological process may be an additional new therapeutic field to deal with this pervasive disorder.

P-03-014
Increased anxiety-like behaviours and impaired anxiolytic response to benzodiazepines in prodynorphin knock out mice is assoctiated to alterations in Gaba a receptor subunits gene expression and MAPK signaling pathway

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Objectives: This study evaluated the role of the prodynorphin gene (PDYN) in the emotional response, anxiolytic action of benzodiazepines and alterations of the GABA A receptor subunits, as well as signalling pathways involved in anxiety of prodynorphin knock out (PDYN KO) and wild type (PDYN WT) mice.
Methods: Emotional responses were evaluated using light dark box, elevated plus maze and social interaction tests. GABA A receptor subunits gene expression was measured by Rt-PCR. Basal immunodensity of FADD, ERK, MAPK, JNK and AKT was measured by western blot.
Results: PDYN KO mice exhibit anxiogenic-like behaviours in all the experimental paradigms assayed compared to WT mice. The administration of bromazepam in WT mice significantly increased the time spent in the lighted box at both doses tested, however, only 100 µg/kg showed significant but markedly reduced anxiolytic action in PDYN KO compared to WT mice. Decreased expression in a1 and g2 GABA A receptor subunits and marked increased expression in the b6 subunit were found in PDYN KO compared to PDYN WT. Basal immunodensity of FADD was decreased in cerebral cortex and thalamus/hypothalamus of PDYN KO compared to PDYN WT mice. In PDYN KO mice, the activation of anti-apoptotic ERK MAPK was also downregulated in both brain regions. In contrast, pro-apoptotic JNK MAPK was not significantly modulated in PDYN KO mice.
Conclusions: Deletion of PDYN gene increased anxiety-like behaviours and reduced the anxiolytic response to benzodiazepines. These effects may be associated to alterations on GABA A receptor subunits gene expression in the amygdala. The results also suggest that endogenous opioid peptides (DYN) acting on kappa- and/or other opioid receptors tonically stimulate FADD and ERK. In addition, these findings suggest that functional alterations of PDYN gene may be associated to the development of anxiety-related disorders and affect the anxiolytic efficacy of benzodiazepines.

P-03-015
Subtypes not respiratory of panic disorders and their correlation with fear of physical activity

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Objectives: The main objectives of the study aimed to investigate whether there is a population "specific" with predominantly respiratory symptoms, know which subtype of panic disorder, respiratory and non respiratory tract occurs more avoidance of physical activity and test results of diagnostic tests with physical (ergospirometry) and assess whether differences in autonomic parameters between the two subtypes of panic.
Methods: Were included in this study 4 patients with respiratory subtype of panic disorder and not breathing, diagnosed by the SCID (Structured Clinical Intervew for DSM-IV), which were submitted to a stress test (spirometry), Physical Activity Readiness Questionnaire (PAR - Q), metabolic tests, quality of life questionnaire (SF-36), assessment of severity of symptoms of panic, anxiety, depression, QSC scale (Questionnaire of bodily sensations), visual analogue scale unipolar to avoidance of physical activity, scale of problems and objectives, with assessment of avoidance and fear and anthropometric data.
Results: The panic disorder is an anxiety disorder that is characterized by recurrent attacks of panic: sudden crises of malaise and sense of danger or imminent death, accompanied by various physical and cognitive symptoms. It is a complex clinical condition that involves different modalities or clusters of symptoms. Thus, the focus on physical sensations erroneously interpreted as a panic disorder and hypochondria, is basically centered in the autonomic manifestations such as tachycardia and dyspnea. After the evaluations all patients avoidance of physical activity with the scales and diagnoses completed by proven through the test effort.
Conclusions: Therefore, we can conclude that there are people with panic disorder with predominantly respiratory symptoms and showing avoidance of physical activity. The spread of results and conclusions of this work will only be possible with a larger sample.

P-03-016
Quetiapine monotherapy in the treatment of posttraumatic stress disorder: A randomized, controlled trial

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Objectives: Psychotherapy and antidepressants are mainstay treatments for posttraumatic stress disorder (PTSD). Atypical antipsychotics also may be effective in reducing symptoms of PTSD. The following study investigated the efficacy of monotherapy with quetiapine in patients with chronic PTSD using a double-blind, randomized, placebo-controlled trial

Methods: There was a one week placebo phase followed by a twelve week randomized phase. Eighty patients entered the study and 77 had as least one efficacy assessment. The primary outcome measure was the Clinician-Administered PTSD Scale (CAPS). A number of secondary rating instruments were also administered including the Positive and Negative Symptom Scale (PANSS), Clinical Global Impressions –Severity of Illness Scale (CGI-S), the CGI-Improvement Scale (CGI-I), the Hamilton Rating Scale for Depression (HRSD), the Hamilton rating Scale for Anxiety (HRSA) and other psychosocial and safety measures
Results: There was a highly significant (threefold) decline in CAPS composite scores in quetiapine-treated patients as compared with placebo (intent-to-treat analysis, last observation carried forward, p=0.0070, 2-tailed) and on re-experiencing (p=0.0019) and hyperarousal symptom (p=0.030) subscales but not on the avoidance subscale (p=0.56). Greater improvement was observed in the CGI-S (p=0.0030), the CGI-I (p=0.030) and the PANSS composite scores (p=0.0135). The HRSA (p= 0.020) and HDRS (p=0.0093) also declined versus placebo. The average dose of quetiapine was 258 mg daily (range: 50 to 800 mg daily)
Conclusions: These results suggest that quetiapine monotherapy is efficacious in the treatment of PTSD. Larger controlled trials are needed to better define the role of quetiapine and other atypical antipsychotics alone or as adjuncts in treating patients suffering from PTSD.

P-03-017
Agoraphobia-leading women syndrom

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Objectives: The origin of the word agoraphobia is greek word agora=square and phobos=fear; fear of public places, streets and squares as well as separation of safety situations and people.
Methods: Behaviour therapy belongs in "covering" psychoterapy which is primarly interested in actual behaviour of the patient in the broadest sense of that word, from the very beginnings of the motoric and autonomous behaviour, along with private thoughts, feeling and events, till freely expressed situation of fear and passive avoide reaction which expresses agoraphobia.
Results: The material: patient J.D. 27 years old, second marriage, mother of one, sales menager, fear from independent moving lasts for 6 months. The origin of the fear is is traumtic, and the basis are marriage conflicts-weather stay in marriage or to divorce for the second time (two undesirable goals). Type of personality:anxious.
Conclusions: The treatment: behavioural therapy analysis, systematic desensivitation in vivo, therapeutics was achieved; independently mobile in duration of 1 hour (depression as the second phenomenon has dissappeared, anxiety as the leading one is reduced to minimum).

P-03-018
Posttraumatic Stress Disorder (PTSD) and psychotic symptoms

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Objectives: The current study was designed to investigate the prevalence rate of post-traumatic stress disorder (PTSD) with secondary developed psychotic symptoms. We also explored relationship between positive family history, previous psychiatric history and personality disorder with such psychotic symptoms.
Methods: The sample included 60 consecutive attendees at the University Psychiatric Clinic Sarajevo, Out-patient Department for PTSD. All patients fulfilled the Diagnostic and Statistical Manual of Mental Disorders IV (DSMIV) criteria for current and chronic PTSD. Structural Clinical Interview for DSMIV (SCID) was applied for the assessment of current and lifetime psychiatric disorder and the presence of psychotic symptoms. Statistical analyses were performed using Fischer exact and Chi-square tests and when needed Cox proportional hazards regression test.
Results: Our study demonstrated the frequency of war related PTSD followed by psychotic symptoms in the sample of PTSD patient treated at Psychiatric Clinic Sarajevo was 20%. Those figures are consistent to recent study data. Psychotic symptoms such as delusions and/or hallucination were usually paranoid and depressive and related to content to the extreme traumatic experience but different from flashbacks. We did not find family history, previous psychiatric history and personality disorder to be risk factors for developing of psychotic symptoms in PTSD.
Conclusions: Our analysis showed that PTSD and secondary developed psychotic symptoms/disorder may reflect two distinct disorders in some cases (depression with psychotic symptoms) but interestingly in other cases it is not possible to make distinction between separate psychotic disorder and PTSD. This conclusion opens the question of the nosological status for diagnosis of PTSD with psychotic symptoms.

P-03-019
Korean medication algorithm project for generalized anxiety disorder 2009: Initial treatment strategies

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Objectives: This study investigated the consensus about treatment strategies for initial treatment in generalized anxiety disorder(GAD), which represents one subject addressed by the Korean medication algorithm project for GAD in Korea.
Methods: The executive committee for Korean medication algorithm project for GAD, supported by The Korean Association of Anxiety Disorders, developed questionnaires about treatment strategies for patients with GAD, based on guidelines or algorithms and clinical trial studies previously published in foreign countries, especially by International Psychopharmacology Algorithm Project, National Institute for Clinical Excellence, and Canadian Psychiatric Association. Fifty-five(64%) of 86 experts on a committee reviewing GAD in Korea responded to the questionnaires. We classified the consensus of expert opinions into three categories(first-line, second-line, and third-line treatment strategies) and identified the treatment of choice according using a $\chi 2$ test and 95% confidence interval.
Results: For initial treatment of GAD, antidepressants monotherapy and combination of antidepressants and benzodiazepines as anxiolytics were recommended as the first line strategies. Regarding antidepressants, escitalopram, paroxetine CR and venlafaxine XR were selected as first-line treatments and alprazolam, clonazepam and lorazepam were preferred in benzodiazepines. Mean starting dose and mean maximum dose of the drugs were 7.55±3.09 mg and 24.91±8.14 mg in escitalopram, 12.57±2.83mg and 44.76±15.00 mg in paroxetine CR, and 46.81±16.74mg and 223.32±60.64 mg in venlafaxine XR, respectively.
Conclusions: These results, which reflect the recent studies and clinical experiences, may provide the guideline about initial treatment strategies for GAD.

P-03-020
Proinflammatory cytokine and HPA-axis responses to the combined dex/CRH test in remitted subjects with posttraumatic stress disorder and trauma controls

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Objectives: Posttraumatic stress disorder (PTSD) is associated with a long-lasting dysregulation of the hypothalamic-pituitary-adrenal (HPA) axis and the immune system. But there is a lack of data concerning the associations between both systems. The aim of the study was to identify persistent alterations in HPA-axis and immune function and their interactions in subjects with a lifetime PTSD diagnosis.

Methods: Age and gender matched traumatized participants of a prospective-longitudinal community survey (EDSP study) with (n=22) and without (n=17) lifetime PTSD according to DSM-IV criteria were enrolled. The combined dexamethasone (dex) /CRH test evaluating the effects of 1.5mg dex in combination with 100 µg CRH was performed. Beside plasma concentrations of ACTH and cortisol, serum level of systemic proinflammatory cytokine interleukin (IL)-6 was measured under dex suppression and after CRH stimulation. Interviews and questionnaires were conducted assessing childhood trauma and current PTSD and depressive symptoms.
Results: At the time of the tests, all PTSD patients were remitted. No differences between PTSD and trauma controls were observed for the ACTH and cortisol response. However, PTSD subjects showed higher IL-6 levels (M=1.46) after dex than the traumatized controls (M=0.98, t=-1.99, p=0.05). A multiple regression analysis showed that the variation in dex suppressed IL-6 is best explained by residual PTSD symptoms (β=-0.33, p=0.04), current depressive symptoms (β=0.37, p=0.04), and an elevated ACTH response to the dex/CRH test (β=0.66, p<0.001; R^2=0.55, p<0.001).
Conclusions: Subjects with a lifetime PTSD diagnosis show an impaired suppression of IL-6 after dex, which is associated with the residual PTSD symptoms, current depression, and the ACTH response to the combined dex/CRH test.

P-23
Anxiety II

P-23-001
Is there a Metabolic Syndrome in PTSD: Lipid level alterations in veterans with chronic PTSD

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Objectives: To test differences in serum lipid concentrations between veterans diagnosed with chronic PTSD and veterans without PTSD, in a sample of patients narrowly homogenized in the variables of age, BMI, smoking status and with exclusion of factors contributing to lipid changes. To analyze possible differences between groups in socio-demographic characteristics, trauma exposure, coping strategies and QOL.
Methods: Plasma lipid parameters were determined and risk factors calculated for 50 veterans in the PTSD group and 50 veterans in the non-PTSD group. Trauma exposure, coping strategies and quality of life were assessed with Life Stressor List, Manchester Short Assessment of Quality of Life Scale and Hoffman-Lazarus Coping Strategies Questionnaire; socio-demographic characteristics with the use of a questionnaire.
Results: PTSD group had significantly higher levels of all plasma lipid parameters (Cholesterol: 6.54±1.24 vs. 5.4±1.09 mmol/L; P<0.001, Triglicerydes: 2.55±0.68 vs. 1.73±0.77 mmol/L; P<0.001, VLDL-C: 1.14±0.32 vs. 0.78±0.35 mmol/L; P<0.001, LDL-C: 4.49±1.06 vs. 3.46±0.93 mmol/L; P<0.001), except for HDL-C that was significantly lower (0.96±0.18 vs. 1.15±0.24 mmol/L; P<0.001). All risk factors were significantly higher in PTSD group - ERF: 6.96±1.19 vs. 4.71±0.88; P<0.001, ATPIII ten year risk for coronary disease 19.44±7.27% vs. 9.74±4.1%; P <0.001.Secondary traumatization was significantly higher in PTSD group. There were significant differences in socio-economic parameters, in quality of life and in coping strategies.
Conclusions: Our results provide further evidence for association of chronic PTSD and dyslipidaemia, leading increased risk for Coronary Arteries' Disease. The results indicate importance of posttraumatic environment factors and coping strategies for the occurrence and persistence of PTSD.

P-23-002
Safety and efficacy of Venlafaxine in the treatment of depressive disorder comorbid with generalized anxiety disorder

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Objectives: The objective of this, flexible-dose, observational, 12 weeks study was to assess efficacy and safety of Venlafaxine in a group of subjects diagnosed with Depressive disorder comorbid with Generalized anxiety disorder.
Methods: 30 subjects older than 18 years diagnosed with Depressive disorder comorbid with Generalized anxiety disorder with HAM-D21 ≥ 20 and/or HAMD-A ≥ 20 and CGI-S ≥ 4 at baseline. Subjects signed informed consent before entering into this study. HAM-D21, MADRS, HAM-A, CGI-S and CGI-I were used prior to treatment and in 3, 6 and 12 weeks follow up. Safety was evaluated through recording and analyzing of adverse events.
Results: HAM-D21 score decreased from mean of 32.8±5.54 at baseline to 26.63±5.15 after 3 weeks, and 19.57±3.53 at 6 weeks with final mean of 11.40±6.18 after 12 weeks. All above changes were statistically significant (p≤0.01). Equally significant reduction was found in mean MADRS score; from 34.57±6.71 at baseline to 29.70±6.11 in 3 weeks, 20.13±5.03 in 6 weeks and 10.00±7.31 after 12 weeks of treatment. Further on mean HAM-A score was significantly reduced from baseline mean of 36.20±4.15 to 30.27±4.05 in 3 weeks, 22.17±6.11 in 6 weeks and 12.23±8.41 in 12 weeks follow up. Significant decrease in severity of illness score was recorded with CGI, and significant global improvement 7 (23.3%) subjects recovered, and 17 (56,7%) had clinical response, 6 (20%) had symptom improvement. Symptom or severity of illness was not recorded. Tolerability was excellent in 80% of the subjects and very good in 20%. Al subjects completed 12 week course of treatment with Venlafaxine.
Conclusions: Venlafaxine proved to be efficacious, safe and well tolerated agent for treatment of Depressive disorder comorbid with GAD for study subjects.

P-23-003
A controlled trial of Eye Movement Desensitisation and Reprocessing (EMDR) treatment for phobia

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Objectives: The efficacy of Eye Movement Desensitisation and Reprocessing (EMDR) therapy in post-traumatic stress disorder (PTSD) is well established by several controlled studies and meta-analyses. Other indications have been purposed, eg phobia, but with less controlled data on efficacy. Thus, our objective was to study the efficacy of EMDR therapy in 44 out-patients with phobia without PTSD.
Methods: Patients were randomly assigned to two groups, the first receiving 12 sessions of EMDR therapy (n=23) and the second staying on a wait-list during the same 12-week period (n=21). Effect sizes for efficacy of EMDR were determined using Cohen's d.
Results: On the main outcome criteria, ie the improvement of the Behavioral Avoidance Test (BAT), a significant difference was obtained in favour of EMDR (-60% vs -3% ; p<0.001), and this was found also with other clinical scales with effect sizes ranging between 1.85 and 2.90. A complete remission (BAT=0) was observed in 34% of patients treated with EMDR therapy. The results were stable after an 8-week follow-up period. The significant efficacy of the therapy appeared as soon as the sixth session, and the following 6 sessions brought globally no supplementary efficacy. Finally, the existence of traumatic component in the aetiology of the phobia is a strong predictive factor of remission (p=0.02 in a multivariate analysis), with remission rates of 50% versus 8.3% when no trauma was identified.
Conclusions: This study confirmed the efficacy of EMDR therapy in phobia, but essentially in forms with traumatic components.

P-23-004
Initial CAPS measurement after psychic trauma strongly correlates with changes of hippocampal volume after one and after six months

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Objectives: Recent results of neuroimaging studies revealed morphologic changes in the hippocampus, the amygdala and the cingulum in PTSD (1). Functional imaging also showed increased activity in these regions (2). However to date results are inconsistent with studies describing a gain of volume on the one hand and a loss of volume on the other (3). Furthermore the timepoint when those changes happen correlated to trauma is still unknown. We postulated that those changes appear in the acute aftermath of a traumatic event and tested this hypothesis in a sample of underground and streetcardrivers immediately after being involved in a traumatic event (e.g having a motor vehicle accident or witnessing a suicide).
Methods: 10 subjects (underground and streetcardrivers, 2 women, 8 men) who were involved in a traumatic event were examined at 3 different timepoints: within 48 hours, 1 month and 6 months after trauma. At each time we assessed a psychiatric interview according to the SCID and the CAPS as well as questionnaires measuring symptom severity (IES, HAMD, BDI, STAI, SCL 90-R). For this study, we used voxel-based morphometry analyses of magnetic resonance imaging (MR-VBM). Sequences were acquired by using a 1.5 T Magnetom Avanto MRI scanner (Siemens, Erlangen, Germany). All subjects were investigated with a volumetric 3D-T1 weighted sagittal MPRAGE (magnetization prepared rapidly acquired gradient echo) pulse sequence. Also an age and gender matched healthy control group underwent the same study design.
Results: Preliminary analysis of our data showed a highly significant correlation (> p 0.001) between initial scores of the CAPS and the IES with the volume of Hippocampus after one as well as after six months. These results support our hypothesis that the early reactions to a psychic trauma lead to structural volume changes. At the WFSBP meeting we will present the final analysis.
Conclusions: Literature: 1. Asari et al, Cortex, 2008 Sep. 4, Epub ahead of print 2. Bremner, Dialogues Clin Neurosci, 2006;8 (4):445-61. Review

P-23-005
Lymphocyte glucocorticoid receptor expression and functional properties in Balkan war veterans with and without PTSD

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Objectives: Some studies have suggested that changes in glucocorticoid receptor (GR) expression and function in peripheral blood mononuclear cells (PBMCs) are associated with posttraumatic stress disorder (PTSD). The aim of the present study was to examine GR expression and functional properties in PBMCs of Balkan war veterans with and without PTSD in order to differentiate between PTSD- and war trauma-related alterations.
Methods: GR hormone-binding parameters, the number of receptor sites per cell (Bmax) and dissociation constant (KD), were determined by saturation analysis in PBMCs of war veterans with current or lifetime PTSD and without PTSD, and of healthy male volunteers. Functional status of the receptor was assessed by measuring dexamethasone-induced inhibition of lysozyme synthesis. The levels of GR, mineralocorticoid receptor (MR) and heat shock proteins (Hsp90 and Hsp70) were evaluated by quantitative immunoblotting.
Results: An increase of Bmax in PBMCs of war veterans without PTSD vs. healthy controls (p=0.038, Bonferoni) and a rise of GR potency (Bmax/KD ratio) in patients with lifetime PTSD vs. those with the current disorder (p=0.015, Bonferoni) were noticed. Current PTSD coincided with disturbance of the correlation between Bmax and KD that normally exists in PBMCs of healthy subjects. Between-group differences in sensitivity of lymphocytes to dexamethasone were marginally significant, while those in the levels of GR, MR, Hsp90 and Hsp70 were not found.
Conclusions: The results suggest that current PTSD may be associated with impairment of the compensation between GR number and its affinity for the hormone, resilience to PTSD with efficient regulation of the receptor's hormone binding capacity and remission of the disorder with its elevated binding potency.

P-23-006
Pharmacotherapy of the complex Posttraumatic Stress Disorder

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Objectives: Objectives: Clinically the most relevant issues associated with complex posttraumatic stress disorder appear as problems with self-regulation, including affect and impulse dysregulation; transient dissociative episodes; somatic complaints and altered relations with self and others, as well as the symptoms of depression and anxiety. The study was designed to establishe the efficacy of risperidone in the treatment of complex posttraumatic stress disorder.
Methods: Methods: Male war veterans (n=40) with DSM-IV diagnosed PTSD completed 4 weeks prospective, open-labeled trial with risperidone (0,5-3mg per day). The reduction of the total and subscale scores on the Clinician Administrated PTSD Scale (CAPS) and Hamiltone Anxiety Scale (HAMA) were used as primary outcome measures.
Results: RESULTS: At treatment endpoint risperidone-treated patients showed decrease from baseline in total CAPS (54%) and HAMA scores (37%).
Conclusions: Conclusions: Our data suggest that posttraumatic stress disorder improves after taking atypical antipsychotics and shed some light to the possible machanisms of actions of the atypical antipsychotics in severe forms of trauma-related psychopathology.

P-23-007
PTSD and other psychiatric disorders among pows in Bosnia and Herzegovina

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Objectives: About one third of the population, all social groups, in Bosnia and Herzegovina suffers from PTSD, or from one of the other stress related disorder. Aim of this research is to show frequency of the psychiatric disorders among POWs in Bosnia and Herzegovina in period of one year.
Methods: The research conducted from December 2007-December 2008. Sample made 750 patients who were POWs and were treated at Department of Psychiatry Clinical Center of Sarajevo University. Research tools included: Standard Psychiatric Interview, Harvard Trauma Questionnaire (HTQ), Hamilton Anxiety Rating Scale (HAMA), and Hamilton Depression Rating Scale (HAD), and Drug and Alcohol Abuse Checklist.
Results: 675 (90%) patients were male and 75 (10%) female, aged from 25-65. All of them were exposed multiple traumatic events and tortured during war in Bosnia. Length of being in concentration camp was from 1-6 months (average 4 months). Out of total number of POWs, 555 (74%) had delayed PTSD; 75 (10%) suffered from Depression, 120 (16%) from Anxiety disorders. PTSD was co-morbid in 444 (80%) with Personality Disorders, or with Panic attacks, or with drug and alcohol abuse. Flashback, intrusive symptoms, avoidance, nightmare, affective rigidity, los of concentration, depression, suicidal thoughts, anxiety, insomnia, were the most frequent symptoms of PTSD. After treatment 229 (30.53%) of patients had severe Personality disorders after experienced trauma. Majority PTSD patients were chronic.
Conclusions: This research shows that the most frequent psychiatric disorders among POWs was chronic PTSD.

P-23-008
Glucocorticoid receptor mRNA level in war veterans with and without PTSD

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Objectives: Alterations in glucocorticoid receptor (GR) function and protein level were previously found in peripheral blood mononuclear cells (PBMCs) of patients with posttraumatic stress disorder (PTSD). However, the pattern of these alterations was inconsistently reported. The aim of this study was to examine the GR mRNA level in PBMCs of current PTSD and lifetime PTSD patients, trauma controls and healthy subjects (N=20 per group).
Methods: Relative GR mRNA level was determined using TaqMan Real Time RT-PCR. Accurate normalization is the prerequisite for obtaining reliable results in the relative quantification of gene expression. Therefore an expression stability of four potential endogenous controls, β-actin (BA), glyceraldehyde-3-phosphate dehydrogenase (GAPDH), beta-2-microglobuline (B2M) and RNA polymerase II polypeptide A (PolR2A), were analyzed by GeNorm and NormFinder software packages, prior to relative quantification of GR mRNA.
Results: The results obtained pointed to BA and GAPDH as the most suitable reference genes, GAPDH being the most stable single reference gene. For GR normalization we decided to use normalization factor derived from both BA and GAPDH in order to reach the sensitivity needed to detect subtle changes in GR expression. Nevertheless, between-group differences in GR mRNA level were not found.
Conclusions: In conclusion, war trauma and/or PTSD had no effect on BA and GAPDH mRNA level suggesting that this combination of reference genes can be used for quantification of GR mRNA level in PTSD. Differences in GR expression between PTSD patients, non-PTSD subjects and healthy controls were not noticed, suggesting that previously reported alterations in the lymphocyte GR number related to trauma and/or PTSD might be ascribed to post-transcriptional mechanisms involved in regulation of GR hormone binding-activity.

P-23-009
Complement system as a key component of immune respone associated with posttraumatic stress disorder

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Objectives: Posttraumatic stress disorder (PTSD) is the development of psychological and physical symptoms following exposure to one or more traumatic events. PTSD has been linked to the dysregulation of various neuroendocrine and immune systems of the body. Although the possibility of multiple immunological mechanisms has been studied, however the actual molecular mechanism involved in the development of the immune response occurring in PTSD is unresolved. The aim of this research was to examine the major mediator of the immune response: complement system in the pathogenesis of PTSD.
Methods: In the present study we determined the total hemolytic activities of classical pathway (CH50), complement C2 (C2H50), C3 (C3H50) and C4 (C4H50) components, alternative pathway (AH50), factor B (fBH50) and D (fDH50) in the blood serum of 31 patients with PTSD and compared to sex- and age-matched 29 physically and mentally healthy subjects with the same ethnic background. A hemolytic assay was based on the standard 50% complement hemolysis test.
Results: According to the results obtained, the mean values of the CH50 as well as C2H50 and C4H50 in the serum of PTSD patients were significantly 2.1 ($p<0.0002$), 1.2 ($p<0.05$) and 1.6 ($p<0.03$) times higher, respectively, than in the healthy subjects. However, C3H50, AH50, fBH50 and fDH50 were significantly1.5 ($p<0.03$), 1.7 ($p<0.0001$), 1.6 ($p<0.02$) and 2.3 ($p<0.001$) times lower, respectively, in PTSD patients compared to healthy subjects.
Conclusions: Our study is continuing to expand the knowledge of the complement system in PTSD. It is indicated that developing PTSD after a traumatic event is characterized by deregulated immune response including: hypercomplementemia of classical pathway and hypocomplementemia of alternative pathway leading to decreased activity of the complement C3 component. This findings demonstrate that the complement cascade is susceptible to acute psychological stress and suggest a potential mechanism for stress-induced inflammatory activation in individuals with PTSD.

P-23-010
A quality of life in chronic combat related Posttraumatic Stress Disorder (PTSD): A study on Croatian war veterans

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Objectives: The main objective of this study was to examine an influence of various symptoms in chronic combat-related post traumatic stress disorder (PTSD) on the quality of life in this population and to study a role of impaired quality of life in chronic PTSD.
Methods: 246 Croatian war veterans all diagnosed with chronic PTSD were enrolled in this study. They were given self report questionnaires Trauma Symptom Inventory (TSI-A) evaluating different PTSD symptoms and WHO Quality of Life-BREF assessing four different domains.
Results: After Student t- test was performed, the presence of each symptom defined by Trauma Symptom Inventory indicated the impairment of all four quality of life domains in a group of subject suffering from it, except intrusive experience doesn't seem to impair social domain. All quality of life domains were significantly correlated with PTSD symptoms. After the performance of multiple regression analysis, the set of predictors consisting of different quality of life domains significantly predicted the presence of each PTSD symptom, with a low portion of variance being explained. Surprisingly, individual perception of social domain did not predict significantly any of the PTSD symptoms.
Conclusions: As expected, PTSD symptoms lead to impairment of quality of life in the affected population, but impaired quality of life is just one of the weak, but significant predictors of PTSD cluster symptoms leading to conclusion that other multiple factors influence the severity and manifestations of chronic PTSD. Further research, concentrating especially on physical health, in this population is needed.

P-23-011
The connection between coping mechanisms, depression, anxiety and fatigue in multiple sclerosis

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Objectives: The main objective of this research was to show how different coping mechanisms influence the prevalence of anxiety and depression in people suffering from multiple sclerosis. We also aimed at showing how different coping mechanisms contribute to subjective prosperity of the patients emphasizing general health, cognitive functions and fatigue.
Methods: A questionnaire was given to attendants of the VI. Symposium Of Patients Suffering From Multiple Sclerosis. Scales were taken from Multiple Sclerosis Quality of Life Inventory (MSQLI), Hospital Anxiety and Depression Scale (HADS) and COPE inventory. A total of 68 anonymous questionnaires were handed in.
Results: A total of 57, 90% examinees have symptoms of depression, and 63, 20% suffers from symptoms of anxiety. However, majority of the examinees suffers from the combination of these entities. Hypothesis about impact of various coping factors on depression, anxiety, fatigue was validated except an impact on physical state was not proven significant. Predictors improving these states were positive reinterpretation, social emotional support and humor, Predictors worsening these states were planning, acceptance, focus on emotional ventilation and denial
Conclusions: Psychiatric morbidity has a high prevalence in people suffering from MS. Different coping mechanisms can help in improvement of everyday quality of life. We have also shown that fatigue is a major disabling factor that positive coping mechanisms can help overcome.

P-23-012
The investigating of the effectiveness of biofeedback (galvanic skin response) on war veterans with PTSD

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Objectives: The aim of this study was to examine the effectiveness of treatment of biofeedback (galvanic skin response) on war veterans with Post Traumatic Stress Disorder.
Methods: In this research 14 war veterans with PTSD were selected availability sampling and divided into 2 groups of: treatment of biofeedback (n=7) and control group (n=7). seven treatment sessions were individually hold by use of biofeedback method, while control group was waiting. All of the subject was evaluated PTSD Symptom Scale_ Interview (PSS_I) before and after the treatment.
Results: Analysis of data showed that comparison with control group the said treatment biofeedback caused a decrease in PTSD syndrome.
Conclusions: It can be generally noted that experimental groups has been found to be effective on PTSD among Iranian war veterans.

P-23-013
The investigating of the effectiveness of eye movement desensitization and reprocessing on war veterans with PTSD

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Objectives: The aim of this study was to examine the effectiveness of treatment of Eye Movement Desensitization and Reprocessing (EMDR) on war veterans with Post Traumatic Stress Disorder.
Methods: In this research 14 war veterans with PTSD were selected availability sampling and divided into 2 groups of: treatment of EMDR (n=7) and control group (n=7). three treatment sessions were individually hold by use of EMDR method, while control group was waiting. All of the subject was evaluated PTSD Symptom Scale_Interview (PSS_I) before and after the treatment.
Results: Analysis of data showed that comparison with control group the said treatment EMDR caused a decrease in PTSD syndrome.
Conclusions: It can be generally noted that experimental groups has been found to be effective on PTSD among Iranian war veterans.

P-23-014
Posttraumatic stress disorder (PTSD): The impact of changes in diagnostic criteria

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Objectives: Since its inclusion in DSM-III, PTSD has undergone a number of changes in its diagnostic criteria including the expansion of Criterion A (traumatic stressor), the addition of symptom duration (none specified in DSM-III), and the requirement for impairment or distress (Criterion F, DSM-IV only). The impact of changes in PTSD diagnostic criteria were examined using a Canadian PTSD epidemiological sample
Methods: The rates of PTSD and its correlates were evaluated in a nationally representative random sample of 3006 individuals. DSM-III, DSM-III-R and DSM-IV criteria were employed. DSM-III and DSM-III-R rates were re-evaluated, adding Criterion F.
Results: The prevalence rates of lifetime PTSD ranged from 13.4% (DSM-III) to 12.2% (DSM-III-R) to 9.2% (DSM-IV); all rates differed significantly from each other. Regardless of diagnostic criteria, most people reported more than one year duration of symptoms, although rates were significantly higher in those with DSM-IV PTSD (68.2%,p <.0001). Rates of comorbid major depression, alcohol and substance abuse and dependence were also significantly higher using the DSM-IV PTSD criteria and those with DSM-IV PTSD reported significantly higher rates of help seeking. When Criterion F was added to earlier versions, lifetime PTSD rates became much closer to those obtained in DSM-IV: 10.2% (DSM-III) and 9.6% (DSM-III-R).
Conclusions: In contrast to previous versions, DSM-IV PTSD identifies a more severe disorder. Interestingly, changes in Criterion A do not appear to have as much influence on the rates of PTSD as does the addition of Criterion F. This information may be useful for the architects of DSM-V.

P-23-015
Childhood maltreatment accociated with greater symptom secerity and poorer quality of life and function in social anxiety disorder

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Objectives: In studies of anxiety disorders, childhood maltreatment has most often been defined as physical or sexual abuse. We hypothesized childhood maltreatment severity, including emotional abuse and neglect as measured by the Childhood Trauma Questionnaire (CTQ), would be associated with greater symptom severity and poorer function in individuals with generalized social anxiety disorder (GSAD).
Methods: 103 individuals with DSM IV GSAD received the Liebowitz Social Anxiety Scale (LSAS) and completed the CTQ, the Quality of Life Enjoyment and Satisfaction Questionnaire (QLESQ), the Connor-Davidson Resilience Scale (CDRISC), and the Sheehan Disability Scale (SDS) prior to a pharmacotherapy trial. The 28 item CTQ is well-validated with 5 trauma subscales (sexual abuse, physical abuse, emotional abuse, emotional neglect, physical neglect) with established thresholds. Regression models were examined for the CTQ and for subscale thresholds.
Results: Participants were 70% male, with a mean LSAS of 91.0(19.6) and a mean CGI severity score of 5.3(0.9). SAD onset was during childhood (10.7+/-7.6 years), with a mean duration of 26.1(16.5) years. Fully 70% met severity criteria for at least one CTQ subscale. CTQ total score adjusted for age and gender was associated with greater LSAS (B=0.54,t=4.5: p<0.001) and the CGI-S severity (B=0.02,t=4.2: p<0.001), and poorer quality of life (QLESQ: B=-0.17,t=-2.9: p=0.005), function (SDS: B=0.12,t=3.3: p=0.001) and resilience (CDRISC: B=-0.24,t=-2.3: p=0.022). Emotional neglect and abuse were most consistently associated with symptom scales.
Conclusions: Self reported childhood maltreatment, and specifically emotional abuse and neglect, are associated with greater severity and poorer function, resilience and QOL in adults with GSAD.

P-23-016
The behavioral and neurochemical Ladasten effects depend on emotional stress reaction responses

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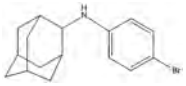
Objectives: The primary aim was to reveal the differences in Ladasten (N-(2-adamanthyl)-N-(parabromphenyl)amine) mechanisms behavioral and neurochemical responses in the inbred mice (C57Bl/6, BALB/C) and rats (MNRA, MR).
Methods: Behavior effects of Ladasten (30-150 mg/kg i.p.) were investigated in the "open field" (OF), elevated plus maze (EPM) and spontaneous locomotor activity (SLA) tests in inbred mice and rats. Monoamine levels were analysed in the hypothalamus, striatum and nucleus accumbens by HPLC with electrochemical detection after MNRA and MR rats exposure in the "open field" test.
Results: Ladasten at doses ranging 30-60 mg/kg i.p. enhanced the behavior in animals with passive (BALB/C mice, MR rats) and active (C57Bl/6 mice, MNRA rats) emotional-stress reaction phenotype in the OF and EPM tests. The estimation of SLA in C57Bl/6 mice as well MNRA rats after Ladasten (30-150 mg/kg i.p.) provided results in support of its psychostimulating action. The same doses of Ladasten in BALB/C mice and MR rats without stressful situation produced no effect. Using HPLC it was shown that Ladasten (30 mg/kg i.p.) increased the level of dopamine and serotonin in the nucleus accumbens and striatum of MNRA rats and did not produce such effect on MR rats with passive behavior in OF.

Conclusions: The analysis of behavioral effects of Ladasten revealed that Ladasten stimulated animals with active phenotype of emotional stress reaction. The data obtained from HPLC study allowed to conclude that the psychostimulating action of Ladasten depends on phenotype of response to emotional stress and mediated by monoamine systems.



P-23-017

Plasma serotonin level of Vietnam War veterans with posttraumatic stress disorder after long-term drug treatment

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Objectives: The study was done to evaluate the relationship between change of plasma serotonin concentration and PTSD symptoms in patients with chronic PTSD who have been on long-term drug treatment.
Methods: Plasma serotonin level of 14 PTSD patients and control group of 28 Vietnam War veterans was measured by high performance liquid chromatography and symptoms were evaluated using CAPS,CES, Mississippi Scale for combat-related PTSD,HAMD-17, and HAS to check PTSD symptom severity.
Results: Plasma serotonin level was significantly higher in PTSD group than in control group($p = 0.006$). All the scales but CES were significantly higher in PTSD group than in control group. There was no significant correlation between plasma serotonin level and PTSD symptoms.
Conclusions: We could not expect the effect of drug treatment and severity of symptoms by measuring only plasma serotonin level. PTSD is complicated disorder which is related with various system, and research about other neurotransmitters are needed for better treatment of PTSD.

P-23-018

Dynamics of biological age dimensions after exposure to extreme situations

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Objectives: Our research was carried out at the Center of Rehabilitation of War Veterans. We studied 106 males aged from 21 to 41 who had suffered from post traumatic stress disorder (PTSD). For comparison we also studied 46 males of old age who did not suffer from PTSD. The group of PTSD victims was divided into two subgroups: 49 patients who had experienced the trauma less than 5 years ago and 57 males who had experienced it more than 5 years ago.
Methods: We used 4 approaches:clinical, experimental (psychological), spectral analysis of the heart rate variability, assessment of biological age according to the scheme of the Institute of Gerontology, Kiev.
Results: The clinical approach showed that the majority of patients suffered from depressive disorders with asthenia and anxiety (68 %), which was similar to the group of old males. Experimental approach demonstrated the signs of psychoemotional hyperactivation in the first group of patients (57%). The second group suffered from "exhaustion" of mental functions (53%) and depression (68%). Asthenia was encountered in the second and the third groups (65% and 69% respectively). In PTSD picture the hyperaction of sympathetic system accelerated heart-vascular activity which provoked atherosclerosis and organism's aging. The patients of the second group, even at rest, showed decline of the total spectrum capacity. Vegetative regulation of heart rate was changed to a slower humoral metabolic regulation. BA outpaced the "supposed" biological age (SBA) for PTSD patients. Actual BA especially exceeded SBA in the second group (by more than 7 standard years). We discovered a direct correlation between premature aging and psychovegetative signs of exhaustion.
Conclusions: Our study of biological age demonstrated the decay of physiological resource after extreme situations and similar changes in psychovegetative sphere of elderly people. Thus, PTSD eventually leads to premature aging and requires rehabilitation.

P-23-019

Caffeine challenge and breath-holding duration in patients with panic disorder

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Objectives: Breath-holding (BH) has been used as a simple probe to increase endogenous carbon dioxide (CO_2). We assessed BH duration in patients with Panic Disorder (PD) in relation to panic attacks induced by caffeine intake.
Methods: BH duration and state anxiety was assessed in 40 PD patients (12 males), both at baseline and after a 400-mg caffeine challenge test.
Results: Patients panicking after caffeine administration (14 patients, 4 males) exhibited a significant reduction of their post-challenge BH duration, while no change of the BH duration was observed in non-panicking patients (26 patients, 8 males). Reduction in post-challenge BH duration was not related to higher anxiety levels -as reflected in the State-Trait Anxiety Inventory-State Form scores- independently of the occurrence of a panic attack. Panickers exhibited significantly lower baseline BH duration, compared to non-panickers.
Conclusions: Our findings indicate that in PD patients, caffeine-induced panic attacks are strongly associated with a significant reduction of BH duration at both pre- and post-challenge. Jointly, these findings suggest that in a subgroup of PD patients, sensitivity to endogenous CO_2 accumulation may underlie both the lower BH durations and the caffeine-induced panic attacks. In this subgroup of PD patients, caffeine might exert its panicogenic properties through the exacerbation of patients' already pathological hypersensitivity to CO_2 accumulation, as indicated by both the significant decrease of their BH duration at post-challenge and by their significantly lower baseline BH duration respectively.

P-23-020

Efficacy of sertindole and combination of flufenazine and one SSRI (fluoxetine or fluvoxamine) in treatment of PTSD patients with psychotic symptoms

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Objectives: Aim of this paper is to evaluate efficacy of treatment of examined patients treated with sertindole as monotherapy and patients treated with both flufenazin and one of SSRIs (fluoxetine or fluvoxamine).
Methods: 40 PTSD patients with psychotic symptoms have been enrolled. All of them are male and were participants of war in Croatia. They are aged 25 to 55, with a duration of symptoms from 5 to 15 years. ECG monitoring has been included. Persons with some beneffits other than medical are not enrolled in the study.The patients have been diagnosed by criteria of ICD-10 classification. PANSS has been used to evaluate psychotic symptoms. Risk of suicide has been evaluated too. Efficacy has been evaluated by PANSS and CGI-I and CGI-S scales. Evaluation is conducted at the beginning of the study and afterwards each two weeks during the 6 months period. In addition to the efficacy estimation, safety, tolerability and compliance have been estimated too.
Results: Final results will be summerized at the end of May, 2009, when the study will be completed.
Conclusions: Pharmacotherapy of psychotic episodes is the most important method in medical treatment. This therapy should include antipsychotic and antidepressive strategies. We expect to menage that by using the atipical antipsychotic alone.

P-23-021
Preliminary data on the French version of the Hypomania Checklist (HCL-32)

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Objectives: The HCL-32 R1 is a self-rating questionnaire on the lifetime history of hypomanic/manic symptoms. The HCL-32 is currently used in many countries and available in more than 20 languages. To date, no patient data were collected with the French version.
Methods: The clinical assessment used the HCL-32 (French) with other scales: Mood Disorder Questionnaires (MDQ), Mood Intensity Scale (MIS), Derogatis Scale (CHESS), Bipolar test and Temperament scales (TEMPS-A) Population: Preliminary data were obtained in a sample of 108 patients attending the CTAH (mood center) and systematically included during a 4-month period. The bipolar diagnosis was made by a senior expert: 99 bipolars (5 BP-I, 87 BP-II or II1/2, 2 BP-III, 4 BP-IV, 1 BP nsa) and 9 non-bipolars. The low rate of non-bipolars is explained by the quality of referral of the mood center
Results: Cronbach coefficient on the HCL-32 is equal to 0,896. The area under the curve in ROC analysis was quite high = 0,93, which suggests a good discriminative property of the HCL-32. The mean score in the BP group was significantly higher than in the non-BP group (22,06 ± 5,95 versus 10,96 ± 5,00, p<0,0001). With a cut-off of 12, sensitivity = 96% and specificity = 77,8%; with a cut-off of 14, sensitivity = 89,9% and specificity = 77,8%. Positive cases with a cut-off of 14 have higher rate of divorce (15,4% vs 5,9%), number of doctors consulted (4,7 vs 3,2) psychiatric hospitalizations (32,2% vs 17,6%), and suicide attempts (34,4% vs 17,6%). Principal component and exploratory factor analyses (varimax rotation with 2 factors solution) showed similar data: presence of 2 major factors "irritability-risk taking-substance overuse" / "elation-hyperactivity". When using the MDQ, lower sensitivity (54,1%) and good specificity (87,5%) were obtained for the diagnosis of bipolarity. Concordance analysis between MDQ and HCL-32 showed that 60% of cases were in agreement. When the MDQ was positive for BP, HCL was also positive in 94%; conversely, when the HCL-32 was positive for BP, the MDQ was positive for only 57%. Links between the HCL-32 and cyclothymia were stronger (concordance 84%) than between the MDQ and cyclothymia (64%) High correlations coefficients were obtained between the HCL-32 and MDQ (0,74) and the HCL-32 and cyclothymia (0,61).
Conclusions: Preliminary data show good psychometric qualities of HCL-32 and are close to published data for other versions. More research is required especially in larger samples of non-bipolar patients.

P-34
Anxiety III

P-34-001
Ex-service men and psychotraumatism in Algeria

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Objectives: ABSTRACT The authors report an established psychotraumatisme stress disorder (PTSD) in 60 ex-service men of the Algerian war; seen in the expertise for a reassessments of their war indemnity (Inability Partial Permanent) 45 years after the independence, these ex-service men continue to have psychological pains signs in silence. This has led to think about psychotraumatisme stress disorder in the face of any anxio-depressive symptomatology in the ex-service men. KEY WORDS: Post traumatic stress disorders, ex-service men

P-34-002
Combination of pharmacotherapy and psychotherapy in the treatment of patients with panic disorder

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Objectives: To establish whether the combination of cognitive-behavioral therapy (CBT) and pharmacotherapy (SSRIs+benzodiazepines) is more effective in treating panic disorder (PD) with agoraphobia than CBT alone.
Methods: The study included 64 adult patients (47 females, 17 males) diagnosed with panic disorder with agoraphobia. Forty-three patients received combined treatment which included medication and CBT. Twenty-one patients received only psychotherapy. Treatment components of CBT included education, in vivo exposure, interoceptive exposure, cognitive restructuring, and relaxation techniques. Fluoxetine and sertraline were used in the study. We also used high-potency benzodiazepines that display a rapid onset of anti-anxiety effect and thus having beneficial effects. Patients with PD were assessed before treatment and after 3 months of treatment with the Panic and Agoraphobia Scale (PAS; Bandelow), the Fear Questionnaire (FQ; Marks & Mathews), the Agoraphobic Cognitions Questionnaire (ACQ), the Hamilton Anxiety Rating Scale (HAM-A), the Illness Attitude Scale (IAS), and the Symptom Checklist-90-Revised (SCL-90-R). One-way analysis of variance (ANOVA) and t-test were used to determine statistical significance.
Results: The combined treatment group demonstrated significantly greater improvement in panic and agoraphobic symptoms. The better outcome in combined group was observed in the most measures with all applied instruments – total score on the PAS (F=21.165, p<0.001), physical concern items and loss of control items on the ACQ (F=97.15, p<0,05; F=57.53, p<0.05), the scores on the SCL-90-R subscales of phobia (F= 11.43, p<0.001), agoraphobic avoidance on the FQ (F=1.30, p=0.001), total score on the HAM-A (F=4.09, p<0.05), and the effects of symptom score at the IAS (F=6.56, p<0.05). Completed analysis revealed superiority of combined therapy over CBT across all performed measures.
Conclusions: Combined therapy is more effective for patients with panic disorder with agoraphobia than psychotherapy alone in a short-term treatment.

P-34-003
HPA-axis behavior is correlated with personality

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Eric Vermetten, Goran Knezevic, Gordana Matic, Zeljko Spiric, Svetozar Damjanovic

Objectives: Hypothalamic pituitary adrenal (HPA) axis functioning, as measured by the dexamethasone suppression test (DST), has been extensively investigated in psychiatric disorders eg depression or PTSD. Behavior of HPA axis can be well described by regulatory parameters such as the low dose (0,5 mg) dexamathasone suppression test (ldDST), but also by nocturnal variation, and the cortisol awakening response (CAR). We hypothesize that ldDST and the non pharmacological regulatory behavior is characterized by several mechanisms: psychopathology, personality/temperament, and/or experience of life/war stress.
Methods: We analysed data from 391 subjects in 4 groups: current PTSD lifetime PTSD, trauma controls and healthy controls. All subjects were recruited in Serbia, mostly Belgrade region. All subjects were hospitalized for three days in which standardized data-acquisition took place, including psychological assessment (SCID, assessment war and life stress, CAPS and personality assessment by NEO-PI, neuropsychol assessment). Blood was drawn from an i.v. line at 13 time points (starting at 2200h) with one hour intervals.
Results: Across groups a correlation between ldDST and CAPS was found. A correlation was found with NEU,EXTRA, CONSC; in a stepwise regression analysis only CONSC survived. When data on ldDST were redistributed in quartiles, the upper and lower quartiles of ldDST showed differences on personality measures. Correlations of impulsivity was found with CAR, nocturnal pattern, as well as ldDST. Discriminant analysis on lower level dimensions of CONSC was significant.

Conclusions: HPA axis self-regulatory behavior, assessed via ldDST, CAR and nocturnal cortisol pattern was correlated to the trait of CONSC. This personality trait includes elements as self-discipline, carefulness, thoroughness, organization, deliberation and need for achievement, and can be conceptualized as iopposite of impulsivity. The long held belief that cortisol suppression holds specificity for psychopathology may still be true but this relation is decomposed to one of the trait factors, and the level of stress experience. The implications need to be further thought through as well as the mechanisms.

P-34-004
Predictors of clinical response to placebo in patients with anciety disorder

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Roxana Galeno

Objectives: The propose of this study is to identify clinical predictors related to good clinical response in patients with anxiety disorders treated with placebo.
Methods: The revision was realised in two clinical trials, double-blind, placebo controlled, parallel-group, in outpatients with Generalized Anxiety Disorder and Panic Disorder. The remission criteria was the decrease in scores of CGI-S and CGI-I, in at least two points between the start and the end of the study. By statistical analysis, was analyzed the relationship between good clinical response to placebo and several factors like sex, age, civil state, labor situation, initiative for the treatment, amount of previous psycopharmacologic treatments, the age when the desease started, the time of the disease and severity of anxiety disorder.
Results: In the analysis of these two trials it was observed that 14 patients received placebo during the randomization phase: 9 with poor clinical response and 5 with good clinical response. It was found, with statistically significance, a relationship between respondered patients to placebo with stable labor situation and with the number of previous psychopharmacological treatments. In the other hand, the analysis with the others factors were no differences.
Conclusions: Although this is a small study, it was possible to identify predictors of good clinical response to placebo like laboral stability and the presence of previous psychopharmacological treatments. These data could be useful in the future in order to identify respondered and non-respondered patients in placebo treatments and also in planning of clinical trials with placebo.

P-34-005
Cannabinoid receptor ligands suppress anxiety-related effects of d-amphetamine and nicotine in the elevated plus maze test in mice

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Marta Kruk

Objectives: The mechanisms by which nicotine and amphetamine modify anxiety-related behavior have not yet been completely elucidated. Thus, several findings suggest that endocannabinoid system may be involved.
Methods: The present study was designed to analyze the influence of CB1 cannabinoid receptor ligands on behavioral actions of d-amphetamine or nicotine, including crossover effects, using the mouse elevated plus maze (EPM) test. In this paradigm, anxiolytic activity is indicated by increases in time spent in open arms or in number of open arms entries; anxiogenic effects are characterized by decreases in these measures. Briefly, d-amphetamine (2 mg/kg) was administered acutely or daily for 8 days. On the 9th day, mice were challenged with d-amphetamine (2 mg/kg) or nicotine (0.1 mg/kg), and were tested in the EPM for 5 min. Additionally, a distinct group of mice was pretreated with an acute (0.1 mg/kg) or subchronic nicotine (6 days), and subjected to nicotine (0.1 mg/kg) or d-amphetamine (2 mg/kg) challenge on the 7th day. The cannabinoid receptor ligands, WIN 55,212-2, a CB1 receptor agonist and rimonabant, a CB1 receptor antagonist were injected prior to each injection of d-amphetamine and nicotine. The statistical analyses were performed using one-way analysis of variance with post-hoc Tukey test.
Results: We observed that acute anxiogenic and subchronic anxiolytic effects of both psychostimulants as well as the development of full cross-tolerance to their anxiogenic effects were dose-dependently blunted by ineffective, per se, doses of WIN 55,212-2 (0.25 and 0.5 mg/kg) and rimonabant (0.5 and 1 mg/kg).
Conclusions: Our results provide the pharmacological evidence for the specific involvement of endocannabinoid system in mediating the anxiety-related behavior induced by d-amphetamine and/or nicotine administration.

P-34-006
Parental anxiety and quality of life in children with blindness in Ababasire institution

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Objectives: Introduction: Nowadays, Quality of life is one of the important aspects in programming and do service for disabled persons. And Blindness is the most common important groups of physical handicapped. Parents are very important person in child's life that their psychological status can affect their disabled children's quality of life. And anxiety is one of the most psychological disorders in parent of disabled children. Object of this research is to determine relation between parental anxiety and quality of life in children with blindness in Ababasire institution, Isfahan, in emotional and social dimensions. Finding: There were significant correlation between parental anxiety and blind children quality of life in Emotional∆social domains. (P<0/01) quality of life significantly decreased with increased level of parental anxiety.
Methods: Material and **Methods:** This study is a correlation study and its subjects were selected with census method, So that 94 blind child with their parents were studied. Data gathering was done through 2 questionnaires. One of them was "Hamilton Anxious Questionnaire" which is standard and another one was "Quality of life" that measure two domains including emotional, social. Validity and reliability was assessed with content validity and test-re-test method. (0/89) Data were analyzed using SPSS, via statistical tests including the Kendall's tau b.
Results: Discussion and Result: In respect to the above results, upgrading mental health and reducing anxiety in parents of blind children is really necessary and there must be some affective actions about this. Key word: parental anxiety; quality of life; blind, emotional domain, social domain

P-34-007
Relationship between Hepatocyte growth factor and anxiety and depression

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Objectives: Hepatocyte growth factor (HGF) is induced in neurons during ischemia and is neuroprotective against post-ischemic delayed neuronal death in the hippocampus. HGF might play an important role in the maturation and functioning of these neurons in the hippocampus. Our aim was to determine what effect HGF antisense has on anxiety in rats.
Methods: HGF antisense or plasmid was infused at a constant rate into cerebral lateral ventricles and its effect on anxiety in rats was monitored. In forced swimming test, rats that received antisense DNA increased the length of time that they were immobile in the water.
Results: In forced swimming test, rats that received antisense DNA increased the length of time that they were immobile in the water. In the elevated plus maze test, the black and white box test and conditioned fear test, HGF antisense administration caused all indicators of anxiety to increase. Number of HGF-positive cells in C1 of hippocampus was significantly decreased in the HGF antisense-infused group compared to the vehicle- and scrambled oligonucleotide-treated group.
Conclusions: These results indicate that inhibition of HGF induces an increase in depression and anxiety-related behaviors suggesting a depressive and anxiogenic-like effect.

P-34-008

The reletionship between depersonalization, derealization and number of traumatic events during childhood and adolescence in healthy individuals

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Objectives: The goal of this study was to explore the relationship between early traumatic events before 18 years of age and the rate of depersonalization and derealization in healthy subjects. With regard to other studies we hypothesized a higher and more intensive experience of depersonalization and derealization in individuals with significant trauma events during childhood or adolescence.
Methods: The study included 52 healthy individuals (34 women and 18 men). The depersonalization and derealization frequency and intensity were measured by Cambridge Depersonalization Scale (CDS). The type and frequency of trauma events were evaluated by Early Trauma Inventory Self Report - Short Form. The anxiety and depression rate was measured by Beck Anxiety Inventory and Beck Depression Inventory-II.
Results: We did not found any relationship between trauma events during childhood and the rate of depersonalization and derealization. There is a negative correlation between the CDS values and the age. The depersonalization and derealization rate has a positive correlation to the intensity of anxiety and depressive symptoms. The BDI score has a positive correlation to the total score of traumatization. There is no difference in experienced depersonalization and derealization between men and women.
Conclusions: The rate of depersonalization and derealization has no correlation to the number of trauma events experienced during childhood by healthy individuals. This finding does not support the hypothesis of repeated dissociation as a defensive mechanism in childhood. In our future studies, we will focus on the finding of positive correlation between dissociation and anxiety and depressive symptoms using factor analysis in a larger sample of subjects. Key words: depersonalization, derealization, trauma events, anxiety, depression This project is supported by IGA NR 9323-3 and CNS MŠMT ČR 1M0517

P-34-009

Mental fatigue after brain injury and the supporting systems of the brain

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Objectives: Mental fatigue is a common and disabling symptom after a skull trauma. The mental fatigue could make it impossible to go back to work, as the person is able to be mentally active just for short periods. Glutamate signaling is essential for information processing in the brain, including learning and memory formation. Low levels and fine-tuning of extracellular glutamate are considered necessary to keep a high precision in information processing, and thereby a high efficiency in the information handling within the CNS. From experimental data the astrocytes are considered the most important cells for clearing the extracellular space from glutamate during glutamate transmission. Mechanisms underlying the mental fatigue at the cellular level are not fully understood. Our hypothesis suggests a dysfunction in the systems of the brain that support the glutamate transmission. **Objectives:** To examine mechanisms at the cellular level that could underlie mental fatigue.
Methods: Primary cultures of astrocytes co-cultured with neurons or endothelial cells. The capacity of the astrocyte glutamate transport and the expression of the glutamate transporters GLAST and GLT-1 are studied under the influence of cytokines and oxidative stress.
Results: In the presence of neurons the astrocyte glutamate uptake capacity is augmented compared to the uptake capacity in astrocytes in monoculture, and GLT-1 is expressed. TNF-alpha and oxidative stress of the cells prominently impair the astrocyte glutamate uptake capacity and down-regulate the expression of glutamate transporters.
Conclusions: Mental fatigue is a problem of utmost importance in our high-technology society, where there are increasing demands on our mental capacity. The capacity of astrocytes to clear the extracellular space from glutamate is attenuated by TNF-alpha and oxidative stress, which appear in brain injury. These results support our hypothesis that one mechanism behind the appearance of mental fatigue is impaired supporting cell functions in the brain.

P-34-010

Anxiolytic efficacy and time to onset of pregabalin in patients with Generalized Anxiety Disorder: Open label, non-comparative, flexible-dose study

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Objectives: Pregabalin is an alpha(2)-delta ligand approved in the EU for the treatment of neuropathic pain, generalized anxiety disorder (GAD), and adjunctive treatment of partial onset seizures. We report the efficacy and tolerability of the agent in the treatment of GAD in the clinical practice setting [1], with particular focus on onset of action.
Methods: In a 4-week open-label observational trial, 331 physicians (mainly psychiatrists) documented 578 consecutive adult patients with GAD. Severity of GAD was rated using a 100 mm visual analogue scale (VAS anxiety) and the Hospital Anxiety and Depression Scale (HADS-A).
Results: Physicians were free to choose the doses; most patients received an initial dose of 150 mg/d (49.3%) and the final dose was typically 150 (39.4%) or 300 mg/d (32.2%). Mean VAS anxiety scores decreased from 62.3 (baseline) to 26.5 (final). A 30% and 50% reduction was achieved by 73.9% and 63.0% of subjects. The median time to the 30% and the 50% improvement was 7.0 and 11.0 days, respectively, while the median time to a 10-point improvement was 4.0 days. The mean HADS-A score was significantly reduced from 15.4 ± 3.4 at baseline to 13.2 ±3.4 at week 1 and to 9.5±4.2 at week 4. Tolerability was good as evidenced by a low rate of adverse events (n= 26, mostly mild or moderate), and a low rate of discontinuation from treatment (n = 7 patients).
Conclusions: Under clinical practice conditions 4 weeks of pregabalin treatment produced significant improvement in anxiety in GAD patients. The onset of action was rapid which facilitates therapy in this patient group. [1] Möller HJ, Brasser M, Kasper S, Volz HP, Boerner RJ, Bandelow B. Wirksamkeit und Verträglichkeit von Pregabalin bei Patienten mit GAD in der täglichen Praxis (in press).

P-34-011

Pregabalin treatment for Generalized Anxiety Disorder under clinical practice conditions: Global response as assessed by patients and physicians

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Objectives: Pregabalin binds to the alpha2-delta subunit of voltage-gated calcium channels. A comprehensive clinical registration program has confirmed the efficacy and tolerability of the drug for the treatment of Generalized Anxiety Disorder (GAD). We aimed to investigate pregabalin in this indication in a real life setting.
Methods: In a 4-week open-label non-interventional observational trial, 331 physicians assessed the efficacy of pregabalin in 578 adult GAD patients applying various scales, among them the global impression of change scales for patients (PGIC) or physicians (CGIC), respectively. Physicians prescribed pregabalin based on their clinical judgement.

Results: Most patients received an initial pregabalin dose of 150mg/d (49.3%) and the final dose was typically 150 (39.4%) or 300 mg/d (32.2%). At the final visit in the PGIC assessment, 69 (12.1%), 254 (44.5%), and 193 (33.8%) subjects reported that their overall status was very much, much, and little improved, respectively; 31 (5.4%), 12 (2.1%), and 3 (0.5%) subjects considered their status unchanged, slightly worse, or much worse, respectively. Overall, 516 (90.4%) subjects were considered PGIC responders. Improvement in PGIC was observed across all subgroups (by age, gender, presence of depression, and first-line therapy). In the CGIC assessment, at final visit 57 (10.0%), 236 (41.3%), and 205 (35.9%) were considered to have had a marked, moderate, or minimal improvement, respectively, in overall status. A total of 62 (10.9%) subjects had no change and 3 (0.5%) and 1 (0.2%) subjects had minimal and moderate worsening in status, respectively. Overall, 498 (87.2%) subjects were considered CGIC responders at the final visit.
Conclusions: With pregabalin treatment, improvement in general status as assessed by the patient or physician was noted in these GAD patients under everyday practice conditions.

P-34-012
Efficacy of ECT in chronic, severe, antidepressant – and CBT refractory posttraumatic stress disorder: An open, prospective study

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Objectives: To assess through an open uncontrolled study the effect of ECT on patients with chronic, severe, antidepressant- and CBT-refractory PTSD.
Methods: Between January 1, 2005, and December 31, 2005, all consenting adults (n=20) with severe, chronic, extensively antidepressant-refractory PTSD were prospectively treated with a fixed course of 6 bilateral electroconvulsive therapy (ECT) treatments administered on an outpatient basis at a twice-weekly frequency. The primary outcome measure was improvement on the Clinician-Administered Posttraumatic Stress Disorder Scale (CAPS). Baseline refractoriness was defined as a failure to respond to an adequate course of at least 4 different antidepressant drugs along with 12 sessions of cognitive behavior therapy. Response to ECT was defined as at least 30% attenuation of CAPS ratings, and remission as an endpoint CAPS score of 20 or less. After ECT, patients were prescribed sertraline (100-150 mg/day) or mirtazapine (15-30 mg/day).
Results: All but 3 patients completed the ECT course. An intent-to-treat analysis (n=20) showed statistically and clinically significant improvement in the sample as a whole: CAPS scores decreased by a mean of 34.4%, and depression scores by a mean of 51.1%. Most of the improvement in CAPS and depression ratings developed by the third ECT; that is, by day 10 of treatment, itself. The improvement in CAPS ratings was independent of the improvement in depression ratings; and improvement in CAPS did not differ between patients with less severe vs more severe baseline depression. The response rate was 70%; no patient remitted. In the completer analysis (n=17), mean improvements were 40% and 57% for CAPS and depression ratings, respectively, and the response rate was 82%. Treatment gains were maintained at a 4-6 month follow-up.
Conclusions: ECT appears to improve the core symptoms of PTSD independently of improvement in depression, and may therefore be a useful treatment option for patients with severe, chronic, medication- and CBT-refractory PTSD.

P-34-013
Cognitive mechanisms involved in PTSD and its treatment

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Objectives: The post traumatic stress disorder (PTSD) is an anxiety disorder that occurs after exposure to a trauma. It is characterized by intrusive memories, avoidance, hypervigilence and social dysfunctions, persisting for at least one month. These symptoms are underlined by a hypothesised impairment in cognitive processing in PTSD patient. PTSD has high prevalence lifetime rates (8-10% in the USA) and important comorbidities (87% associated depression, anxiety, addictions…). The Eye Movement Desensitization and Reprocessing (EMDR) is one of the efficient treatment options. Our study aims at exploring the psychological and cognitive mechanisms involved in PTSD and its treatment by EMDR.
Methods: 20 PTSD patients and 20 controls (matched for age, sex and educational level) were evaluated, both before and after therapy, for their personality trait (NEO-PIR), anxiety (STAI), depression (Beck), and PTSD symptoms (only for patients PCL-S, MPSS, IES, PDI). They also performed the Stroop, Emotional Stroop, and DOT tests. Two-way repeated measures ANOVAs with Population as a between factor and Treatment as a within factor were used to analyze these data.
Results: Our results show that after EMDR therapy, patients' scores on STAI, Beck and all PTSD scales significantly decrease from pathological to normal standards. Most comorbid disorders fade. Moreover, patients have an attention bias in terms of disengagement from emotional stimuli with negative valence, before therapy but not after.
Conclusions: Impairments in PTSD patients are thus substantiated via psychological and cognitive markers. We would like to explore similar paradigms at the cerebral level to better understand neuronal mechanisms involved in the PTSD pathology and its treatment.

P-34-014
Differential rearing condition interferes with caffeine's effect in the adult rats

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Objectives: Differential rearing condition has been reported to modify the neurochemical properties of the adult animals and alter the responsitivity to addictive drugs. The main objective of the present experiments was to investigate the effect of different rearing conditions from weaning on the open field behavior of caffeine-treated rats.
Methods: Male Wistar rats were obtained from weaning (21 days of age) and reared in two different conditions: either singly (isolation rearing) or in groups of five-six rats/cage (social rearing) in the same room for four weeks before the open field testing. Each rat was placed into an open field arena for a 5 min test.
Results: The results demonstrated that untreated isolation reared rats exhibited locomotor hyperactivity, reared significantly more but defecated significantly less than socially reared rats. Both socially and isolation reared rats spent more time in the outer zone ($P<0.05$), however, isolation reared rats entried and spent more time in the inner zone than socially reared rats. Intraperitoneal injection of caffeine (10 and 20 mg/kg) significantly produced locomotor hyperactivities (indicated by increase total zone transitions and number of reared) in the socially reared rats, but had no effect on the isolation reared rats.
Conclusions: These results indicate that social isolation rearing from weaning enhances locomotor activity but prevents the effect of caffeine in the adult rats.

P-34-015
Effect of barakol on the elevated plus-maze behavior of social and isolation reared rats

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Objectives: Barakol was isolated from the fresh young leaves of Cassia siamea, a plant used in Thai traditional medicine. The objective of the present experiments was to investigate the behavioral effect of barakol on the rat elevated plus maze in social and isolation reared rats.
Methods: Male Wistar rats were raised from weaning (21 days of age) either alone (isolation rearing) or groups of five-six rats/cage (social rearing) for five weeks before behavioral testing. Both socially and isolation reared rats were placed individually onto the elevated plus maze for a 5 min test.
Results: The results demonstrated that pretreatment with barakol (5, 10 and 25 mg/kg i.p.) to the socially reared rats produced a dose-related anxiolytic profiles (increase in the percentage of open arm entries and time spent) on the elevated plus-maze compare with the saline-treated control rats. However, the anxiolytic-like property of barakol was not observed in isolation reared rats.
Conclusions: These results indicate that social isolation rearing prevents the anxiolytic-like effect of barakol in the adult rats. This abnormality may involve alterations of central neurotransmitters in the isolation reared rats.

P-34-016
Stress during brain development reduces the anti-aggressive effect of clonidine

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Objectives: Stress during brain development such as social isolation rearing from weaning has been shown to alter the adult animal behaviours and modify the responsitivity to many psychoactive drugs. The purpose of the present experiments was to investigate the effect of social isolation rearing on the anti-aggressive effect of clonidine by using the social interaction test
Methods: Male Wistar rats were raised from weaning either alone (isolation reared rats) or in groups of five-six rats per cage (socially reared rats). Four weeks later, both isolation and socially reared rats were exposed to the social interaction test (10 min) either without drug treatment or following saline or clonidine (0.01 and 0.03 mg/kg, i.p., 30 min before testing). The following behaviours were measured: the latencies and time spent in aggressive interaction, social interaction, and passive interaction and the frequencies of aggressive, avoidance and exploring behaviours.
Results: Under high light in an unfamiliar arena, the isolation compared to the socially reared rats had significantly ($P<0.01$) more aggressive interactions (biting and boxing the partners). Passive interactions (sitting or lying in contact with the partners) did not occur in both isolation and socially reared rats. Pretreatment with clonidine (0.01 and 0.03 mg/kg) decreased the aggressive behavior in a dose-related manner, but induced passive interactions in both groups. These effects of clonidine were significantly less in the isolation reared rats ($P<0.01$).
Conclusions: The results indicate that stress during brain development enhances the aggressive behaviour and reduces the anti-aggressive effect of clonidine.

P-34-017
Diagnostics and rehabilitation of patients with posttraumatic stressful frustration

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Objectives: patient with posttraumatic stress at the age from 21 till 45 years (33 women, 17 men). Among the surveyed patient there was: 27 patients with posttraumatic stress (F.43.1), 16 - sharp reaction to stress (F.43.0), 7-frustration (F.43.2).
Methods: structured clinical diagnostic interview, MMPI, a method of colour elections by Lusher, the Missisipian scale for self-estimation posttraumatic stress, a questionnaire depression by Beck. Processing of the received results spent a method of variation statistics. Reliability of distinctions estimated with the help t - criterion St'yudent, nonparametric criterion X2.
Results: repeated dreadful dreams 38 people (76,0 %), persuasive memoirs on the gone through psychoinjuring event 47 people (94,0 %) Were observed. The alarm 39 people (78,0 %), a sleeplessness 42 people (84,0 %), depression 16 people (32,0 %), decrease in interests to daily activity 17 people (34,0 %), difficulties of concentration of attention 32 people (64,0 %), vegetative infringements 16 people (32,0 %), ($\Delta \leq 0,005$) was marked. Psychodiagnostic researches diagnosed posttraumatic stress at 41 people (82,0 %), have revealed separate signs posttraumatic stress at 9 people (18,0 %). According to test by Lusher at 37 people (74,0 %) the expressed emotional intensity was marked, emotional instability - at 31 people (62,0 %). Under Beck's test the alarm was registered at 38 people (76,0 %). Treatment was spent: medicamentous, physiotherapeutic, psychotherapy (any muscular relaxation by Jackobson, regular decintesion through imagination, behavioural, cognitive, psychodynamic). After carrying out of control researches the analysis of data reflected decrease in expressiveness of symptoms. Considerable improvement both subjective, and objective state of health of the patient was registered.
Conclusions: basic diagnostic criteria posttraumatic stress are revealed. The system of medical-rehabilitation actions should have complex character and hold in itself medicamentous therapy, psychotherapy and psychocorrection.

P-34-018
Syndrome of medical posttraumatic stressful dezoder at children of preschool and early school age

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Objectives: research was spent among patients of children's rehabilitation branch of our Center. 23 children at the age from 5 to 7 years: 17 girls (73.7 %), and 6 (26.1 %) boys were exposed to research. Survey spent in 3 months after treatment of children in children's rehabilitation branch concerning with various somatic pathology.
Methods: kliniko-psychiatric, psychological (the test for revealing of the latent midical fears), Styudent's statistical research methods.
Results: All children have informed, that in the beginning of treatment they reacted to manipulations (intravenous and intramuscular introduction of medicines) painful sensations and fear. During the course of treatment reduction of painful sensations was marked by all patients; considerable reduction of a pain-18 people (78,3, %); considerable reduction of fear before manipulations-20 people (87 %). At survey in 3 months it has been revealed: avoiding behaviour at 13 persons (56,5 %), 9 girls and 4 boys; persuasive repetitions gone through at 7 persons (30,4 %), all girls; hyperexcitablites at 8 persons (34,8 %), 4 girls and 4 boys; the latent medical fears have been revealed at 14 persons (60,9 %), 8 girls and 6 boys.
Conclusions: Thus, by us it is revealed enough the big percent of cases of posttraumatic stressful frustration at children of 5-7 years after banal medical manipulations ($p=0,005$), that shows necessity of search methods of decrease in painful sensations among children at treatment carrying out.

P-34-019
Parity of biological and psychological age in psychiatric practice

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P-34-020
Posttraumatic Stress Disorder: predictors factors

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Objectives: Acute Stress Disorder (ASD) can cause clinical distress or impaired functions and can cause a Posttraumatic Stress Disorder(PTSD). This investigation sought to determine predictors factors that cause PTSD after the presentation of ASD in injured workers.
Methods: This was a prospective study with follow-up at six months. Patients were from Hospital del Trabajador de Santiago with a work accident. An interview was administered by psychiatrist to obtain medical history, diagnosis and treatment. Patients completed the following test: Acute Stress Disorder Scale, COPE Scale, Beck Depression Inventory, Composite International Diagnostic Interview. After 6 months a Magnetic Resonance Imaging (MRI) was taken of the brain, in 10 patients with PTSD and 10 without PTSD to measure hippocampal volume. Classical statistical measures were used for data analysis(Software SAS JMP5.1)
Results: Sample was constituted by 35 patients.Patients were 22 women (63%) Average age of 37,5 years.Traumatic event was assault in 21 cases (60%), traffic related injuries in 4 cases (11%), and other 10 cases (28%). PTSD was diagnosed in 21 patients (60%). Comorbidity with depression was high, 27 cases (77%). Hippocampal was abnormal in 9 of patiens with PTSD and 2 without PTSD Average of treatment time were 138 days SD 43,7 with a range between 50-216 days. Strategies of coping do not appear such a predictors factors.
Conclusions: - ASD resulting from accidental injury, may lead to a higher prevalence of PTSD - Development of PTSD is frequent in women, and gender appears like a good predictor. - High comorbidity with depression. - Is noticeable that hippocampal volume is abnormal in patients with PTSD - The findings do not support other predictor as important factors to future PTSD

P-04
Childhood & Adolescent Disorders I

P-04-001
Epidemiology of PANDAS in children with and without comorbidity of streptococcal ethiology

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Objectives: Despite of the recent advances in treatment of streptococcal infections, the problem of pediatric autoimmunology neuropsychiatric disorders associated with streptococcal infection (PANDAS) is still poorly estimated. The main clinical symptoms of PANDAS can be associated with obsessive-compulsive disorders, tics, mobile hyperactivity, emotional lability, sindrom Touretto and etc. Aim: to evaluate the epidemiology of PANDAS in children with diagnosed streptococcal infection
Methods: Methods: we conducted case-control study of 71 patients in age of 5-17 years included 21 patients with PANDAS and 50 patients without it. We evaluated PANDAS risk in case and control group via odds ratio index (OR). The ethiology of streptococcal infection was confirmed by oropharyngeal swab for streptococci group A, B and S.pneumoniae.
Results: Result: the most of PANDAS patients were boys (15 patietns, 71,4%), the most acute symptoms of PANDAS disorders were at the age of 8-9 years. These patients had risk to be exposed to streptococcal A infection and pneumococcal infection more then control group (OR=3,8). The associated infection of streptococcal and pneumococcal infection more then 4 times in one child increases probability of PANDAS in 4,2 times.
Conclusions: Conclusions: PANDAS is still remaining underestimated problem of modern clinical medicine and need further research and epidemiology surveillance.

P-04-002
Pattern of psychopharmacological treatment in pediatric bipolar disorders: Comparison between preschool-onset and school-age-onset outpatients

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Objectives: To compare the pattern of psychopharmacological treatments prescribed for a sample of pediatric bipolar disorder (BD) outpatients.
Methods: Subjects were 14 preschool-onset (PSO) and 27 school-age-onset (SAO) BD, both genders, admitted to a child and adolescent outpatient unit (PRATA). The mean age-of-onset of the first mood episode, either depressive or manic/hypomanic episode, was 4.2 years (SD 1.3) for PSO group and 8.9 (SD 1.6) for SAO group. The mean age-of-referral to PRATA was 7.8 (SD 2.6) for PSO and 11.3 (SD 2.5) for SAO. All subjects were face-to-face interviewed and assessed by Diagnostic Interview for Children and Adolescent (DICA-IV) to receive a definite diagnosis of DSM-IV BD. The Clinical Global Impression (CGI) rated the symptomatic severity and the Children's Global Assessment Scale (CGAS) measured the global functioning. All enrolled patients presented CGI>2 during the admission.
Results: Comparing PSO vs. SAO group during admission, the former was more severe (0% vs. 22.7% with CGAS≥51) and presented a trend to more psychiatric comorbidity (43% vs. 33%). About 80% of both groups have already been medicated before admission to PRATA, generally with mood stabilizers and antidepressants. The mean duration of observation was similar between the groups (p>.05). Currently, the majority of the patients are in mood stabilizer (monotherapy) and/or a second generation antipsychotic. Both groups have presented substantial improvement in relation to baseline, being PSO group with 21.4% CGI≤2 and 50% of CGAS≥51, and SAO with 37% CGI≤2 and 62.9% of CGAS≥51.
Conclusions: The amount and the types of medication prescribed and the overall improvement did not differ significantly between two groups. Even the very early-onset of the PSO group, the patients presented acceptable response to the proposed therapeutic schedule.

P-04-003
No effect of x-inactivation on twin discordance in IQ and behavioral problems at middle childhood

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Objectives: The role of X-inactivation in complex human traits such as intelligence and behavior is unknown so far. X-inactivation has been linked to the process of chorionic splitting in monozygotic (MZ) twins: dichorionic monozygotic (DC) twinning, unlike monochorionic monozygotic (MC) twinning, occurs prior to the time of X inactivation. Although members of MZ twin pairs are identical in genomic sequence, they may differ in patterns of gene expression as well as in complex traits. X-inactivation can be a source of differential gene expression and has been suggested as a source for variations in intelligence and behavioral problems. We expected that if X-inactivation were causally involved in variations of intelligence and behavioral problems, we would find a positive statistical interaction between gender and chorion type for within twin-pair differences in these traits in MZ twins.
Methods: At a mean age of 10 years, behavioral problems were measured with the Child Behavior Check List (CBCL) in 324 MZ twin pairs of the East Flanders Prospective Twins Survey and intelligence was measured with the Wechsler Intelligence Scale for Children (WISC-R) in 286 MZ twin pairs. Aside collecting information on gender, chorion type, gestational age, and birth weight, within-twin pair differences were calculated and statistical regression analyses were carried out focusing on the interactions between gender (male or female) and chorion type (MC or DC) for within twin-pair differences in scores for WISC-R and CBCL.
Results: Gender and chorion type did not show a positive statistical interaction for within twin-pair differences in scores for WISC-R or CBCL.
Conclusions: This study indicates that X-inactivation is not involved in variations of intelligence and behavioral problems at middle childhood in this twin sample.

P-04-004
Mental pathology in parents of children suffering from psychosomatic disorders

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P-04-005
Methylphenidate alteration of neurotransmitters and synaptic parameters in PC12 cells

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Objectives: Stimulants are part of the standard-of-care treatment for attention-deficit/hyperactivity disorder (ADHD). Methylphenidate (MPH), with history of use spanning approximately 5 decades, is first-line stimulant treatment for ADHD. Nonetheless, the long-term neurochemical effects of MPH still lay in the darkness. Therefore, it is greatly important to understand the mechanism of action of this psychostimulant. In this study we attempted to disclose whether MPH influences neuronal cell gene expression and neurotransmitter release in a dose dependant manner.
Methods: Using Pheochromocytoma (PC12) cells we investigated the effect of MPH on synaptic gene expression levels. PC12 were cultured and treated in a dose dependant manner with one dose of MPH (0/ 1/ 10/ 100 nM and 1/ 10/ 100 μM) for 48 hours. Gene expression level of synaptotagmin (Syt) 1 and 4, syntaxin 1a (Stx1a) and synaptic vesicle glycoprotein 2C (SV2C) were measured using quantitative-real-time-RT-PCR. HPLC was used for the measurement of neurotransmitters and metabolites intra- and extracellularly: dopamine (DA), 3, 4-dihydroxy-phenylacetic acid (DOPAC), homovanillin-acid (HVA), noradrenalin (NA), 3-methoxy-4-hydroxy-phenylglycol (MHPG), serotonin (5-HT), 5-hydroxyindole-acetic acid (HIAA).

Results: MPH treatment in PC12 cells caused alterations in gene expression of all investigated synaptic genes. Especially, Syt-1 and -4 mRNA decreased significantly with 1nM MPH treatment. Treatment with MPH caused alterations in DA, NA and 5-HT release in a dose dependant manner. Specifically, intracellular decrease in NA and increase in 5-HT turnover was observed.
Conclusions: In this current study, we found MPH induces synaptic gene expression alteration in a dose dependant manner, in particularly in low MPH doses. These effects might be as a result of DA and NA uptake inhibition as well as via signal transduction cascades. This fact points to diverse effects of MPH on cell metabolism and signal transduction which might not be only a result of solely of dopamine-transporter blockage as previously postulated.

P-04-006
Social and behavioral characteristics of children with Rubinstein-Taybi Syndrome

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Objectives: Little research has been conducted regarding the behavioral aspects of children with Rubinstein-Taybi syndrome, a multiple congenital anomaly syndrome mapped in 16p13.3. Previous findings suggested some possible behavioral patterns including autistic features. However, studies to date have been limited by the lack of control group or a small sample size. Our aim was to determine whether there is a specific pattern of behaviors in children with Rubinstein-Taybi syndrome.
Methods: Caregivers of 39 children (mean age = 8.4 years) with Rubinstein-Taybi syndrome and 39 children matched on developmental level, age and gender (mean age = 8.6 years) were administered the Child Behavior Checklist and the Children's Social Behavior Questionnaire. The two groups were then compared on measures of socio-behavioral problems.
Results: Children with Rubinstein-Taybi syndrome did not exhibit higher internalizing or externalizing behavioral problems than what was expected for their age/developmental range. However, children with Rubinstein-Taybi syndrome displayed some specific behaviors: short attention span, stereotyped behaviors, poor coordination, and overweight. Within the Rubinstein-Taybi syndrome group, the presence of an identified CREB Binding Protein gene abnormality was possibly specifically related to the motor difficulties through impaired motor skills learning.
Conclusions: Some specific behaviors were more frequent in the Rubinstein-Taybi syndrome group and were possibly of clinical relevance. These results are important for families and professionals who may wish to address these issues. They point to the need for early assessment and management in order to enhance quality of life in children with Rubinstein-Taybi syndrome.

P-04-007
Pilot study to correlate circulating Cytokine and Cortisol levels in South African children presenting acutely to a sexual abuse clinic

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Objectives: The development of psychopathology has, in recent years, been linked to perturbations in circulating cytokine levels and in the hypothalamic-pituitary-adrenal axis in patients, retrospectively, reporting early life adversity. Cortisol, the major stress hormone secreted on this axis, acts as a potent anti-inflammatory agent. Alterations in cortisol secretion are known to have an impact on the level of circulating pro and anti-inflammatory cytokines. However, although these pertubations are hypothesized to affect brain development, there is a dirth of data on the relationship between cortisol and cytokine profiles in children who report early life stressful events. Therefore, the purpose of this pilot study was to elucidate the cytokine and cortisol profiles of children aged between 6-12 years of age presenting acutely at a sexual abuse clinic.
Methods: 12 female children between the ages of 6 – 12 years had blood samples taken to determine their HPA axis and cytokine profiles at time of examination by a paediatrician. Blood samples were only drawn from children who were strongly suspected of being victims of sexual abuse.
Results: Th1 and Th2 cytokine profiles for 12 children have been delineated and correlated with circulating plasma cortisol levels
Conclusions: This pilot study is important as it delineates the correlation between circulating cytokine and cortisol levels for children presenting at a sexual abuse clinic. In addition, this research enables our long-term aim to establish whether evidence of pathological levels of Th1/Th2 circulating biomarkers, following reported sexual abuse, may have an impact on pscyhopathology. Additionally, these findings facilitate the establishment of effective diagnostic and treatment programs for recovery and prevention of long-term sequelae.

P-04-008
Issues of behavioral problems among adolesents of Georghian schools

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Objectives: The purpose of the study was to determine the prevalence of behavioral problems in children and adolescents in Georgia, and to define the bio-psycho-social factors affecting and facilitating in development of behavioral problems in terms of effectively and purposefully planning children and adolescents Mental Health psycho-preventive measures.
Methods: The study was carried out in public schools – in total 1374 children and adolescents between 12-17,(males 42%, females-48%)Specially elaborated Psychosocial questionnaire,Rey- Tailor Complex Test and Recognition Trial (RCFT) Rubinstein Self-Evaluation Test, Rokich Value Test The data was analyzed by the univariative tests - X2 test, multivariate (Dispersive) analysis logistic regression.
Results: Statistical analysis revealed that the adolescents, who have impaired speed of cognitive function, have behavioral problems more often. ($X2=3.750$, $P<0.05$) The same is shown in adolescents who reveal disrupted memory pattern - they evidently frequently have behavioral problems. ($X2=11.080$ $P<0.02$), It confirms that, in the adolescents who have serious behavioral problems, frequency of neurodysfunction is higher than in the adolescents not having these problems.(Pearson Chi-Square=8.71 $P<0.01$). Presence and influence of the neurodysfunction achieves its maximum at the early puberty and is deceased at the end of the puberty. In our survey, the main determinants of behavioral problems proved to be:Male gender,Biological predisposition expressed as neurodysfunction, Addictive behavior of parents, siblings or friends,Conflict situation in families, Family members' conviction;
Conclusions: On the basis of the obtained results it is possible to consider, that exept some psychosocial problems neuropsycholgical disfunction probably caused by neurotransmitters mechanisms, is important pathophysiological link in appearance of behavioral problems.

P-04-009
Psychiatric outcome of paediatric epilepsy surgery

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Objectives: There is a significant association between epilepsy and psychiatric illness particular in patients with medically refractory condition. However, psychiatric outcome after epilepsy surgery was rarely reported. We report psychiatric, behavioural, self-esteem and quality of life outcome in children and adolescents with medically refractory epilepsy that have undergone epilepsy surgery in a regional centre in Hong Kong.
Methods: Child and adolescent patients with medically refractory epilepsy were evaluated systematically before and after surgery. A protocol was designed for the assessment to screen for their mood and behavioural symptoms. It also evaluated the self esteem and quality of life aspects of the patients. Outcome was assessed at 1 month, 3 months, 6 months and 12 months postoperatively.

Results: During the 12 months reported period, four patients had undergone epilepsy surgery. Their age ranged from seven to 18 years. All of them had left-sided focus. Half of them were mentally retarded. None of them suffered from psychiatric illness before the surgery. Three patients were seizure free after operation. There were favourable outcome in mood and behavioural measures up to 12 months after operation for those who are seizure free. Half of them showed a significant improvement in their quality of life. Self-esteem of patients also improved. No significant mental symptoms could be detected in seizure free patients. Improvement was seen as early as one month after operation. One patient with recurrence of seizure developed anxiety symptoms improved with treatment.
Conclusions: Epilepsy surgery is an effective treatment for child and adolescent patient with medically refractory epilepsy. Most patients had favourable psychiatric outcome with improvement in their self-esteem and quality of life. Psychiatric outcome was positively related to seizure outcome after operation.

P-04-010
Short- ,intermediate-, and long-acting stimulant treatment patterns in patients with attention-deficit hyperactivity disorder (ADHD)

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Objectives: ADHD treatment typically involves a combination of behavioral therapy and medication. Treatment often entails trying many stimulants and doses. Optimal ADHD treatment should emphasize minimizing these resource-intensive changes. This US study examined differences in medication persistence, adherence, augmentation, and switching rates among ADHD patients prescribed short acting (SA), intermediate acting (IA), and long acting (LA) stimulants.
Methods: Patients were newly treated (n=47,018), aged ≥6, with ≥1 stimulant prescription from January 2004 to September 2006, and continuously enrolled in a commercial health plan 6 months prior and 1 year following their first prescription. Persistence was defined as the number of days a patient remained on initial drug treatment. Adherence was defined as the number of days of initial drug treatment supplied, divided by total days of persistence. Switch rate was defined as the proportion of patients who changed to a drug of a different duration of action. Augmentation was defined as a prescription for a new ADHD medication of a different duration, concomitant with initial therapy. Statistical comparisons were made using the F-test from one-way ANOVA for means of continuous variables and the chi-square test for proportions of dichotomous variables.
Results: Patients taking LA stimulants had longer persistence (LA: 239.5 vs. IA: 185.6 vs. SA: 186.7 days, p<0.0001) and adherence (LA: 0.56 vs. IA: 0.47 vs. SA: 0.43, p<0.0001) compared to those taking IA or SA stimulants. Compared to SA and IA users, LA users had a lower switch rate (LA: 6.8% vs. IA: 11.8% vs. SA: 12.6%, p<0.0001) and a lower augmentation rate (LA: 9.8% vs. IA: 10.5% vs. SA: 13.1%, p<0.0001).
Conclusions: The findings of greater adherence and persistence, and lower switching and augmentation, with LA stimulants compared with SA or IA stimulants are important considerations for the efficient use of health care resources in the treatment of ADHD.

P-04-011
Stimulant and atomoxetine treatment patterns in patients with attention-deficit hyperactivity disorder

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Objectives: Attention-deficit hyperactivity disorder (ADHD) treatment in the US typically involves combined behavioral therapy and medication treatment. While stimulant medications (amphetamine, methylphenidate) are the primary treatment, non-stimulants (atomoxetine) are also available. Treatment often entails trying several medications and doses. Optimal management of ADHD should emphasize minimizing these resource-intensive changes. This US study examined differences in medication persistence, adherence, augmentation, and switching rates in ADHD patients.
Methods: Newly diagnosed and treated patients (n=60,010), aged ≥6, with ≥1 stimulant or atomoxetine prescription from Jan. 1, 2004 through Sept. 30, 2006, and continuously enrolled in a US commercial health plan 6 months prior and 1 year following their first prescription, were studied. Persistence was defined as the number of days a patient remained on initial drug treatment (stimulant or atomoxetine). Adherence was defined as the number of days of initial drug treatment supplied divided by persistence. Switch rate was defined as the proportion of patients who changed to a drug of a different class (stimulant or atomoxetine). Augmentation was defined as a prescription for a new medication of the other class concomitant with initial therapy. Statistical comparisons were made using t-tests for means of continuous variables and chi-square tests for proportions of dichotomous variables.
Results: Patients taking stimulants had longer persistence (254.2 vs. 154.3 days, p<0.0001) and adherence (0.57 vs. 0.49, p<0.0001) compared to those taking atomoxetine. Compared to atomoxetine users, stimulant users had a lower switch rate (3.7% vs. 20.3%, p<0.0001) and a lower augmentation rate (2.2% vs. 3.0%, p<0.0001).
Conclusions: These findings of greater adherence and persistence, and lower switching and augmentation for stimulants compared to atomoxetine, are important considerations for the efficient use of health care resources in treating ADHD.

P-04-012
Memory processes of adolescent with intellectual disabilities and hearing impairments

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Objectives: Memory functions of adolescent with intellectual disabilities and hearing impairment is observed through level of adoption of contents by applying dynamic work models with computer technique.
Methods: The examination was carried out on 20 adolescents, male and female with mild mental disabilities and hearing impairment over 85dB. Examinees were divided into two groups: control group (N=10) and experimental group (N=10). After being stimulated with programs and work techniques all examinees were tested with the same knowledge test.
Results: Results of the adequate statistical analysis showed the advantage of experimental group in level of cognitive functioning. Statistical particularities are given separately in view of visual memory and learning non-verbal and verbal material by applying dynamic programs and this influenced the experimental group to achieve better results.
Conclusions: On the base of the results we can conclude about the necessity of the implementation of the computer assistive technology in rehabilitation of the children with developmental disabilities.

P-04-013
Biological predictors of re-incarceration in mentally ill young offenders

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Objectives: Mentally ill adolescents released from custody were anecdotally noted to quickly re-enter custody in New South Wales (NSW), Australia. The aims of the present study are to describe demographic and mental health characteristics for this population, rates of subsequent incarceration and descriptors of those who experience a rapid return to custody.
Methods: An ambidirectional cohort study of 51 mentally ill youth consecutively released from custody in the calendar years of 2005 to 2007, comprising a health file audit at the time of release and prospective determination of the earliest return to either juvenile or adult custody, if any. Median follow-up was for 28 months (range 12 to 44 months).

Results: 47% were Indigenous. 43% were from regional communities. Substance misuse was highly prevalent: alcohol 82%, cannabis 100% and amphetamines 59%. In custody 39% were suicidal and 18% homicidal. 57% satisfied diagnostic criteria for schizophrenia or schizophreniform disorder. 90% returned to custody in the follow-up period, 37% of which was to adult jail. Survival analysis found fifty percent had returned to custody in five months. Linear regression analysis found schizophrenia and schizophreniform disorder (p<.001), bipolar disorder (p=.001) and schizoaffective disorder (p=.005) predicted a rapid return to custody. Treatment with antipsychotic medication (p=.006) and duration of treatment (p=.006) prior to release predicted a longer stay in the community.
Conclusions: Biological psychiatric illnesses and treatment factors were significant predictors of rapid re-incarceration for mentally ill youth released from custody. These findings highlight the need for high quality post-release psychiatric care and better integration into community care for this vulnerable group of young people.

P-04-014

The fatherless brain: Impact of paternal deprivation in Peromyscus californicus on social behaviour and on Oxytocin, NMDA and monaminergic synapses in the prefrontal cortex

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Objectives: The oxytocin system has been identified as important in social cognition and behaviour (Winslownd Insel, Neuropeptides 2002), which are impaired by early-life deprivation. In biparental rodents, the lack of paternal care compromises synaptic development in frontocortical areas, e.g., the anterior cingulate (Ovtscharoff et al., Brain Research 2006). The effects of paternal deprivation on prefrontocortical oxytocin, monoaminergic and glutamatergic transmission, and its impact on social cognition and behaviour remain untested.
Methods: We examined the neurophysiological and behavioural effects of complete father-deprivation in California mice (Peromyscus californicus), known for naturalistic monogamous pair-bonding and biparental rearing behaviours. On the third day after birth, neonates were either left with only the mother (father-deprived) or with both parents (control). They were then separated from the parent(s) upon weaning (day 30-40). Experimental testing commenced upon reaching sexual maturity (day 70-105 days). Using in vivo electrophysiology and microiontophoresis, we assessed the function of oxytocin, NMDA, serotonin and dopamine receptors through prefrontocortical pyramidal responses. Moreover, social recognition/behaviour was observed in the social interaction test.
Results: Pyramidal neurons recorded from father-deprived mice exhibited attenuations of excitatory response to oxytocin (134% of controls at maximum iontophoretic current of 30 nanoamperes, p<0.01, Mann-Whitney U-test), potentiation of excitatory response to NMDA (67% of controls at 30 nanoamperes, p<0.01), and no change in 5-HT1A-mediated response to serotonin and in the response to dopamine. These physiological changes were accompanied by decreased social investigation of unfamiliar conspecifics in father-deprived pairs (64% of control pairs, p<0.05; 53% of father-deprived-control pairs, non-significant). There was no difference in social investigation of familiar (cage-mate) conspecific between father-deprived and control pairs.
Conclusions: These findings show that father-absence during critical neurodevelopmental periods induce impairments in social cognitive function in adulthood. These developmental liabilites are associated with disturbances in the function of key prefrontal neurotransmitters essential to normal social cognitive development.

P-04-015

Correlation between variants of the DRD4 gene and intra-individual variability of behavior in Attentional Deficit/Hyperactivity Disorder (ADHD)

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Objectives: To explore the association between variants of DRD4 and the performance of ADHD children and their healthy sibs in a Go/Nogo Task, focusing on the intra-task evolution of behavioral response.
Methods: We studied 20 discordant sib pairs (ADHD patient and unaffected sib) between 8 and 13 years old. VNTR variants at exon III of DRD4 were identified according to standard protocols. In parallel, a visual Go/Nogo Task with Nogo probability of 10% was applied. Behavioral response to the task was characterized in terms of "mean reaction time", "omission errors", "commission errors" and "intra-subject variability of reaction time". In order to analyze the temporal evolution of response regarding DRD4 genotype, the task was divided in 10 consecutive "time-blocks" and data were modelled by mean of a mixed effect model that assigned a random effect to each subject and fixed effects to variables "genotype" and "time-block relative position" (from 1 to 10). Genotype groups were defined as follows: Homozygous for the DRD4 4-repeat allele were considered as controls and subjects with any other genotype were considered as the risk group. Results were controlled by age and sex.
Results: There were significant effects of "time-block relative position" on "intra-subject variability of the reaction time", "omission errors" and "commission errors", independently of genotype and ADHD status. Genotype but not ADHD status had a significant effect on "intra-subject variability of reaction time" (p= 0,015). Finally, there was a significant interaction between "time-block relative position" and "genotype" in omission and commission errors (p= 0,0019 and p=0,007).
Conclusions: To analyze the temporal evolution of behavioral variables is relevant for characterizing the cognitive processes underlying ADHD and their genetic correlation.

P-04-016

Effects of a single bout of intense physical exercise on working memory functions in adult attention deficit/ hyperactivity disorder

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Objectives: The aim of the present experiment was to investigate the immediate effects of a non-pharmacological intervention, i.e., intense physical exercise, on attention deficit/hyperactivity disorder (ADHD) related working memory deficits. Given the known impact of physical exercise on central neurotransmitters, we hypothesized analog effects on these cognitive symptoms as described by Frank and colleagues, caused by stimulant medication (Frank MJ, Santamaria A, O'Reilly RC, Willcutt E, 2007. Testing Computational Models of Dopamine and Noradrenaline Dysfunction in Attention Deficit/Hyperactivity Disorder. Neuropsychopharmacology 32, 1583-1599).
Methods: Eighteen men with the DSM-IV diagnosis of ADHD participated in this randomized controlled cross-over study. Subjects were either unmedicated (n=8) or abstained from their methylphenidate medication for at least 24 hours prior to testing. The study involved two conditions presented at different days, spaced at least one week apart (control condition: 15 min of being sedentary; exercise condition: two exercise bouts of about 3 min each on a bicycle ergometer, separated by a 3 min break). Immediately after the respective intervention, subjects took part in parallel versions of a modified AX-continuous performance task (see Frank et al., 2007).
Results: As in the prior study by Frank et al. (2007), ADHD subjects' sensitivity to working memory contextual information was reduced during the sedentary control condition. Following exercise, sensitivity to contextual information increased significantly, comparable to the effect of stimulant medication in the study by Frank et al. (2007).

Conclusions: We conclude that a single bout of intense exercise can positively impact on working memory deficits in ADHD. Future studies have to elucidate whether the working memory improvement by intense physical exercise can enhance cognitive functioning of ADHD patients in daily life.

P-04-017
Sensory abnormality profiles in adults with developmental disorders: Autism spectrum disorder (ASD) versus attention deficit and hyperactivity/impulsivity disorder (ADHD): Usefulness in diagnosis and treatment implications

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Objectives: According to DSM - IV terminology, the diagnosis of Autism Spectrum Disorders (ASD) is based on the presence of Wing's triad, characterised by impairments of social interaction, communication and imagination. Several neurocognitive theories have tried to explain these characteristics (Theory of mind, central coherence deficiency, executive dysfunction), but an overall encompassing theory still eludes us. Although there is evidence that sensory information processing is abberant in ASD, it is not considered to be a primary feature in the official nosological systems. Some researchers have conceptualised ASD as a sensory integration disorder, whereby sensory dysfunction is the primary characteristic feature, accounting for the typical triadic impairments. Testimony to this is the fact that many autistic individuals report unusual sensory perceptual experiences, and have acquired perceptual styles to ward of a maelstrom of extraneous information. The aim of this descriptive study, was to obtain a detailed picture of the sensory profile of thirty adults with an ASD, and compare them with these of thirty individuals with ADHD.The comparison did not only refer to the overall difference in frequency of sensory problems, but also examined the specific pattern of sensory abnormalities within each diagnostic category
Methods: Participants which were included completed the Adolescent/Adult Sensory Profile (AASP), a self report questionnaire, measuring four quadrants of sensory processing, as identified by Brown and Dunn (2002). In addition, we administered a semi-structured questionnaire to elicit the occurrence of synaesthesia in both cohorts.
Results: As this stydy is ongoing, the final results will be reported at the congress.
Conclusions: Recommendations are made, as how the assessment of sensory problems can be utilised to tailor interventions, in order to address the afflicted individual's particular needs.

P-04-018
Psychiatric comorbidity in adults with Autism Spectrum Disorder

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Objectives: Individuals with Autism Spectrum Disorders (ASD) often display symptoms from a broad variety of diagnostic categories. The primary aim of this cross sectional study, was to compare the psychiatric co-morbidity in patients with ASD, to a psychiatric control group. We defined co morbidity as referring to the occurrence of two or more disorders together, irrespective whether they are causally related or not. The study of psychiatric co morbidity has important implications: firstly, the identification and treatment of co-occurring problems or disorders may affect the long term outcome. Secondly, the examination of the factors underlying the co-morbidity can facilitate insight into the aetiology of the individual disorders.
Methods: Patients were retrieved from our specialised ADHD/ASD out patient clinic. The diagnostic trajectory entailed semi-structured interviews, collateral information and an extensive neuropsychological battery, all of which were processed via a LEAD –conference (Longitudinal Evaluation using all Available Data). Fifty four patients with ASD were consecutively included and compared to 32 identically assessed patients who did not qualify for an ASD/ADHD diagnosis. Diagnostic criteria from DSM IV were applied for all diagnoses, but we abandoned the DSM pre-emptive rule, since it impedes the use of categorical diagnoses to describe the particular problem constellation in a particular patient. Patients with an IQ < 75 were excluded.
Results: More than half of the patients with ASD (56 %) suffered from a current co morbid condition, as opposed to 63 % in the control group. Substance use/dependence, ADHD and personality disorders were the most common diagnoses in the ASD group, whereas affective pathology and personality disorders were most prominent in the control group.
Conclusions: Our findings correspond with those reported in prior studies. Delineating co morbidity emphasises the necessity of treating superimposed problems and disorders, and may be helpful for advancing psychiatric nosology.

P-15
Childhood & Adolescent Disorders II

P-15-001
The effects of Adderall XR on driving in adolescents with Attention-Deficit-Hyperactivity Disorder

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Objectives: In adolescence ADHD is associated with an increased likelihood of motor-vehicle accidents and risk for associated injuries. The objective of this study is to investigate if driving performance changes as a result of one missed dose of Adderall XR because it is not uncommon for adolescents to forget to take their medication.
Methods: A double-blind randomized crossover placebo control study was used to assess the effect of missed medication in 14 adolescents. Participants were tested in a 6-channel DriveSafety driving simulator on two consecutive days, once with their usual dose of Adderall XR and once with the placebo. For these adolescents Adderall XR was the medication of choice. Simulator testing occurred 1, 8 and 12 hours after the medication or placebo challenge. Testing times were chosen to reflect the start of a school day, the end of a school day, and evening activities. It was especially important to test 1 hour post-administration because this time has never been tested before. As well, given that the fact that the duration of Adderall XR is 12 hours, it is important to see its effectiveness 12 hours post dose. Hazard response times, collisions, lane deviations, driving speed, and unnecessary braking events were measured as were distractibility and dangerous driving practices
Results: Driving performance and measures of distractibility were either marginally or significantly affected by the missed dose of Adderall XR, and in some cases these effects became significantly worse as the day progressed.
Conclusions: These results indicate that missing just one dose of Adderall XR may have a hazardous effect on driving performance that day.

P-15-002
Assessment of psychopathological characteristics of children with complex neurological dysfunction

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Objectives: A high degree of psychiatric disorders has repeatedly been described among children with brain disorders (Goodman R et al., 1997, Craven C. et al., 2002) but we lack knowledge of clinical appearance of psychopathological characteristics of children with complex neurological dysfunction. The purpose of this study was firstly, to assess psychopathological characteristics of children with complex neurological dysfunction; secondly, to tie together these psychopathological characteristics with their neurological diagnosis.

Methods: The study was carried out in the EEAP- Paediatric Hospital Lenval of Nice.We observed 50 children aged from 9 to 23 years with confirmed complex neurological dysfunction, between January 2005 and June 2008 (42 months). All patients were underwent structured battery of neurological and psychomotor tests.We've studied their fillings; we've observed them and when it was possible we interviewed them. Therefore, we utilized observable behaviours in structured and non-structured situations, questionnaires and diagnostic interviews, the history of specific target symptoms (Bernstein K., 2000) As a result we assessed the clinical diagnosis and prevalence of psychopathological characteristics based on DSM IV-TR.
Results: Children with complex neurological dysfunction showed clinical disorders coded on axis I of DSM IV-TR, diseases usually first diagnosed in infancy, childhood, or adolescent. For all patients we observed generic psychopathological disorders as learning, motor skills, communication, attention-deficit, elimination disorders and mental retardation (coded on axis II). In addition of these generic diseases we established personal clinical characteristics as: cognitive disorders, mental disorders due to a catatonic type condition, psychotic, anxiety and mood disorders, sexual disorders not otherwise specified.
Conclusions: Children with brain disorders have a higher-than-expected rate of psychiatric disorders (Goodman R,Scott S, 1997). This investigation underlines the psychological characteristics of children with complex neurological dysfunction. This may help us to determine a personalized and integrated programme of rehabilitation specified to these kinds of patients. Children with complex neurological dysfunction have problem to find a healthy equilibrium between internal and external factors.

P-15-003
Creative and developmentally sensitive approaches to treating Needle Phobia in a tertiary paediatric hospital setting

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Objectives: This poster outlines a treatment model for children presenting with needle phobia in the context of repeated medical procedures and chronic medical illness.
Methods: Three case studies of children aged 7-12 years whose needle phobia was compromising their medical care are presented. Chronic medical conditions require repeated procedures which are invasive and anxiety provoking. The emotional and psychological sequelae can be debilitating and potentially compromise the short and long term quality of life of the child. The aim of treatment is to equip children with effective coping skills to manage the anxiety and overall chronic illness. Parents are actively encouraged to partake in therapy to reinforce coping skills.
Results: The successful treatment model includes Cognitive Behaviour Therapy (CBT; e.g. cognitive restructuring, systematic desensitization, exposure therapy, problem solving), Family Therapy (e.g. narrative therapy, metaphors), relaxation, hypnosis (e.g. imaginal exposure, distraction), medical play and drawings. Liaison with nursing and medical staff, including anaesthetists is seen as a vital part of the overall treatment of the child. Where indicated, pharmacological treatment is also used in combination with psychological strategies to help reduce the child's overall anxiety.
Conclusions: Cognitively consistent treatment utilized in the three diverse cases illustrates successful outcomes in both younger, more concrete thinking children and older, more abstract thinking children. Techniques outlined can be applied to the treatment of other more general paediatric psychological conditions.

P-15-004
Differences in hypothalamic-pituitary-adrenal axis functioning among children with ADHD predominantly inattentive and combined types

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Objectives: Some evidence suggests that the HPA axis may be dysfunctional in children with Attention-Deficit/Hyperactivity Disorder (ADHD). The aim of this study was to investigate whether a different pattern of HPA axis activity is found between the inattentive (I) and combined (C) subtypes of ADHD, in comparison with healthy control children.
Methods: A total of 100 prepubertal subjects (52 children with ADHD combined type [ADHD-C], 23 children with ADHD predominantly inattentive type [ADHD-I]) and 25 healthy control subjects) were studied. The effects of stress were studied by comparing cortisol responses to a psychosocial stressor, consisting of a public speaking task.
Results: Children with ADHD-I showed an elevated cortisol response to the psychosocial stressor, in contrast to children with ADHD-C who showed a blunted cortisol response to the psychosocial stressor. When a distinction was made between responders and non-responders (a subject was classified as a responder when there was an increase in cortisol reactivity), hyperactivity symptoms were clearly related to a lower cortisol reactivity to stress.
Conclusions: The results indicate that a low cortisol responsivity to stress may be a neurobiological marker for children with ADHD-C, but not for those with ADHD-I. Directions for future research and clinical implications are discussed.

P-15-005
Attachment and genetics in ADHD children: Insecure attachment as a risk factor for comorbidities

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Objectives: We are studying the interaction between genetic and environmental factors in ADHD children. Attachment and parenting styles could affect the development of ADHD as well as the presence of comorbidities.
Methods: 46 ADHD children, between 7 and 13 years old and 24 controls were recruited. The children which have been diagnosed with ADHD according to DSM-IV criteria and Child Behavioral Check list underwent psychometric, psychological, electro-encephalo-graphic, genetic (DRD4 and DAT1) and sleep studies plus a full neuro-pediatric examination. Controls underwent the same procedures to discard mental and neurological illnesses. Level of attachment security with the mother was obtained applying the Security Scale (SS) from Kerns, Kaplan, Cole (1996). Mothers were separately interviewed.
Results: Security Scale showed higher levels of insecurity in ADHD children with comorbidity (ADHD/COM(+)) compare to Controls and ADHD children without comorbidity (ADHD/COM(-)). This difference was statistically significant (Kruskal-Wallis p value <0,001). Genetic studies showed preponderance of DAT1-10R, one of the candidate genes for ADHD, but not for DRD4-7R.
Conclusions: This is the first study showing insecure attachment associated to ADHD with comorbid behavior. Insecure attachment (according to Kerns scale) was positive associated with oppositional disorder, social phobia, disocial behavior and anxiety. We discuss the participation of epigenetic factors in the development of ADHD which could point towards specific types of therapeutic interventions.

P-15-006

Treatment and psychosocial background in incarcerated adolescents from Austria, Turkey and former Yugoslavia

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Objectives: Psychosocial background in delinquent juveniles is an understudied object within European countries. Adolescents with migration background represent a substantional proportion of juveniles in custody. The nature of the relationship between ethnicity and risk for psychosocial adversities is not fully understood. We investigated differences in psychosocial background within three ethnicities (Turkish, Former-Yugoslavian, Austrian) in an Austrian pre-trail detention facility.
Methods: A semi-structured interview (Multidimensional Clinical Screening Inventory for delinquent juveniles, MCSI) was used to assess treatment received (psychiatric and psychotherapeutic treatment) and psychosocial background (family background, forensic and psychiatric family history) in juveniles entering an Austrian pre-trail detention facility. The final study sample consisted of 278 juveniles: 55.4% Austrians (mean age 16.88, SD=1.52), 14% Turkish (mean age 16.28, SD=1.23) and 30.6% Former-Yugoslavians (mean age 16.47, SD=1.41).
Results: Mental health services were significantly less used by juveniles with migration background. In the Austrian sample family dysfunction as well as reported parental substance misuse was significantly more prevalent than in the Turkish or Former-Yugoslavian samples. Turkish juveniles had a significantly poorer school performance than Austrians. Juveniles from Former-Yugoslavia had significantly less often attended schools that offer higher education.
Conclusions: Migration background seems to influence health care utilisation and to predispose towards certain psychosocial adversities. There is a general need of establishing psychosocially orientated prevention strategies and cultural sensitive treatment approaches concerning ethnic minorities.

P-15-008

Neurophysiological investigation of control mechanisms in children with Tourette syndrome

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Objectives: Tourette syndrome is a recurrent disorder characterized by alternate periods with exacerbation and remission of motor and vocal tics. The aim of the study was to investigate causes and mechanisms of tics exacerbation.
Methods: 10 children with Tourette syndrome (11.2 + 2.4 years old) and 10 healthy children (11.5 + 2.8 years old) were trained to achieve self-control over their slow cortical potentials (SCP) using neurofeedback (10 sessions, trials with voluntary increase and decrease of SCP). Contingent negative variation (CNV, reaction time paradigm, Cz with linked mastoids as reference, 5 sec time constant, 20 trials, EOG control) was recorded 10 times in each child with the Tourette syndrome and one time in each healthy child. Tic severity was evaluated on each day of CNV or SCP recording with both Yale-Tourette-Syndrome-Symptomelist and standard video recordings.
Results: Children with Tourette syndrome demonstrated significantly lower CNV amplitudes than healthy children ($t = 4.23$; $p < 0.001$). Although healthy children learned regulation of their SCP during only two sessions, Tourette patients were unable to achieve control over their SCP (ANOVA Session x Diagnosis x Difference between increase and decrease of SCP: $p = 0.04$). Moreover, CNV amplitude correlated negatively with the number and severity of tics: the more severe tics were observed on the day of recording, the lower CNV amplitude ($r = -0.44$; $p = 0.02$; $r = -0.49$, $p = 0.007$).
Conclusions: Since the CNV amplitude and ability to influence SCP represent neurophysiological mechanisms of self-control, this study demonstrates that patients with Tourette syndrome are characterized by insufficient control mechanisms. It seems likely that the abnormal control mechanisms are associated with the number and severity of tics and may explain exacerbations in particular patients.

P-15-009

Prediction of inattention symptoms at childhood to verbal and non-verbal working memory at adolescence

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Objectives: To investigate the prediction of inattention at early childhood to verbal and spatial working memory at adolescence in a large ethnic Chinese population.
Methods: The sample included 401 probands (male, 85%) with DSM-IV attention-deficit/hyperactivity disorder (ADHD), 213 siblings (male, 42%), and 175 unaffected controls (male, 73%), aged 9 to 17 years (mean age 12.02±2.24). All the participants and their mothers were interviewed by using the Chinese Kiddie-Schedule for Affective Disorders and Schizophrenia-Epidemiology version for the childhood and current ADHD symptoms and diagnosis and other psychiatric disorders. The participants were assessed with the WISC-III including digit spans, and Spatial Span (SS) and the Spatial Working Memory (SWM) of the Cambridge Neuropsychological Test Automated Battery. Multi-level models were used for data analysis.
Results: Univariate analyses revealed inattention, hyperactivity, and impulsivity symptoms at childhood significantly predicted decreased digits recalled in the backward digit span task; had shorter spatial span length and more usage errors in the SSP; increased total errors (4-box, 6-box, and 8-box problems) and strategies utilized in searching the box with blue token in the SWM. If the three ADHD core symptoms were included in the model, only inattention maintained the significant prediction (all p values < 0.001). After further controlling for comorbidity, age of assessment, treatment with methylphenidate, and Full-scale IQ, increased childhood inattention symptoms still significantly predicted worse verbal ($p = 0.008$) and spatial (p ranging from 0.017 to 0.002) working memory, and spatial span ($p = 0.047$, 0.036) at adolescence.
Conclusions: Our findings suggest that childhood inattention symptoms predict impaired verbal and spatial executive functions at later developmental stage after taking other ADHD symptoms, demographics, medication, and intelligence into account. Early identification and treatment for inattention is needed to offset impaired working memory at later childhood and adolescence.

P-15-010

Peculiarity of diagnostics and treatment of early child schizophrenia on residual organic background

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Objectives: The aim of investigation was to establish the consequences of yearly manifestations of schizophrenia in children with pronounced residual signs of organic cerebral insufficiency, which last years become more frequent. Material: 43 children with manifestation of schizophrenic process at the age of 6 months-2,5 years. All children had preliminary diagnosis: residual signs of yearly cerebral affection with: "autistic-like behavior", or "hyperdynamic" syndrome, or "neurosis-like" syndrome, or "retardation of mental development".
Methods: psychopathological, clinical.
Results: In all cases was unfavorable anamnesis, disturbance of yearly development by organic type, high muscular tone, tremor of fingers and chin, yearly head's holding, dysplasias, evident neurological signs, symptoms of hydrocephaly and hypertension. By 12 children epileptiform fits appeared on background of schizophrenic symptoms or preceded its. Diagnosis of schizophrenia was corroborated by dynamic observation and forming of specific defect with increase of autistic disorders and emotional deficit, decrease of activity, appearance of signs of psychic infantilism, ridiculous behavior and eccentricity. Clinical picture of illness was characterized as catatonic-regressive (14 patients), manic-catatonic (4 patients), heboid (7 patients), catatonic-hebephrenic (2 patients), schizoaffective (8 patients), neurosis-like with predominance of obsessions and delirium-like fantasy generation (8 patients). Ill children got during 2-5 years only medicines against residual-organic symptoms, and this medicines could not eliminate basic psychopathological symptoms. Objective reasons of difficulties of psychopharmacological treatment for children with yearly child schizophrenia are intolerance or bad tolerance of majority of psychotropic agents by prescribed for yearly age dosages.

Medicines of first line in this cases are neuroleptics of new generation – risperidon and seroquel with small (nearly homeopathic) dosages, and in case of need its combination with small dosages of behavior correctors (thioridazine, neuleptil).
Conclusions: The dangerous of late diagnosing of child schizophrenia consists in absence of adequate therapy and correctional-rehabilitative treatment, and consequently in deepening of specific defect and social dysadaptation.

P-15-011
The terms of cessation of prophylactic psychotropic therapy by circular schizophrenia in children and adolescents

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P-15-012
The dopamine deficit theory of Attention-deficit/Hyperactivity disorder (ADHD) needs re-examining

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Objectives: Although psychostimulants alleviate the core symptoms of attention-deficit/hyperactivity disorder (ADHD), recent studies confirm that their impact on the long-term outcomes of ADHD children is null. Numerous articles assert that they correct an underlying dopaminergic deficit of genetic origin.
Methods: Here, and in my review article (Trends in Neuroscience, 2009, 32:2-9) I question this assertion on the basis of a critical reading of the literature.
Results: First, psychostimulants inhibit monoamine uptake and enhance extracellular dopamine. However, this fact cannot support the dopamine deficit theory because psychostimulants also improve attention in healthy children. Second, imaging studies of extracellular dopamine in ADHD patients show inconsistent results. Third, the most robust finding in ADHD genetic is its association with a variable number tandem repeat polymorphism in exon 3 of the D4 dopaminergic receptor gene. The 7-repeat allele is more frequent in ADHD patients (23%) than in healthy subjects (17 %). This difference is statistically significant but insufficient to support the dopamine deficit theory. Fourth, specific inhibitors of noradrenaline uptake (atomoxetine), and noradrenergic agonists (clonidine) are as potent as psychostimulants on ADHD. Fifth, dopaminergic agonists and L-DOPA, which correct a dopamine deficit in Parkinson's disease, are inefficient in ADHD. Sixth, functional imaging studies do not support simpler models positing that ADHD is a disorder resulting from activity deficits in a few isolated brain regions. Seventh, animal models bearing experimentally induced abnormalities in their dopaminergic system, and rodents strains selected for their behavior mimicking ADHD, do not support the dopamine deficit theory.
Conclusions: This theory is often put forward in texts written for the general public to assert that "there is no way to prevent ADHD" (NIH site) and that psychostimulant medication is the most appropriate treatment. However, because this dopamine deficit theory is weak, it should not be put forward to bias the evidence-based management of ADHD.

P-15-013
Behavior of ADHD children playing video games

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Objectives: The objective of this to study was to describe and compare the behavior of children with ADHD (Attention Deficit/Hyperactivity Disorder) and control children playing video games.
Methods: In total, 50 children (6-16 years) were recruited (29 ADHD children and 21 controls). We used the Child Behavior Checklist and the Problem Videogame Playing scale (PVP scale). This instrument gives objective measures of problem use, which can be considered as an indication of addictive videogame playing. We designed a questionnaire for the parents, eliciting qualitative information about their child's videogame playing.
Results: There were no significant differences concerning frequency or duration of play between ADHD children and controls but differences were observed on the PVP scale. None of the controls scored above four whereas 10 hyperactive children answered affirmatively to five or more questions. These children presented a greater intensity of the disorder than the other ADHD children.
Conclusions: No differences concerning video game use were found. Moreover, ADHD children exhibited more problems associated with videogame playing. It seems that a subgroup of ADHD children could be vulnerable to developing dependence upon video games.

P-15-014
French version of The Liebowitz Social Anxiety Scale for children and adolescents: A pilot study

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Objectives: Social phobia has onset during early adolescence and is associated with significant impairment in social and educational functioning of adolescents. However, there are few scales in French literature to evaluate social anxiety for child and adolescents. The aim of this study was to examine validity of French version of the Liebowitz Social Anxiety Scale in childhood and adolescents (LSAS-CA).
Methods: The sample consisted of fifty subjects, aged between 8 and 17 years (15 social phobia patients, 15 ADHD patients (Attention Deficit/ Hyperactivity Disorder) and 20 controls). We used the Child Behavior Check List (CBCL) and the Multidimensional Anxiety Scale for Children (MASC). Subjects were also assessed for social anxiety with Liebowitz scale for children and adolescent (French version).
Results: Subjects with social phobia had significantly higher LSAS-CA total and subscale scores than ADHD subjects and controls. Moreover, statistical correlations were significant, between LSAS-CA total score and CBCL (internalizing disorder, particularly withdrawal) or MASC (total score, physical symptoms, social anxiety and separation anxiety).
Conclusions: French version of this scale appears to be a reliable tool for assessing childhood social phobia (social and performance anxiety and avoidance ratings). Further studies on LSAS-CA (French version), both in clinical and non clinical samples, are needed.

P-15-015
An open-label study of treatment of the early-onset bipolar disorders with risperidone long-acting injection

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Objectives: To study the effects of risperidone long-acting injection (RLAI) formulation in controlling and stabilizing the acute manic/hypomanic phase of teenage-onset bipolar disorders (BD).
Methods: This is an open-label study of the RLAI in 10 BD (type I and II) teenagers during their manic/hypomanic phase. The mean age of sample was 13 (SD=2.3), ranged 10 to 16 years. The location of study was a children and adolescents affective disorder outpatient clinic. All patients were assessed through a face-to-face clinical interview and Diagnostic Interview for Children and Adolescent (DICA-IV) to receive the definite diagnosis of DSM-IV BD. The Clinical Global Impression (CGI) rated the symptomatic severity, and the Children's Global Assessment Scale (CGAS) measured the global functioning. After therapeutic failure or manic relapse due to oral medication non-adherence, with legal-guardian written consent, the RLAI was started at 25mg every 2 weeks. The patients also were routinely monitored concerning their prolactin level, liver enzymes, cholesterol, EEG, and ECG. Standard parametric and non-parametric statistics analyzed the outcome variables, with 0.05 significance levels.

Results: The RLAI was effective in improving BD, with progressive control and stabilization of manic/hypomanic symptoms after 4 to 8 weeks. There was a significant difference ($p<0.05$) between baseline and current mean score of CGI, which decreased from 5.8 (SD=0.9) to 2.9 (SD=0.7), and CGAS, which increased from 20 (SD=7.3) to 49 (SD=10.3). 80% of patients were in monotherapy and the treatment duration ranged 3 to 6 months. In general, patients did not present significant side or adverse effect, and RLAI did not increase the prolactin, blood glucose, and cholesterol level throughout treatment.
Conclusions: The RLAI was found to be well tolerated and effective in improving BD, by lowering CGI and increasing CGAS. Randomized controlled double-blind clinical trial of RLAI in a larger sample of BD teenager-patients is warranted.

P-15-016
Psychotic disorder in childhood: A case report

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P-15-017
Behavior of the children with cochlear implant

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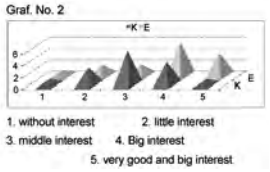
Objectives: In this project we define behavior as a concrete activity in relation of a child towards the demands of his/her situation of egzistention. The behavior was controlled throw: relation towards other children, parents, and unknown people, to himself, interest of learning speech and the mood that child manifests during the therapy. The aim of the study is to show that the cochlear implant contributes the child maturity and that improvement we monitor through the mentioned behavior patterns.
Methods: The sample was consist of the 30 children at the early age (3 years to 7 years), both sex rate, average intellectual functioning which rehabilitation treatment last 12 months.
Results: The results point out that children with cochlear implant are less aggressive, less dependent and have higher quality of social interactions with parents and unknown people. In relation towards themselves they show higher readiness for postponing the needs and accepting the bans. They were also extremely motivated and in good mood for learning speech, rehabilitation therapy and success in learning speech and language.
Conclusions: We can conclude about necessity of early treatment for the harmonies behavior children with cochlear implant at early age.



P-15-018
A comparative study of disability among patients suffering social anxiety disorder and comorbid depressive disorders

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Objectives: In recent years, we have come to recognize that social phobia is common, highly comorbid with other conditions such as depression. Despite the availability of these findings, there have been very few data demonstrating that persons with social phobia and/or depression in the community are impaired by their disorder. The current study aimed to demonstrate the disability attributed to social anxiety disorder (SD) whether it occurs alone or co-occurring with Depressive Disorders (DD).
Methods: The study was performed on three groups of females, each composed of 15 subjects. The first group is composed of patients diagnosed with SAD, the second group is composed of SAD and DD, while the third one was a control group. The groups were subjected to clinical psychiatric examination, and psychometric evaluation using; Social Phobia Inventory (SPIN), Sheehan Disability Scale (SDS); and Beck's Depression Inventory (BDI).
Results: The mean scores of SDS were higher in patients with SAD and patients with SAD and comorbid DD compared to controls. Also, patients with SAD and DD had higher mean scores in social and family parameters of the SD than patients with SAD alone.
Conclusions: Social anxiety disorder is associated with considerable degree of disability. The disability is increased when SAD co-occurs with DD. The substantial disability should not be minimized and targeted in treatment plans to improve patients quality of life.

P-15-019
Clinical and epidemiological study of parentally-deprivedprimary school children in Alexandria

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Objectives: The systematic study of stressful life events has demonstrated the probable relationship between life adversities and the risk of psychological disturbances in children. The aim of this work was to investigate the relationship between parental deprivation (PD) and psychiatric disturbances in primary school children.
Methods: The study was carried out on I) index group 63 children exposed to PD and II) control group 63 matched children for age and sex and living with both biological parents. Psychiatric interview was carried out for all children with psychometric study using Kovac's child depression inventory and child behavior checklist, parent and teacher forms.
Results: PD was found in 7.9% of the recruited sample and all forms of PD was related to emotional and behavioral disorders among the children compared to controls.
Conclusions: PD was a considerable childhood life adversity which attributed to emotional and behavioral disorders in children.

P-15-020
Comorbidity of eating disorders among patients with bipolar disorders

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Objectives: Associations between Eating Disorders(ED) and affective disorders have often been suggested in several epidemiological studies. There is a need to elucidate such comorbidity, as it can cause many risks to the patient. These risks can not only cause the patient to suffer further with bipolar disorder, but they can also do damage to the body and eventually prove fatal if left untreated. This study aimed to detect Eating Disorders (DD) among patients with Bipolar Disorder (BPD)
Methods: The study was performed on two groups of females, the first composed of 30 female patients with BPD and the second is composed of 15 healthy controls. Clinical psychiatric examination and Psychometric evaluation using Barcelona Bipolar Eating Disorder (BEDS). The scale helps to quantify disordered eating behaviour in bipolar patients.
Results: The mean scores of BEDS were significantly higher in patients with BPD than controls. ED was found in 65.9% of patients with BPD, and the most prevalent disorder was binge eating disorder. There were relations between studied parameters (type of BPD, age of onset of BPD, race, family history of BPD, and use of medication) and ED, but none reached statistical significance.
Conclusions: In conclusion, eating disorders were common comorbid conditions found among bipolar patients. BEDS was a useful screening tool to diagnose ED among bipolar patients. Addressing comorbid ED in the management plan of bipolar patients would help in improving their quality of life and decreasing the risk of morbidity and mortality associated with comorbid ED.

P-44
Childhood & Adolescent Disorders III

P-44-001
Comparisonal investigation of Rap personality disorder in youngster

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Objectives: Personality disorder, formerly referred to as a Character Disorder, is a class of mental disorders characterized by rigid and on-going patterns of feeling, thinking, and behavior. The underlying belief systems informing these patterns are referred to as fixed fantasies or "dysfunctional schemata" (Cognitive modules). The inflexibility and pervasiveness of these behavioral patterns often cause serious personal and social difficulties, as well as a general functional impairment.So the study examined a new view in personality and mental disorders named Rap disorder. In the domain we compare the youngster with and without disorder. The Rap disorder people are known with unusual hair model ,nihilistic and anarchistic thinking, unusual and bizarre behavior, reading of meaningfulness poet and sings ,doing immoral behavior against society norms and so on.
Methods: Method research is Causative –Comparative (Ex post facto). 200 youngster ,100 with the disorder and 100 without the disorder, were randomly selected and Eysenc's Personality Questionnaire (EPQ) was administered on them.
Results: Findings showed the Rap youngster are high in extroversion and emotional instability than normal youngster.
Conclusions: It is recommended that the appropriate behavior education specially moral and religious education can avoid tendency to this behavior disorder and reduce the bad effects of the behavior in society.

P-44-002
Emotional intelligence and mental health in university students

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P-44-003
Impact of schoolastic stressors on general health and achievement motivation among university students

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Objectives: The present Study is an attempt to investigate the impact of Schoolastic Stressors on general health and achievement motivation among university students.
Methods: Sample population were 600 university of students that were randomly selected and Kamkart & Bahary achievement motivation inventory (KBAMI), general health questionnaire (GHQ) and schoolastic stressors questionnaire (SSQ) were administered on them. Pearson correlation cofficient was used in order to answer the research questions.
Results: The data analysis showed that increasing schoolastic stressors decrease achievement motivation and general health. On the other hand decreasing schoolastic stressors increase achievement motivation and general health
Conclusions: Findings can be used in educational planing in order to setting plans to decrease schoolastic stressors and as a results enhancing of academic motivation and academic achievement.

P-44-004
Adult Attention Deficit Hyperactivity Disorder association with Synaptosomal-Associated Protein (SNAP-25) polymorphisms

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Objectives: The synaptosomal-associated protein of 25 kDa (SNAP–25) gene is a presynaptic plasma membrane protein and an integral component of the vesicle docking and fusion machinery mediating secretion of neurotransmitters. Previously, several studies reported association between SNAP-25 and attention deficit hyperactivity disorder (ADHD). We investigated whether these SNAP-25 polymorphisms (Mn1I T/G and DdeII T/C) were also associated with ADHD in the Turkish population.
Methods: Our study comprised unrelated 79 subjects who met DSM-IV criteria for Adult ADHD and 73 controls and all were of Turkish origin. Genetic analyses were performed and patients were evaluated with Wender-Utah and Turgay rating scales.
Results: SNAP-25 DdeII polymorphism was not associated with ADHD but there was a statistically significant difference between ADHD patients and controls for SNAP-25 Mn1I polymorphism ($p<0.05$). For SNAP-25 Mn1I polymorphism patients with GG genotype had higher average of Wender-Utah and Turgay Rating Scale scores than patients with TT and TG genotype.
Conclusions: We detected a significant association of the Mn1I polymorphism in our ADHD sample. G alleel would be a predisposing factor for ADHD which was similar to previous findings. Our study also revealed that SNAP-25 Mn1I polymorphism was also associated with symptom severity of ADHD. This study is also, the first report on the association of SNAP-25 with ADHD in the Turkish population.

P-44-005
Validation of the Children's Sleep Habits Questionnaire in a Greek sample

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Objectives: Sleep impacts a lot on child's development, by influencing physical growth, behavior, emotional and cognitive functioning. On the other hand, sleep disturbances are common among school children, having a prevalence of 20-30% accordingly various epidemiological surveys. Instruments, which have been developed, for the assessment of sleep difficulties in children are either questionnaires answered by parents of younger children or direct questionnaires for adolescents. The Children's Sleep Habits Questionnaire (CSHQ, Owens et al., Sleep 2000, 23:1043-1051) is a parent-rated instrument, which can be used for either younger or older children. To validate the Children's Sleep Habits Questionnaire in a Greek sample since no similar instrument existed for use in Greek populations.
Methods: For the standardization and validation of the Greek translation 531 children (316 males and 215 females) with mean age 8.9 years ± 3.2 years and range from 2 to 18 years were recruited. Control sample consisted of 201(37.9%) children and clinical sample consisted of 330 (62.1%) children (120 with psychiatric disorders and 210 with neurological disorders).
Results: Cronbach's alpha for the total score of the Children's Sleep Habits Questionnaire was high, being 0.88 for the children group and 0.75 for the control group. Alphas of the individual subscales of the questionnaire were also quite satisfactory for the majority of them, as were intercorelations among subscales.
Conclusions: The Greek version of the General Children's Sleep Habits Questionnaire was found to be an easy – to – use parent - rated instrument, whose application on children and adolescent sample of wide age-range was shown to be valid and having satisfactory psychometric properties.

P-44-006
Children's sleep motor phenomena: Differential diagnostics with epileptic seizures

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Objectives: The aim of this study was to define differential-diagnostics criteria for epileptic or nonepileptic children's sleep motor phenomena.
Methods: Comparative assessments of anamnesis, clinical findings, night polysomnography or video 32-channels EEG monitoring of 117 children were conducted. All children from 4 to 14 applied for medical aid for the first time. Children were divided into two groups: first - 45 with epileptic sleep motor phenomena (frontal epilepsy - 6, temporal epilepsy - 11, rolandic epilepsy - 16, juvenile myoclonic epilepsy – 12); second - 72 with nonepileptic sleep motor phenomena (sleepwalking, sleep terrors – 45, sleep myoclonia – 8, rhythmic movement disorder – 5, periodic limb movement disorder – 14). Data were analyzed with Biostatistics 4.03.
Results: For the first group progressive increasing frequency (94% vs.14%), appearance of motor phenomena during day sleep (35%), earlier appealability are more significant. Hyperactivity (46% vs. 10%), cognitive disorders or development delay (62% vs. 10%), severe sleep complains (77% vs. 30%) are significantly likely for the first group. Epileptic seizures occurred in the second half of the night, in 1, 2 stages and during change-over or awakening in REM, whereas parasomnias occurred at the end 1 or/and 2 cycles of sleep always from deep slow-wave sleep. Movement disorders occurred during the whole night in surfacial sleep stages and REM. Complex motor phenomena with tonic often asymmetric component are typical only for epileptic seizures. We observed 77% ictal and 86,4% interictal EEG activity in the first group and 84% long EEG arousals during motor phenomena in the second group.
Conclusions: The following differential-diagnostic criteria for epileptic sleep motor phenomena were defined: 1) Progressive increasing frequency, appearance during day sleep 2) Combination with hyperactivity, cognitive disorders, development delay, sleep complains 3) Complex motor phenomena with tonic asymmetric component during sleep The presence of these criteria demands night polysomnography with 32 channels EEG to exclude epilepsy.

P-44-007
Autism, smelling behavior and obsessive compulsive disorder: Case series

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Objectives: Smelling behavior might be the manifestations of obsessive compulsive disorder and autism. Autism is a debilitating neurodevelopmental disorder. Many areas of the brain show abnormalities in autism.
Methods: Seven male patients with age range 15-38 have been presented in that case series. The sample was recruited from the child psychiatry department of Bakirkoy Training and Research Hospital of Psychiatry, Neurology and Neurosurgery in Istanbul, Turkey.
Results: All of the patients suffered from a variety of autistic symptomatology since childhood. They failed to have normal social interaction, impaired language and restricted stereotyped patterns of interests and activities. Beside this autistic symptomatology, obsessive compulsive behaviors have been presented as they got older. In adolescence and adulthood they had obsessions including fears of contamination, symmetry, hoarding, aggressive impulse and somatic. Somatic obsessions might be presented with preoccupation with smelling. All of the cases smelled the objects and then use or eat them. One of the cases smelled the clothes, and then wears them; the other one didn't eat the food unless he liked the smell of it. Their compulsions included repetitive hand washing, ritualistic checking, and need for symmetry and precision, he also needed to ask or confess.
Conclusions: We propose that OCD with smelling behavior in autistic spectrum might be a subtype of autistic disorder.

P-44-008
Emotional regulation in a family context: A study in adolescent cannabis abusers and their parents

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Objectives: Impaired emotional functioning is commonly associated with a large spectrum of adolescents' self-harm behaviors, notably substance abuse. Although several environmental factors have been identified as contributors to the development of some emotional characteristics, studies in which intergenerational associations of affective styles have been explored are relatively scarce. Among substance abusers, our objective was to explore the relationships between parents' and adolescents' emotional functioning, particularly depression, anxiety and alexithymia.
Methods: Data from 91 patients with a cannabis use disorder [mean age=17.5(±2.3); 75 males, 16 females] and 139 of their parents [87 mothers; 52 fathers] were examined. Participants completed the 13-item Beck Depression Inventory (BDI-13), the State and Trait Anxiety Inventory-Y form (STAI-Y), the 20-item Toronto Alexithymia Scale (TAS-20) and the Bermond-Vorst Alexithymia Questionnaire-version B (BVAQ-B). A series of multiple regression analyses was performed to determine the relative contribution of both parents' affective scores to the prediction of each adolescent's scores.
Results: As expected patient's affective scores were related to their substance use modalities. In addition, results indicated that mother's BDI-13 score was the strongest predictor of adolescent's BDI-13, STAI-Trait and BVAQ-B scores. Moreover mother's STAI-State scores were positively associated with their child STAI-State score, whereas mother's STAI-Trait score predicted adolescent's TAS-20 score. Regarding paternal emotional predictors, no significant association was found with their depression and anxiety scores, but father's TAS-20 alexithymia score was significantly associated with their child's BDI-13, State and Trait STAI, and TAS-20 scores. Moreover, fathers' BVAQ-B score predicted significantly their child's BVAQ-B score.
Conclusions: These results suggest there may be intergenerational transmission of emotional dimensions from parents to children, yet varying according to the parent's gender. Our conclusions underline the appropriateness of family designs for a better understanding of the development of various adolescent's emotional and behavioral impairment, specifically in substance use disorders.

P-44-009
Attention deficit hyperactivity disorder among Ukrainian primary school children: Prevalence and co-morbid conditions

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Objectives: To evaluate the prevalence of associated conditions in a group of primary school children with attention deficit hyperactivity disorder (ADHD) and to describe the clinical characteristics and their relationships with core symptoms.
Methods: A 2 staged procedure in which primary school pupils aged 6 to 10 years (n=1072) were assessed for DSM-IV criteria of ADHD by their teachers in the first stage and their parents in the second stage. A flexible criterion was used for estimating the prevalence. Assessment was performed using the following scales: Kiddie - Sads - Present and Lifetime (K - SADS - PL), Yale Global Tics Severity Scale (YGTSS), Yale-Paris Self-Injurious Behavior Scale (YPSIBS), ADHD screening rating scales (Conner's, SDQ), Childhood Depression Rating Scales (CDRS), neuropsychological profil.
Results: The prevalence of ADHD was 7.9 %. The prevalence of the subtypes were: predominantly inattentive 5.3 %, hyperactive / impulsive 1.4 % and combined 1.2 %. The co-morbid conditions include oppositional defiant disorder (ODD – 31.7 %), conduct disorder (CD - 11.3%), anxiety disorder (26.3 %), depression (19.6 %),speech and school skills development disorder (21.9 %). While ODD and CD were associated with the hyperactive / impulsive subtype, anxiety / depression was associated with inattentive ADHD subtype.Tourette syndrome was found in 5.5% and self injury found in 3.5% children.

Conclusions: Our findings support the cross-cultural validity of ADHD. Some, presumably connected variants multiple co-morbid conditionsare described with different endophenotypes. There are likely processes to explain the etiologi and pathophysiology of ADHD and associated conditions with the involvement of biological, psychological, and social factors. Stressfull prescool life events and stress reactivity can modify genetic and biological processes to contribute to simplex disorder. Endophenotypes, or genetic expression of neural systems involved in ADHD, will be important in the study of thecomorbidity disorders pathogenesis and its treatment.

P-44-010
Treatment and rehabilitation of the children with autism spectrum disorders (ASD) and schizophrenia

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Objectives: To study influence of paliperidone (which the OROS extended release system) therapy and medical - social rehabilitation (MSR) on cognition and social functioning of the children with the ASD and shizophrenia.
Methods: We observed 32 children: 17 – with the ASD in the age from 5 to 10 years and 15 with SCH, shizofreniform and delusional disorders. Children with ASD were divided into 3 groups: on paliperidon monotherapy; receiving sensory integration and cognitive-behavioural and social skills trainings; receiving complex therapy; with schizophrenia - into the next 3 groups: receiving conventional antipsychotic therapy; which aggravations was reduced by paliperidon at hospital conditions and which received faltering laitance therapy after acute phase treatment; which early social intervention (ESI), MSR and paliperidone therapy We stadied: cognition, clinical displays of disorders (PANSS, CARS), social functioning (SAFE).
Results: Parameters of cognition in-group of children with ASD, receiving paliperidon on a background of active rehabilitation were on the higher level, than in groups of comparison. Patients with schizophrenia prove positive influence of long-term therapy by paliperidon and ESI on cognition. At long-term therapy of paliperidon children with schizophrenia on a background of active MSR with participation of family productive infringements, duration of disease and number of psychotic episodes in anamnesis, practically, did not influence on a level of social functioning. Intervention strategies also must be consistent with the developmental, social, and cultural aspects of the youth and his or her family.
Conclusions: Cognition disorders in the greater degree influence to the level of social functioning at the ASD and early schizophrenia, than negative symptoms of disorder. Long terminal therapy by paliperidon raises efficiency of sensory integration and cognitive trainings for the children with ASD and severe cognition disorders and social reintegration at early demonstrating schizophrenia.

P-44-011
Catatonia in autism and other neurodevelopmental disabilities

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Objectives: This paper reviews the presence of catatonia in neurodevelopmental disabilities, with emphasis on autism spectrum disorders. Clinical presentations are reviewed, followed by catatonia treatment algorithms including lorazepam and ECT.
Methods: A review of the English-language literature on catatonia in autistic, developmentally disabled and otherwise neurologically impaired populations. This was combined with the author's experience with patients with autism and other neurodevelopmental disabilities who developed catatonia.
Results: Catatonia is a unique neurobiological syndrome with multiple psychiatric, neurological, medical and drug-related etiologies. Most commonly associated with bipolar affective illness, catatonia has also been found in 12-17% of patients with autism. Various neurodevelopmental disorders may similarly present with catatonia. Blueprints for treatment of catatonia include lorazepam and electroconvulsive therapy. The following cases are presented: Pt 1: A 14 year-old male with congenital hydrocephalus and a pre-pontine cyst who lapsed into profound catatonia. Pt 2: A 15 year-old female with encephalitis of unknown origin and catatonic deterioration. Pt 3: A 19 year-old male with high-functioning autism and catatonia characterized by alternating stupor and extreme psychomotor agitation with self-injury. Pt 4: A 15 year-old male with congenital agenesis of the cerebellum and vermis in frank catatonic stupor. Pt 5: A 14 year-old male with autism and prominent catatonic deterioration complicated by hypothermia and bradycardia.
Conclusions: Catatonia can be readily seen in a variety of neurodevelopmental conditions including autism. Catatonia is eminently treatable with lorazepam and/or ECT in this population. Treatment barriers should be recognized and remedied.

P-44-012
Riluzole for affective and behavioral disturbance in autism

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Objectives: This paper reviews the novel usage of riluzole, an antiglutamatergic and neuroprotective agent, for affective and behavioral stabilization in autism.
Methods: A review of the English-language literature on riluzole usage for pediatric and adult psychopathology, combined with the author's experience with two autistic patients who demonstrated prominent affective stabilization and reduction in self-injury and aggression with riluzole.
Results: Riluzole was developed for usage in amyotrophic lateral sclerosis, and is the only drug to slow the progression of this devastating neurological disease. Riluzole inhibits release of glutamate, the primary excitatory amino acid in the brain, and enhances GABA-A receptor function. Riluzole has demonstrated efficacy in open-label trials of adult unipolar and bipolar depression as well as pediatric and adult obsessive-compulsive disorder. Case reports have additionally documented benefit in trichotillomania and self-injury. There is not yet published literature on riluzole usage in autism, but the following cases are presented: Pt 1: A 20 year-old male with autism, depression with suicidality and self-injury who demonstrated a partial response to electroconvulsive therapy and traditional adjunctive psychopharmacology. Riluzole addition provided sustained remission of residual symptoms. Pt 2: A 9 year-old male with autism, cyclical mood disturbance and extreme self-injury towards the head requiring extensive protective equipment for safety. Riluzole conferred both affective stabilization and prominent reduction in self-injury.
Conclusions: Riluzole is a new psychopharmacological agent. Efficacy has been demonstrated for mood and anxiety disorders in the typically-developing population. Similar positive benefit may be seen for psychopathology in autism, and merits further investigation.

P-44-013
The comparison of between social skills in 2 groups of children with ADHD and LD

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Objectives: This study compared the amount of the social skills in two special groups of students with attention deficit/hyperactivity disorder (ADHD) and with learning disabilities (LD).
Methods: Any group consisted of 30 elementary boys 8 to 11 aged those matched approximately in class (from second grader to fourth grader). Participants selected from the regions of 6, 11 and 12 of Tehran (Iran). In the first phase, from any region, 5 schools selected randomly in different area of those regions. Then the participants diagnosed and selected by means of rating scales and private interview. Evaluation tools consisted of social skills rating scale (SSRS), pupil rating scale (PRS) and children's syndrome inventory (CSI-4).
Results: Results indicated no significant differences were found between students with LD and with ADHD on social skills.

P-44-014
Elective mutism: Epidemiology, clinical characteristics, dynamic

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Objectives: This study was aimed to investigate the following objectives: (i) the clinical forms of elective mutism (EM), (ii) the psychological and patho-psychological characteristics of elective mute children, (iii) the epidemiology and (iv) the EM dynamic.
Methods: To reach this goal, the application of different techniques was undertaken. As those were used: ABM-WISC test, clinical, patho-psychological investigation methods. 70 children with elective mutism syndrome aged 3 to 18 years were tested as a total.
Results: Main results can be summarized as follows: All the subjects demonstrated refusal to talk. It was ranged from whisper speech to a total refusal to talk aloud. Gender distribution was approximately equal, but the small prevalence for boys as 1:0.8 was observed. However, in case of EM duration time more than 4 years we observed significant prelevance for girls as 1:2. Research of EΔprevalence at schools and kindergartens of the Central district of Moscow was revealed 39 for the first time the revealed patients from 20 thousand persons including pupils of elementary schools and children of kindergartens, that makes 0.2 % (1:500). Psychologically children with EM demonstrated sensitivity, anxiety, rigidity, lack of confidence, shyness, touchiness, negativism, puerility, and obsessive traits. Speech development level differed significantly: there were only 20% of patients without any speech difficulties. Half of children suffered from phobias (50%). Most often these were obsessive phobias of doing something wrong, but also phobias of speech and of public speaking. The data kept away catamnesis reveals at a part of patients the tendency to preservation of problems of communications (28 %), to a long current (8 %) and generalisations EM with total mutism (8 %).
Conclusions: The conclusions can be made that the revealed large prevalence in a combination to low detectability and a long-term running for any cases testifies to necessity of active revealing of EM patients and the multidisciplinary approach to treatment and rehabilitation.

P-44-015
Cruel treatment with children in the family and correction methods

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P-44-016
No alterations in Serum Brain Derived Neurotrophic Factor levels in Attention Deficit Hyperactivity Disorder (ADHD).

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Objectives: The Attention Deficit Hyperactivity Disorder (ADHD) is one of the most common neuropsychiatric disorders observed during child development, characterized by hyperactivity, impulsiveness and inattention. Recently, it has been proposed that brain-derived neurotrophic factor (BDNF) may be implicated in the pathogenesis of ADHD. Recent experimental evidences have reported significant alterations in BDNF serum levels in some childhood pathologies of the neurodevelopment like autism, whereas no data are available for ADHD. Aim of this study was to analyze the potential alterations of BDNF serum levels in a samples of ADHD patients compared with a control group
Methods: In the study were enrolled 36 drug-naïve ADHD children and a control group of 36 unrelated volunteers. No significant difference in sex distribution, mean age and BMI was evidenced among the groups. BDNF levels were measured by an ELISA method. Univariate analysis of variance was used for comparing BDNF means in patients versus controls and to evaluate the effect of significant covariates.
Results: BDNF serum levels in patients with ADHD were not significantly different than those of controls (ADHD mean ± SD : 38.85 ± 10.80 ng/ml; Controls mean ± SD: 40.53 ± 9.07 ng/ml, $t = 0.718$ $p = 0.475$) (Figure 1.). Univariate analysis of variance, taking into account the covariates age, sex and BMI confirmed the negative results ($F = 0.105$, $p = 0.747$).
Conclusions: This is the first study that analyzes serum BDNF concentrations in ADHD patients. The results obtained did not evidence alterations in the BDNF serum for this disorder. Further studies are in progress in a larger sample stratified for diagnostic subgroups, neuropsychological and psychopathological characteristics in order to verify the utility of serum dosage as possible diagnostic marker.

P-44-017
Sleep spindle activity in kindergarten children is associated with slow wave sleep (SWS) and coping strategies

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Objectives: Sleep spindles, i.e. EEG- features of Non-REM-sleep, are linked to efficient cortical-subcortical connectivity, intellectual abilities and "off-line" memory consolidation during sleep. However, there is little knowledge concerning the relationship of spindle activity to stress response and coping strategies.
Methods: In a cross-sectional study of forty one five-year old kindergarten children we examined stress-induced HPA system activity by saliva cortisol measurements and sleep regulation by sleep EEG-monitoring. Stress response was measured during application of a standardized psychological challenge appropriate at this age (McArthur Story Stem Battery, MSSB). Sleep EEG spindles were visually scored and put into relation to macrostructural sleep, coping and HPA activity parameters.
Results: Spindle density correlated with the amount of NREM-stage 4 sleep ($p < .001$). No correlation was found between spindle density and REM-sleep variables. Stress induced HPA-activity correlated positively with coping strategies with high-ego-involvement (i.e., positive emotions; $p < .001$); while there was no correlation with low-ego-involvement strategies like "denial" or "avoidance". Though spindles were not directly associated to stress-elicited HPA-activity, spindle activity correlated with coping such as "positive emotions" ($p = .001$). A negative correlation was found between spindle activity and "denial" and "avoidant strategies" ($p= .009$; $p= .050$).
Conclusions: In kindergarten children sleep spindles correlate with SWS. Spindle activity is elevated in children with coping involving positive, high ego-involvement; in contrast, low ego-involvement during stress is associated with reduced spindle activity. It seems to depend on coping strategies whether stress challenges lead to increased spindle activity during sleep.

P-44-018
Gender differences in mental health problems in early adolescence

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Objectives: To examine gender differences in mental health problems in Thai adolescents.
Methods: This is a retrospective study. The sample consisted of 83 male and 55 females adolescents aged 10-15 years who were referred to a mental health center in Bangkok, Thailand. The charts of these cases were systematically reviewed. Male and female cases were compared on family characteristics, clinical presentation, diagnoses and treatment.

Results: Most cases were first-born and in the 10-12 years age group. There were no significant differences between male and female cases in demographic or family characteristics except for a higher rate of fathers' death in the female sample. As for the presenting problems, academic underachievement, problems related to attention and hyperactivity, and disruptive behaviors were most common problems in males. Somatic complaints, disruptive behaviors and anxiety/fear/irritability were most common in females. Underachievement was significantly higher in males and somatic complaints were significantly higher in females (p>.05). Regarding diagnosis, ADHD, gender identity disorder and disruptive behavior disorders were most common in males. Adjustment disorders, ADHD and mood disorders were most common in females. The comparison between both groups found adjustment disorders, mood disorders and somatoform disorders to be significantly higher in females than in males (20% vs. 3.6%, 12.7% vs. 2.4%, 14.6% vs. 4.8% respectively, p>.05). There was no significant difference in the rates of psychotropic medication in both groups.
Conclusions: Male and female youth differ in many aspects of mental health. Understanding these disparities will help clinicians and policymakers to deliver better mental health care both in treatment and prevention.

P-44-019
Symptomatology and defense mechanisms of adults with ADHD

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Objectives: To evaluate the defense mechanisms used by Attention-Deficit/Hyperactivity Disorder (ADHD) patients compared to those used by controls and the relationship with ADHD symptoms.
Methods: Ninety-eight adult ADHD patients (DSM-IV-TR criteria) were evaluated with the ASRS and the Defense Style Questionnaire (DSQ-40). The DSQ-40 scores of the patient sample were compared to normative values (Blaya, 2006).
Results: ADHD patients showed more Immature defense style. Significant relationships were found between defense mechanisms and ADHD symptoms. ADHD patients used more fantasy and acting out compared to controls. Fantasy correlated significantly with attention symptoms and acting out with impulsive symptoms.
Conclusions: ADHD patients differ from controls in their use of defense mechanisms and there are positive correlations between symptoms and defense style. These findings could lead to the development of specific psychotherapeutic interventions and to elucidate psychodynamic aspects of ADHD patients.

P-44-020
Sleep-related eating disorder and Zolpidem: An open interventional cohort study

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Objectives: Sleep-related eating disorder (SRED) refers to a clinical condition of compulsive eating during sleep under impaired level of consciousness. The prevalence varies from 3.4% to 16.7% among different clinical populations. The exact etiology remains uncertain but recent evidences suggested that zolpidem was strongly associated with SRED.
Methods: We have identified and prospectively followed up a series of SRED subjects from our psychiatric clinic. They were invited for clinical and polysomnographic assessment and the option of taking off zolpidem was offered to patients.
Results: 10 subjects (7 female), mean age of 50.2 ± 13.7, presented with recurrent sleep-related eating features. The mean duration of SRED at the time of initial assessment was 2.5 years (range 0.5 - 6). Majority suffered from depression (8/10). SRED frequency varied from only a few times (4/10) to nearly nightly attacks (3/10). Half of them reported cooking behavior under impaired consciousness. Seven subjects underwent polysomnography. Only one subject demonstrated brief automatism of arising from bed. Five subjects had obstructive sleep apnea syndrome. The mean follow-up duration was 18.2 months (range 5 - 29). Six subjects stopped zolpidem, 2 had dosage adjusted, and 2 subjects refused to take off the medication. For those subjects who have taken off or decreased in zolpidem intake, almost all reported simultaneous disappearance of SRED symptoms. For the two patients who were still taking zolpidem, 1 had no further attacks after decreasing dosage of the concurrent antidepressants, and 1 still had SRED.
Conclusions: Albeit an open interventional cohort study, the timely correlation of cessation of SRED symptoms with the decrease of zolpidem dosage provided further evidence of the role of zolpidem in precipitating SRED in susceptible patients.

P-05
Neurodegenerative Disorders I

P-05-001
Regular moderate physical exercise improves mood and quality of life in older patients with atrial fibrillation

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Objectives: Affective disorder has not been considered appropriately in patients with atrial fibrillation (AF) representing a chronic disorder with reduced quality of life. Adequate ventricular rate (VR) control in permanent atrial fibrillation (AF) is not easy to accomplish. The aim was to assess whether regular moderate physical activity elevates the parasympathetic tone to the atrioventricular node and decreases VR during permanent AF but also improves psychic wellbeing.
Methods: Ten patients (59±10y) with permanent AF underwent moderate physical exercise (45min walking/jogging, 2/week). To analyze VR control, we performed Holter-ECG recordings, physical exercise treadmill tests, and lactate tests. Adequate ventricular rate (VR) control in permanent atrial fibrillation (AF) is not easy to accomplish. The aim was to assess whether regular moderate physical activity elevates the parasympathetic tone to the atrioventricular node and decreases VR during permanent AF but also improves exercise-related lactate threshold and psychic wellbeing before, during and after 4 months of training. Psychiatric interviews and psychometric examinations of mood and quality of life (SKID, BDI, HAM-D, SF-36) were obtained, too.
Results: Six of ten patients revealed a previous psychiatric history, four showed subclinical depressive symptoms and one a depressive episode. After training there were significant ($p<0.05$) improvements with decrease in VR (24 hours, exercise) and increase of lactate threshold (exercise), accompanied by improved general health perceptions in 7/8 quality of life dimensions. Enhanced global physical health was significantly higher in case of more pronounced depressive symptoms ($r=0.86$; $p<0.01$). Importantly, in three patients reductions/terminations of cardiac drugs could be undertaken.
Conclusions: Regular moderate physical exercise should be accounted for VR control during AF. Regarding the high prevalence of affective symptoms in our AF patients, bodily-oriented rehabilitation might minimize comorbid chronic affective disorder. ACKNOWLEDGEMENT This work was partly financed by the European research project 'MyHeart' (6th framework, IST 507816).

P-05-002
EEG complexity in Alzheimer's disease: Multiscale entropy analysis

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Objectives: Multiscale entropy (MSE) analysis is a new nonlinear analysis method of measuring the physiological system's complexity. MSE focuses on evaluating signals by multiple coarse-grained sequences which are described as scale factors (SFs), and therefore provide a intrinsic understandings of complex temporal fluctuations in the underlying EEG dynamics. The present study was conducted to explore the EEG abnormality in drug naive patients with Alzheimer's disease (AD) using MSE.
Methods: We recorded the EEGs from 16 scalp electrodes in 15 AD patients and 18 age-matched healthy controls (HC). We calculated MSE values of each artifact-free epochs of 60s on the basis of EEG. As for severity of cognitive function, Mini-Mental State Examination (MMSE) score was evaluated among AD.
Results: At lower SFs, MSE values were lower in AD than in HC. At higher SFs, MSE values were significantly correlated with MMSE score in AD. We divided AD group into two groups using a cut-off score of MMSE score between 15 and 16. At higher SFs, the AD group with lower MMSE score showed significantly higher MSE values compared to HC and the AD group with higher MMSE score. However, there was no significant difference of MSE values between HC and AD with higher MMSE score.
Conclusions: Results of lower EEG complexity at lower SFs in AD well agree with previous findings. At the same time, considering the fact that AD is characterized by the loss of functional interaction between different brain regions, results of higher EEG complexity at higer SFs in severe AD could reflect neuronal disconnectivity among different brain regions. Entropy-based algorithm on EEG with multiple scaling using MSE could explore more precise functional abnormalities as well as the etiology of AD, both of which were difficult to evaluate using traditional EEG analysis.

P-05-003
Rivastigmine and behavioral disorder of the patients in the centers for old persons

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Objectives: Agitation is one of the most serious psychiatric syndromes with the patients suffering from the Alzheimer Disease(AD).Goal of this study has been to establish efficiency of the Rivastigmine in controlling behavioral disorders ,agitation in the first place,of the persons with AD in parental centers.
Methods: The research was carried out for the period of eight months in three parental centers in Belgrade.The Rivastigmine group consisted of 42 patients with diagnosed AD.Rivastigmine was introduced to those patients in the first 30 days from the day of diagnosis. Control group of patients consisted of 39 patients of the same age with diagnosed AD,who did not receive Rivastigmine.In the course of the research following measuring instruments were used:Global Deterioration Scale ., NPI 12 / Neuropsychiatric Inventory Questionnaire,and MMSE /Mini Mental State Examination. Both,typical and atypical antipsychotics (Haloperidol, Risperi don,Olanzapine,Kvetiapine) were included in the analysis.
Results: During the seven months of the Rivastigmine application ,68% of the patients from the Rivastigmine group had no need for introduction of antipsychotics for controlling their agitation or irritability. The total use of antipsychotics (typical and atypical) was significantly higher in the Control group (27 %) compared to the Rivastigmine group (11%)
Conclusions: In the parental centers the patients with AD ,who were treated with Rivastigmine ,have had better control of their behavioral disorders, if compared with the patients who did not receive the treatment with the inhibitor of cholinesterasis. The patients who received Rivastigmine have reduced the use of the antipsychotic medicines.

P-05-004
Cerebrolysin in the treatment of dementia mixed type and Alzheimer's disease

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Objectives: To investigate the evolution of neuropsychological functions in patients diagnosed with dementia in Alzheimer's disease and mixed dementia treated with donepezil and memantine associated with neurotrophic factors – Cerebrolysin, compared to those who did not received neurotrophic factors.
Methods: The study was prospective, parallel group, in which patients were allocated to one of the treatment blocks for 6 months. All of the patients were on a stable dose, 10 mg donepezil and 20 mg memantine for at least 3 months before starting the study. 39 patients were enrolled, 24 mixed dementia and 15 Alzheimer's dementia, 9 men and 30 women. Patients had a Mini Mental State Examination score between 12 to 19 at baseline, were over 55 years of age, had a CT scan within the previous 12 months consistent with the diagnosis of dementia and were receiving ongoing therapy with donepezil and memantine. From the group of 24 patient with mixed dementia (mean age: 72,45 years, 55 – 89 years old; MMSE mean score: 15,37) 13 were receiving Cerebrolysin 5 ml/day, 10 days a month for 6 months. From the group of 15 patients with Alzheimer's disease (mean age:68,93 years, 55 – 81 years old; MMSE mean score:15,73) 8 were receiving Cerebrolysin. Patients were assessed at the beginning of the study, after 1 month, at 3 months and at the end of study. Cognitive, ADL and global measures were collected.

Results: Donepezil associated with Memantine and Cerebrolysin produces a significant improvement of clinical symptoms, a long – term stabilization and a slow down of the neurodegenerative process in Alzheimer's disease patients.
Conclusions: Patients who received neurotrophic factors had a better evolution of the cognitive performances. However, improvements were moderate and further studies are needed to determine if neurotrophic factors represent a therapy of choice for these patients.

P-05-005
Safety, efficacy, and biomarker findings of PBT2 in targeting ?-amyloid as a modifying therapy for Alzheimer's disease: A phase IIa, double-blind, randomised, placebo-controlled trial

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Abstract: Background: PBT2 inhibits the copper- and zinc-mediated toxic oligomerisation of amyloid-β (Aβ) seen in Alzheimer's disease (AD). Strong preclinical efficacy were observed and clinical safety studies have been completed.
Objectives: A phase IIa study, to assess the effects of PBT2 on safety, efficacy, and biomarkers of AD. Methods: Community-dwelling patients over age 55 years were recruited to this 12-week, double-blind, randomised trial of PBT2. Patients were randomly allocated to receive 50 mg PBT2, 250 mg PBT2, or placebo. Inclusion criteria were early AD (MMSE 20-26 or ADAS-cog 10-25), taking a stable dose of acetylcholinesterase inhibitor for at least 4 months, a modified Hachinski score of 4 points or less, and CT or MRI results that were consistent with AD. The principal outcomes were safety and tolerability. Secondary outcomes were plasma and CSF biomarkers and cognition. Analysis was intention to treat.
Results: 78 patients were randomised and completed the study. No serious adverse events were reported by patients on PBT2. Patients treated with PBT2 250 mg had a dose-dependent (p=0•023) and significant reduction in CSF $A\beta_{42}$ concentration compared with those treated with placebo (difference in least squares mean change from baseline was -56•0 pg/mL, p=0•006). Cognition testing included ADAS-cog, MMSE, and a neuropsychological test battery (NTB). Of these tests, two executive function component tests of the NTB showed significant improvement over placebo in the PBT2 250 mg group: category fluency test (2•8 words, p=0•041) and trail making part B (-48•0 s, p=0•009).
Conclusions: The safety profile is favourable for the ongoing development of PBT2. The effect on putative biomarkers for AD in CSF is suggestive of a central effect of the drug on Aβ metabolism. Cognitive efficacy was on two measures of executive function are consistent with the rapid improvements in cognition seen in transgenic mice.

P-05-006
The implication of oxidative stress in a rat model of Parkinson's disease

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Objectives: Parkinson's disease (PD) stems from the loss of dopamine caused by the degeneration of the dopaminergic neurons of the substantia nigra. The nature of this degeneration remains unclear, although current theories suggest that reactive oxygen species are involved in the disease process. The administration of 6-hydroxydopamine (6-OHDA) into the brain of the rat produces a well-established model of PD. Many investigators have demonstrated that 6-OHDA induces oxidative stress which can lead to the induction of apoptosis. The effects of 6-OHDA are age-dependent as there is a greater effect seen in aged animals compared with young animals. The purpose of the present study was to determine the development of oxidative stress that is generated in a substantia nigra (SN) and ventral tegmental area (VTA) 6-OHDA lesion model of PD through assessing the antioxidant enzymes activities in the temporal and frontal lobes homogenates.
Methods: Male Wistar aged rats, 22-23 month-old, were used for all experiments. 6-OHDA lesions: substantia nigra lesion; ventral tegmental area lesion. Biochemical estimations: determination of superoxid dismutase (SOD), glutathione peroxidase (GPX) and malondialdehyde (MDA) activities.
Results: The data were recorded 2 weeks after neurosurgery. Lesioning of substantia nigra and ventral tegmental area with a low dose of 6-OHDA induced significant reduction in SOD and GPX specific activities and non-significant reduction of MDA concentration in the temporal lobe rather than in the frontal lobe homogenates, comparative with sham-operated control group. Also, the role of the substantia nigra is more prominent than that of the ventral tegmental area.
Conclusions: Our results support that oxidative stress plays a role in the damage produced by substantia nigra and ventral tegmental area injection of 6-OHDA, and that indices of oxidative stress could potentially be important markers for evaluating therapeutic strategies and their effects on 6-OHDA-induced dopaminergic neurotoxicity.

P-05-008
Crime or illness? The mystery of Frontotemporal Dementias

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Objectives: We report a case of a 56 year old man suffering from a major depression with psychotic symptoms, who was referred to our hospital from prison. The patient has been arrested two years ago after he had tried to kill his wife. Until then he has been in psychiatric therapy because of a depressive syndrome. The medication has been partly stopped. Two years ago he was already clinical apparent with a change of personality, social isolation and a depressed mood.
Methods: After several weeks of treatment in our hospital with combined antidepressive and neuroleptic medication consisting of sertraline, trimipramine and olanzapin the patient improved significantly as to his affective status and showed a remarkable stabilization. However, slight cognitive deficits were still persistent.
Results: The neuropsychological investigation showed dysfunction of frontal brain lobe. In the cranial MRI scan were signs of cortical atrophy in frontal and temporal lobe, the PET of the brain showed hypometabolism in frontal cingulum. Altogether the findings of the anamnestic data, the psychopathology, the somatic and blood cell examinations, the anatomical and functional scans of the brain, the neuropsychological testing and the clinical course can be interpreted as an early dementia of frontotemporal lobe.
Conclusions: Frontotemporal dementias are rare subtypes of progressive cognitive decline. In these there is barely any impairment of memory and disorientation, moreover clinical prominent are progressive changes in personality, of motivation and of social behavior. Therefore these types of dementia are rarely diagnosed and often with several years delay. This case illustrates the diagnostic difficulties, possible mistakes and their consequences till the illness is finally diagnosed.

P-05-009
Donepezil reverses beta-amyloid-induced deficits in long term potentiation in rat hippocampal slices

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Objectives: Donepezil is a potent acetylcholinestarese inhibitor used for the treatment of Alzheimer's disease. Recent findings indicate that low concentrations of beta-amyloid peptide (Abeta) impair long-term potentiation (LTP), a cellular model for learning and memory. The purpose of this study was to determine whether Abeta effect on LTP can be reversed by therapeutically-relevant concentrations of donepezil (1 μM).

Methods: The experiments were performed on rat hippocampal slices. Extracellular recordings were made from the pyramidal layer of the CA1 region. To elicit synaptic responses, Shaffer collateral/commissural afferents in stratum radiatum were stimulated. The intensity of test stimuli was adjusted to elicit the population spike (PS) of about 50% of its maximal amplitude. LTP was induced by one train of high frequency stimulation (HFS; 100 Hz, 1 s). Drugs were applied by addition to the perfusate from 15 min before to 5 min after the tetanus. The data were statistically treated with the Mann-Whitney U-test and Student's t-test.
Results: In the control group, the amplitude of PS 30 min post-tetanus reached 139±8% (n=7). Abeta (200 nM) did not cause any changes of the baseline PS amplitude, but markedly suppressed the LTP induction or even caused the depression of PS: the amplitude of PS 30 min post-tetanus was 82±15% (P<0.01), as compared with the control group. Donepezil in concentration of 1 μM showed no effect on the baseline but the LTP was enhanced with increased amplitude of PS 30 min post-tetanus being 158±13% (n=5). The signifcant suppression of LTP, observed after application of Abeta alone, could be markedly prevented when donepezil was co-administered with Abeta: the amplitude of PS 30min post-tetanus was 127±9% (n=5, P<0.05), as compared with Abeta group.
Conclusions: Donepezil in concentration of 1 μM antagonizes the suppressive action of 200 nM Abeta on LTP in rat hippocampal slices.

P-05-010
Benefit of analyzing biological markers in cerebrospinal fluid in diagnosing Alzheimer's during a consultation with an expert from a Centre Mémoire de Ressources et de Recherche

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Objectives: The reliability of analyzing biological markers - Aβ1-42, total Tau proteins and phosphorylated Tau proteins – in cerebrospinal fluid (CSF) to help diagnose Alzheimer's does not need to be proven, but for a specialized and experienced clinician, its actual benefit among other techniques (clinical, neuropsychological, imaging) still needs to be clarified. The objective of this study was to evaluate if analysis results for these markers did or did not contribute to the final diagnosis.
Methods: A retrospective study in which we compared the diagnosis with or without the results of marker analysis in CSF. Only patients over the age of 70 examined by an experienced clinician were included. Analyses of CSF were carried out using an immunoassay technique (ELISA) with a kit marketed by Innogenetics®.
Results: 80 CSF samples were analyzed, of which 48.75% had a probable Alzheimer's profile. The diagnoses of 41 patients who fit in the inclusion criteria were analyzed. In 43.9% of cases, the analysis of biomarkers was helpful: in 26.8% of cases it helped confirm an initially hesitant diagnosis and in 17.1% of cases it modified the initial diagnosis. The final diagnosis was confirmed by the progression of the disease observed during the follow-up care of the patients.
Conclusions: Analyzing biomarkers noticeably helps in diagnoses when consulting an expert at a memory impairment center and could be even more important for less specialized centers.

P-05-011
Effects of apolipoprotein E genotype on behavioral and psychological symptoms in Alzheimer's disease

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Objectives: Behavioral and psychological symptoms of dementia (BPSD) are common in patients with Alzheimer's disease (AD) and have a serious impact on their quality of life and institutionalisation. Genetic determinants of BPSD in AD have been demonstrated and apolipoprotein E (APOE) ε4 allele is the only risk factor robustly associated with AD. However, previous investigations on APOE have produced inconsistent findings on BPSD. We explored the relationship between the APOE ε4 allele and a wide spectrum of behavioral and psychological symptoms of AD patients
Methods: Sixty two subjects with probable AD were recruited from the Dementia clinic. All the subjects had been examined by psychiatrists with advanced training in neuropsychiatry and dementia research according to the protocol of the Clinical Research Center for Dementia (CRCD) supported by the Ministry of Health and Welfare, Korea and met both the DMS-IV criteria for dementia and the NINCDS-ADRDA criteria for probable Alzheimer's disease. The subject's behavioral and psychological symptoms were assessed during an interview with the informant by using the Neuropsychiatric Inventory (NPI) consisting of 12. According to the defined criteria, the severity of each item was classified into 3 grades (from 1 to 3) and frequency of each one was classified into 4 grades (from 1 to 4). The NPI score (severity×frequency) was calculated for each item and the presence or absence of behavioral and psychological symptoms were also rated.
Results: There is no relationship between the APOE ε4 allele and BPSD, even after controlling for the effects of age at onset, sex, education level, duration of illness, and severity of dementia.
Conclusions: There was no statistical significant difference in BPSD between subjects with and without APOE ε4 allele in Korean elders with AD.

P-05-012
Genetics and epigenetics of depression in Alzheimer's disease

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Objectives: Depression in patients with Alzheimer's disease (AD) is associated with poorer quality of life. Studies have described gene-environment interactions between life events and polymorphisms in the 5HT transporter and BDNF genes and depression in children and adults but not in AD patients. In addition, the expression of the BDNF gene is highly complex with multiple promoters subject to epigenetic modification and transcripts which show differential patterns of expression in different regions. Our objective was to examine the relationships between polymorphisms in the BDNF and 5HT transporter genes, epigenetic modification in the BDNF gene and life events in depressed patients with AD.
Methods: The HTTLPR and STin2 polymorphisms of the 5HT gene and the Val66Met polymorphism of the BDNF gene were genotyped for ~1000 probable AD patients with behavioural data including the Cornell scale of Depression. Demographic data were used to quantify stressful life events including history of illness, chronic disability, death of spouse and lone accommodation. Post mortem brain tissue was available for 45 patients and methylation of the BDNF promoter was examined in 4 different brain regions of these patients as well as in their lymphocyte DNA. Methylation of the BDNF promoter was examined using the Sequenom MassARRAY EpiTYPER platform following sodium bisulfite treatment of genomic DNA. Interactions between life events, genotypes of the 5HT transporter and BDNF genes and epigenetic modifications in the BDNF gene were investigated.
Results: Preliminary results show no significant associations between the examined polymorphisms and depression in AD but a significant association between the number of stressful life events and depression (p=0.005). Analysis of epigenetic modifications in lymphocyte DNA and brain tissue is taking place at the moment and significant associations will be presented.
Conclusions: This novel approach seeks to correlate methylation patterns with genotypes and life events and examine the possibility of detecting a peripheral biomarker for depression in AD.

P-05-013
Examining gene-gene interactions between tau haplotypes and ApoE4 in Alzheimer's disease

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Objectives: Tau protein (MAPT) is the core element of neurofibrillary tangles, the major hallmark of Alzheimer's disease (AD). As a result of a chromosomal inversion, two non-recombining MAPT locus haplotypes (H1 & H2) are distinguished. Early researches suggested H1 to play a main role in AD, but some studies did not replicate this association. To find the clue for these controversies recent reports propose the investigation of ethnicity factors and gene-gene interactions (epistasis). Based on the fact that Apolipoprotein E4 (ApoE4) has a broad role in AD pathology with several synergistic connections and its possible influence on tau phosphorylation, the present study investigated possible interaction between MAPT haplotypes and ApoE4 in Hungarian Caucasian AD cases (n=91) and control (n=83) population.
Methods: Chi2 probes and logistic regression based synergy factor analysis were used to examine interactions. Genotypes were determined by the means of PCR.
Results: The difference in MAPT H1 allele frequency was nonsignificant in AD (78%) and control individuals (73.5%). These results indicate that in both groups the representation of H1 haplotype accords well with the frequency of ~ 75% in Middle-Eastern and European populations which was determined earlier. In this manner MAPT H1 haplotype carriage can not be associated to AD in the Hungarian population. The broadly supported finding that carrying ApoE4 allele is a risk factor of AD was replicated, since ApoE4 carriers were significantly overrepresented (34.1% vs. 20%) compared to the control population. Though a specific combination of ApoE4 and H1 alleles were found to be associated to AD (14.5% vs. 30.8%), synergy factor analysis did not reveal interaction between them.
Conclusions: Our findings support the notion that while ApoE4 might be involved in AD pathology, the MAPT H1 allele neither associates nor interacts through an epistasis with ApoE4 in the development of the disease in the Hungarian population.

P-05-014
Creutzfeldt-Jakob dementia and psychiatric symptoms

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Objectives: The purpose of this study is to describe a case of bovine spongiform encephalopathy that started with predominantly affective psychiatric pathology.
Methods: a 48-year-old woman, with no personal or family psychiatric record, consulted us with regard to a clinical profile that had been developing for about three months, with a predominance of depressive symptoms. The presence of atypical symptoms such as sporadic visual hallucinations, changes in behaviour and personality, hypogeusia and hyposmia, was the first reason for suspecting an underlying neurological pathology
Results: after the patient was admitted to the Department of Neurology and was thoroughly examined, she was diagnosed for incipient frontotemporal dementia vs Creutzfeldt-Jacob dementia. The rapid developmet of the illness determined the definitive diagnosis, later confirmed by necropsy
Conclusions: the presence of atypical affective symptoms, together with subtle neurological signs, even without cognitive deterioration, rules out a somatoneurological illness. Psychotropic drugs were able to control some of the behavioural disorders

P-05-015
Symptomatic treatment of delirium

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Objectives: We set out to perform a descriptive analysis of the administration of psychotropic drugs to patients diagnosed for delirium and admitted to a general hospital with 940 beds. When delirium is accompanied by agitation, it is normally necessary to administer antipsychotics, although there are no clear guidelines as to which specific drug should be used
Methods: We assessed the case history and sedative treatment administered to 98 patients diagnosed for delirium according to criteria DSM-IV and ICD-10, excluding any alcoholic aetiology. The study includes all the requests for psychiatric interconsultation concerning this diangosis made in 2008
Results: 69% of the patients were men with an average age of 74.5 years. The pathology most frequently associated with delirium was systemic illnesses including infections, neoplasias and diverse postoperative conditions (41%). In 12% of cases there was comorbidity with dementia. The drug most frequently admimistered was parenteral haloperidol, (48%) followed by oral haloperidol (40%), oral/parenteral tiapride (31%), atypical antipsychotics (19%) Lorazepan (14%) and other drugs such as Gabapentine and rivastigmin (7%)
Conclusions: Haloperidol, both oral and parenteral, is still the drug of first choice in the treatment of delirium. The atypical antipschotics risperidone,quetiapine and olanzapine were used successfully in a fifth of cases

P-05-016
Classifying what? How dementia classifications shape the concept of "normal" aging

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Objectives: Currently the distinction between normal and pathological age-associated cognitive decline is being reconceptualised through the broad use of diagnostic tools, including neuroimaging, biomarkers, and neuropsychological testing. By tracing the occurrence of "new" disorders such as mild cognitive impairment (MCI) back to the diagnostic criteria of Alzheimer´s disease (AD), I want to demonstrate the major impact of dementia classifications on the definition of "normal" aging.
Methods: Classifications require diagnostic criteria that can be operationalised, e.g. neuropsychological test values, for which precise thresholds can be set. The explanatory reach of such criteria and thresholds shall be critically evaluated from an epistemological point of view, especially with regard to the conceptualisation of "normality" via normal data. A theoretical and clinically informed approach is used.
Results: Diagnostic tools are developed to identify pathological entities, making "normality" (here: normal variants) a non-distinctive feature. Failure to describe what "normal" aging actually is allows for the extension of technology-driven classifications of mental disorders. The emergence of MCI as a pathological condition may seem inevitable, since diagnostic guidelines are made to label deviation from, not divergence within "normality".
Conclusions: In search of better diagnostic criteria for AD in the upcoming new editions of the classification systems ICD and DSM, their impact on defining "normal" aging must be considered. Classifying forms of dementia evokes the examination of potential prodromal stages, such as MCI. Hence, the conception of "normal" aging is altered due to the characterisation of MCI as pathological. However, what it means for individuals to age "normally" cannot solely be described in negative terms, as having no striking cognitive or neuropsychiatric complaints.

P-05-017
Inflammatory biomarkers in Alheimer's Disease: Clinical correlates

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Objectives: Neuroinflammation is involved in the pathogenesis of Alzheimer's disease (AD). Pro-inflammatory cytokine like tumor necrosis factor-alpha (TNF-alpha) and interleukin-6 (IL-6) are over-expressed whereas neurotrophic factors such as insulin-like growth factor I (IGF-I) tend to be reduced in AD brains. Recently we reported that serum TNF-alpha levels are increased and correlate negative with IGF-I in AD patients (Alvarez et al, Neurobiol Aging, 2007). The interactions between inflammatory and trophic factors at the peripheral level, as well as their potential influence on clinical manifestations of AD are relevant research topics.
Methods: Serum levels of TNF-alpha, soluble TNF receptors (sTNF-RI and II), IL-6, total and free IGF-I were determined by ELISA methods; and the correlations of these factors with cognitive performance and disability scores were evaluated in AD, mild cognitive impairment (MCI) and elderly control subjects (EC).
Results: Serum levels of TNF-alpha, sTNF-RI and IL-6 were increased ($p<0.01$) and total IGF-I values reduced ($p<0.01$) in AD patients as compared with controls. Circulating TNF-alpha and IL-6 correlated negatively with total and free IGF-I, and positively with disability scores in AD patients. Cognitive performance (MMSE) scores showed week but significant negative correlations with TNF-alpha, sTNF-RI and IL-6, and a positive correlation with IGF-I only in the whole sample.
Conclusions: According to our results, peripheral inflammatory biomarkers (TNF-alpha, sTNF-RI and IL-6) are overexpressed in AD, seem to have a negative influence on the production of the neurotrophic factor IGF-I, and are associated with a worsen performance of AD patients in activities of daily living. The present results support the involvement of these proinflammatory parameters in AD pathophysiology and suggest their utility as serum biomarkers to monitor the clinical effects of AD treatments with immunomodulatory activity.

P-05-018
Dementia caused by Sanfilippo B syndrome

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Objectives: Sanfilippo B is one of the autosomal recessive mucopolysaccharidoses (MPS IIIB) caused by a deficiency of N-acetyl-α-D-glucosaminidase (NAGLU), a lysosomal enzyme involved in the degradation of heparan sulfate. Accumulation of the substrate leads to neurological degeneration, behavioural problems and mental decline. The gene encoding NAGLU is located on chromosome 17q21.1 and has been fully characterized. Over one hundred different mutations have been reported and allelic heterogeneity corresponds to the wide spectrum of clinical phenotypes. Compared to other types of MPS, somatic features are relatively mild and specific dysmorphias are lacking.
Methods: A female patient aged 57 years admitted because of dementia is described. Extensive neuropsychiatric and neurological examination was performed as well as metabolic and genetic screening.
Results: Although the patient had a lower IQ and followed special education, symptoms of cognitive and behavioural deterioration emerged after the age of 40. There were flattening of affect, affective instability, uncooperativeness, loss of decorum, anxieties and monotonous speech. Neurological examination showed an apathetic, demented woman without any initiative. She responded to questions short and slowly, but adequate. There was a remarkable hypokinesia with a lack of spontaneous and intentional movements and some dystonia. Reflexes were symmetric and cerebellar function was not disturbed. MRI demonstrated a generalized cerebral atrophy. Skeletal changes included a dense calvarium only. Ophthalmologic and cardiologic examination showed no abnormalities. Metabolic screening demonstrated an increased concentration of heparan sulfate. Enzymatic assay in leucocytes proved a deficiency of N-acetyl-α-D-glucosaminidase. DNA sequencing demonstrated mutations in the NAGLU gene, p.R177W and p.S612G. A male sib aged 66 years had the same metabolic disorder.
Conclusions: In this patient as well as in her brother a metabolic disorder was not previously considered. There is a substantial risk of underrecognition of these disorders, especially in clinical psychiatry.

P-05-019
Pharmacotherapy in intellectual disabilities

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Objectives: Psychiatry in intellectual disabilities is challenging since it offers the chance to study psychiatric symptoms and neuropsychological dysfunctions in relation to a known etiology. The same holds for the investigation of psychiatric manifestations of neurologic diseases in which a bottom-up approach is in general followed that starts with the emergence of pathology in the brain and attempts to understand clinical syndromes out of this pathology.
Methods: The literature was scrutinized for syndrome specific treatment strategies.
Results: Critical evaluation of the literature revealed that almost all studies deal with psychotropics applied for challenging behaviours in people with intellectual disabilities. The current practice is dominated by inadequate concepts that are based on the idea that IQ and disturbed behaviour are useful entities for treatment. In addition, there is a paucity of data about pharmacological treatment for specific syndromes and of evidence-based information that could guide the clinician in the treatment of individual patients. Moreover, pharmacokinetic and pharmacodynamic data in this population are absent.
Conclusions: Intellectual disability is not a disease but a metasyndrome including a very heterogeneous group of clinical maladies ranging from genetic to nutritional, infectious, metabolic or neurotoxic conditions. The IQ criterion itself is hardly informative and does not relate to specific cognitive impairments in different diseases with intellectual disabilities. The same holds for the term challenging behaviour that is an amalgam of behavioural disturbances such as aggression, stereotypies, destructive behaviours, self injury and self stimulation as well as psychiatric symptoms. Psychopharmacological treatments based on these two premises are therefore nonsensical. An algorithm for psychopharmacological treatment should therefore be based on an understanding of etiology (e.g. genetic and metabolic disorders, comorbidities and environmental factors), pathophysiology (e.g. vascular anomalies and endocrine dysfunctions) and pharmacokinetic parameters related to the P450 isoenzyme system.

P-05-020
White matter lesions in Korsakoff syndrome

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Objectives: Korsakoff syndrome is a heterogeneous condition with respect to the degree of memory and cognitive impairment as well as the extent of structural brain damage. Its etiology is still largely unknown since only a small percentage of heavy drinkers with thiamine deficiency develop this disorder. Diencephalic damage is associated with memory impairment and cerebral atrophy with other cognitive impairments. White matter lesions (WML) are hyperintense areas on FLAIR MRI in the cerebral white matter and can be seen in a range of different clinical conditions such as normal aging, Alzheimer disease and stroke. WML are associated with cognitive and executive dysfunctions irrespective of the condition. Leukoaraiosis is also linked to depression and disability in the elderly and subclinical functional impairment in the non-disabled as well as with metabolic syndrome. Sofar, leukoaraiosis has not been systematically evaluated in Korsakoff syndrome.
Methods: In a group of 40 patients hospitalized because of Korsakoff syndrome, T2 weighted and FLAIR MRI scans were evaluated for the presence of WML. All patients underwent an extensive neuropsychological test battery, including among others WAIS, Rivermeade Behavioural Memory Test, California Verbal Learning Test, Stroop Color Word Test and Tower of London Test to assess IQ and deficits in cognitive and executive functioning.

Results: In all patients neuropsychological testing confirmed the clinical diagnosis of alcohol amnestic disorder. A varying degree of WML was found in about half of the patients that could be correlated with functional impairments. In addition, MRI scanning confirmed the heterogenous structural abnormalities as demonstrated in Korsakoff syndrome.
Conclusions: WML may contribute to the clinical picture of Korsakoff syndrome. It is hypothesized that pre-existing small vessel disease may be a risk factor in the vulnerability to develop Korsakoff syndrome after thiamine deficiency.

P-24
Neurodegenerative Disorders II

P-24-001
Peculiarities and treatment of delirium in geriatrics patients with traumatic injuries

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Objectives: The goals of this study are (i) to determine clinical peculiarities of delirium in patients 65 years of age or older having musculoskeletal injuries; (ii) determine comorbidity between delirium and the injury with the accompanying somatic pathology; (iii) based on these results, determine the risk factors and the necessary therapy.
Methods: We have studied a total of 157 patients with musculoskeletal injuries and used both clinical psychopathological and instrumental methods to examine them. The laboratory analysis included blood tests (general and biochemical), computer tomography and magnetic resonant tomography, Doppler ultrasound, X-ray, electrocardiography, echoencephalography, and electroencephalography. Mini-mental scale examinations (MMSE) have also been performed. We used the Karnovsky measure and Functional Independence Measure (FIM) to estimate functional activity. The severity of injuries was measured using the Abbreviated Index Severity (AIS). The weight was measured using the Body Mass Index (BMI). Particular care was taken to ensure statistical significance of our results.
Results: We have found that (i) 61 out of 157 (39%) patients studied developed delirium (F05.x.) according to ICD-10; (ii) the probability for a patient to develop delirium is proportional to the patient's age, the severity of the injury, and the amount of blood loss; (iii) the risk factors are anemia, obesity, low mobility as a result of injury, and cardiac arrhythmia; (iv) effective treatment includes combination of somathic etiopathogenetic therapy with cerebral vessel and neurometabolic therapies and with the increase in patient's mobility.
Conclusions: We present statistically significant results showing that elderly patients with musculoskeletal injuries frequently develop delirium which aggravates the primary condition and its outcome. The problem of delirium in gerontology is becoming ever more important as the aging of the population in Russia as well as in the rest of the world leads to a significant increase of the fraction of gerontological patients in hospitals.

P-24-002
Effects of glycine on learning, memory ability and hippocampal gene expression of APP, PS1, BACE in rats with Alzheimer disease

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Objectives: To investigate the effect of glycine on learning and memory ability in rats with Alzheimer disease (AD) induced by D-galactose and AlCl3 and its possible mechanisms.
Methods: Wistar strain rats were given D-galactose 60 mg·kg- 1·d-1,ip,and AlCl3 5 mg·kg- 1·d- 1,ig,once daily for 90 d. Since the 20th day of D-galactose and AlCl3 intraperitoneal injection, the rats in glycine group had been treated with glycine by intragastric administration 50mg·kg-1·d-1 for 70 days. Subsequently, learning and memory ability of the mice was evaluated by Morris water maze, biochemical methods to assay acetylcholine(ACh)and acetylcholinesterase(AChE)contents in whole brain,RT-PCR to determine the expression of amyloidβ-protein precursor(APP), presenilin-1(PS1)andβ-site APP-cleaving enzyme(BACE) genes and Aβ1-40 immunohistochemical staining to observe morphological changes in hippocampus.
Results: Rats intragastric administration with glycine, mice had shorter latency (P< 0.05) and less error times (P<0.05) in water maze test compared with those in AD model group. At the same time, glycine down regulated the expression of APP, PS1, BACE mRNA (P<0.05) and Ach content reinforcement,AChE activity decline in hippocampus, which emerged Alzheimer-like pathological changes.
Conclusions: The combined use of D-galactose and AlCl3 may well make an animal model whose pathological changes are very similar to those of Alzheimer's disease. Glycine improves the learning and memory ability of AD rats, its mechanism may be related to the downregulated expression of APP, PS1, BACE mRNA. Key words:D-galactose;aluminum trichloride;Alzheimer's disease;learning;memory;models

P-24-003
Study on Chinese herb Danshen-Dahuang on learning, memory ability and hippocampal Tau and Aß in rats with Alzheimer disease

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Objectives: To investigate the effect of Chinese herb Danshen-Dahuang on learning and memory ability in rats with Alzheimer disease (AD) induced by D-galactose and AlCl3 and its possible mechanisms.
Methods: Wistar strain rats were given D-galactose 60 mg·kg- 1·d-1,ip,and AlCl3 5 mg·kg- 1·d- 1,ig,once daily for 90 d. Since the 20th day of D-galactose and AlCl3 intraperitoneal injection, the rats in Danshen-Dahuang group had been treated with Danshen-Dahuang extraction by intragastric administration 10 g·kg-1·d-1 for 70 days. Subsequently, learning and memory ability of the mice was evaluated by Morris water maze, biochemical methods to assay Tau albumen and Aβ1-40 immunohistochemical staining to observe morphological changes in hippocampus.
Results: Rats intragastric administration with Danshen-Dahuang, mice had shorter latency (P< 0.05) and less error times (P<0.05) in water maze test compared with those in AD model group. At the same time, Danshen-Dahuang are markedly decrease the level of Tau albumen in the brain and the expression of Aβ in the hippocampus of rats.
Conclusions: Conclusions The combined use of D-galactose and AlCl3 may well make an animal model whose pathological changes are very similar to those of Alzheimer's disease. Danshen-Dahuang improves the learning and memory ability of AD rats, its mechanism may be related to play an important role in the prevention and cure of AD. Key words:D-galactose;aluminum trichloride;Alzheimer's disease;learning;memory;models

P-24-004
The study on the level of intestinal endotoxemia in Alzheimer's disease rats

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Objectives: The objective of the present study was to explore the level of intestinal endotoxemia (IETM) in the model of Alzheimer disease's rats which were established by D-galactose and aluminum trichloride (AlCl3).

Methods: Adult Wistar rats were subjected to 90 days of intraperitoneal injection with D-galactose and AlCl3 to establish the Alzheimer disease's model. After the administration, the study and memory ability of the Alzheimer disease's rats were observed by Morris water maze; The level of Lipopolysaccharide (LPS) in the sera of Alzheimer disease's rats was determined by tachypleus amebocyte lysate method; The level of tumor necrosis factor-α (TNF-α) and interleukin-1 (IL-1) in the sera of Alzheimer disease's rats were determined by radioimmunity method; The express of amyloid β-protein precursor (APP), presenilin 1 (PS1) and β-site APP-cleaving enzyme (BACE) in hippocampus of Alzheimer disease's rats were detected by RT-PCR.
Results: Compared with the normal control, the level of LPS in the sera and the express of APP, PSI, BACE mRNA in the hippocampus of Alzheimer disease's rats were markedly increased (P<0.01).
Conclusions: The model of Alzheimer disease's rats which were established by D-galactose and AlCl3 is accompanied IETM. This result suggests that IETM play an important role in the development of Alzheimer disease. [KEY WORDS] intestinal endotoxemia; lipopolysaccharide; Alzheimer disease; D-galactose; aluminum trichloride; model

P-24-005
Amisulpride in the treatment of very late onset schizophrenia

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Objectives: Late or very-late-onset schizophrenia-like psychosis has not been well studied and various treatment issues remain unresolved. Late or very-late-onset schizophrenia-like psychosis is markedly more common in women, is more often associated with the occurrence of paranoid symptoms, less severe cognitive impairment, and a need for lower doses of antipsychotics for its treatment. The objective of the present study was to evaluate the efficacy and safety of amisulpride monotherapy in a diagnostically homogeneous group of elderly patients suffering from very-late-onset schizophrenia without cognitive impairment.
Methods: Twenty-six patients of mean age 76.2 ± 5.8 years, fulfilling both the recent consensus criteria for very late-onset schizophrenia-like psychosis and the DSM-IV-TR criteria for schizophrenia, were assessed using the Brief Psychiatric Rating Scale, the Clinical Global Impression Scale and the Positive and Negative Syndrome Scale at baseline and five weeks following amisulpride (50-200 mg/day) administration; in addition, the presence of abnormal movements was evaluated with the Simpson-Angus Scale, the Barnes Akathisia Scale, and the Abnormal Involuntary Movement Scale.
Results: A highly significant (p<0.001) improvement in the measurements of psychotic symptoms was observed in all patients. Amisulpride was very well tolerated by the patients and no clinically significant adverse effects were observed. Scores on all abnormal movement scales did not differ significantly prior to and after amisulpride treatment.
Conclusions: Preliminary results indicate that amisulpride appears to be an efficacious and safe atypical antipsychotic for the treatment of very-late-onset schizophrenia-like psychosis.

P-24-007
Behavior and attention disorders at the children with intellectual disabilities

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Objectives: The paper discusses areas of behavioral functioning of children with intellectual disability, such as behavior with or without hyperacitivity and attention disorders.
Methods: The study covered 124 children with mild intellectual disability attending elementary schools in Belgrade. The Conners rating scale was used in educational settings, and tested developmental areas behavior in the classroom, participation in the group and attitude towards authority were covered.
Results: The results of our study suggest the presence of disorders in behavior and attention functioning ranging from 11.2% to 40.4% and their relationship with cognitive functioning and school achievement, determined by Pirsons "r"
Conclusions: We have highlighted the importance of the use of multimodal approach such as:
- Pharmacotherapy
- Behavioral intervention
- Team work (professionals and non-profesionals)
- Multimodal treatment (combination of the therapeutical approach)
- Complementary treatment (education and psychosocial interventions)
- Individualy based treatment such as pharmacotherapy and behavioral interventions.

P-24-008
Age-dependent induction of neurofibrillary tangles in transgenic mice overexpressing a non-mutant human tau isoform

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Objectives: Neurofibrillary tangles (NFTs) are neuropathological hallmarks of Alzheimer's disease (AD) and related tauopathies. However, NFTs identical to those found in AD brains have also been detected in the brains of cognitively normal individuals as they age. We investigated the effects of aging on NFT formation in a mouse model of tauopathies.
Methods: We examined extremely old transgenic (Tg) mice, that is, more than 30 months of age, overexpressing the smallest human brain tau isoform.
Results: Extremely old Tg mice have very many NFTs in several brain regions. Moreover, ultrastructurally, these lesions contain straight tau filaments comprising both mouse and human tau proteins. Isolated tau filaments were also recovered from detergent-insoluble tau fractions, and insoluble tau proteins accumulated in the brain in an age-dependent manner.
Conclusions: Overexpression of the smallest human tau isoform resulted in late-onset age-dependent formation of congophilic tau inclusions with properties similar to those of NFTs in human tauopathies, thereby implicating aging in the pathogenesis of tauopathies.

P-24-009
Exploratory efficacy in cross-maze test depends on neurochemical profile of brain

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Objectives: The specificity of animal reaction to novel environment depends on individual (typological) neurochemical status maintaining certain level of synaptic homeostasis in brain (Kovalev et al., 2008). This profile includes the neurotransmitter receptors, ion channels, neurotrophines, etc. This work is aimed to study the brain NMDA- and nicotinic receptors characteristics, as well as BDNF content in mice diverging for exploratory efficacy in the cross-maze test.
Methods: Behavioral pattern of animals was evaluated in plus-maze test (Salimov et al., 1995). Radioligand ex vivo assay was provided using [3H-G]-MK-801 (210 Ci/mmol) and [3H-G]-Nicotine (140) in hippocampal and cortical membrane preparations, respectively. The detection BDNF in both brain structures was measured with sandwich format of ELISA method.
Results: The total population of outbred mice (1CR strain) was divided into 2 sub-populations according to their high (EH mice) or low (EL mice) efficacy of exploratory behavior in cross-maze ($\chi 2$ (df=6) = 33.6, p=0.00001). The number (Bmax) of hippocampal NMDARs was higher in EH than in EL mice (3835+332 vs 2710+162 fmol/mg, resp.), as well as the BDNF content (0.177+0.005 vs 0.091+0.005* pg/ug, resp.; p<0.0005). On the contrary, the density of cortical nAChRs was higher in EL (Bmax1=201+25; Bmax2=506 +39*) than in EH mice (Bmax1=140+22; Bmax2=405 +34).

Conclusions: The low exploratory efficacy ("cognitive deficite") in cross-maze test is accompanied by heightened density of neocortical nACh-receptors, by reduced density of NMDA-receptors and decreased BDNF concentration in hippocampus. Thus, the actions of cognitive-enhancing drugs have to involve the correspondent changes in these neurochemical targets (see Firstova and Kovalev, this issue).

P-24-010
Enhancing resilience to stress and quality of life in depressed family dementia caregivers: A randomized placebo-controlled trial of escitalopram

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Objectives: We assessed the potential of an antidepressant drug, escitalopram, to improve resilience to stress and quality of life in depressed family dementia caregivers in a randomized placebo-controlled double-blind trial.
Methods: We recruited 40 family caregivers (43-91 years of age, 25 children and 15 spouses; 26 women) who were taking care of their parents or spouses with Alzheimer's disease and randomized them to receive either escitalopram 10 mg / day or placebo for 12 weeks. We assessed the severity of depression, negative ruminations, resilience, burden, distress, quality of life, severity of care-recipient's cognitive and behavioral disturbances, and proinflammatory cytokines at baseline and at follow up. HDRS scores at baseline ranged between 7-28. The groups were stratified by the diagnosis of major and minor depression.
Results: Most outcomes favored escitalopram over placebo. The severity of depression improved with the drug compared to placebo ($F=5.5$; $df=23$; $P=0.02$). Interestingly, subjects who took escitalopram demonstrated 60% improvement in resilience compared to 2% improvement in resilience in those on placebo ($t=-2.2$; $p=0.04$). We observed reduction in pro-inflammatory cytokine levels correlated with reduction in depression severity ($r=-0.5$) in both treatment groups. Although the magnitude of improvement in depression was greater in subjects with major depression, the final HAM-D scores did not differ between those with major or minor depression.
Conclusions: We concluded that antidepressant use in caregivers can improve depression, boost resilience and energy, ease burden and distress, and improve quality of life. Inflammation may improve as a result of decrease in the depression severity with either drug or placebo. Our results need to be confirmed in a larger sample.

P-24-011
Dementia care in learning disabilities: An audit

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Objectives: We are now faced with the challenges of meeting the mental health needs in the increasing number of ageing individuals with learning disabilities. A diagnosis of dementia in this particular group of patients has been challenging in terms of the difficulties involved in assessment and management. The objective of this audit is to report the compliance of the current practice of dementia care among patients with learning disabilities against the NICE guidelines.
Methods: This audit was performed amongst all referrals made with a suspicion of dementia to the Chester and Ellesmere Port community team for learning disabilities in the U.K. over the past 4 years. Current practice was compared with the NICE guidelines (UK). 16 patients were identified from a log which contained the names of all the patients referred with a suspicion of a diagnosis of dementia in the past 4 years.
Results: A named key worker was identified for every referral made. 12% of patients did not have the folate and vitamin B12 investigated. Dementia information leaflets/dementia medication leaflets were not documented in over 80% of the patients. Structural imaging was done in only 1/3rd of the cases. Dementia specific assessment was repeated within 6 months in only just over 50% of the cases. Carers assessment was not documented in any of the cases. Documentation regarding consent for prescribing acetylcholinesterase inhibitors was observed in only 20% of patients.
Conclusions: This audit reveals that consent and capacity which remains a key issue in patients with learning disabilities were not documented in the majority. A structured performa which follows a standard protocol that would ensure a holistic and consistent approach for every referral made should be used for every patient referred for dementia and this should be regularly discussed during weekly multi-disciplinary team meetings.

P-24-012
Comparison of frontotemporal dementia and healthy volunteers using quantative EEG

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Objectives: Frontotemporal dementia (FTD) is characterized by changes in personality early in its course, deterioration of social skills, emotional blunting and behavioral disinhibition. We performed this study to investigate characteristics of brain electric field in FTD patients using quantitative-EEG (qEEG) analyses.
Methods: Thirteen right-handed FTD patients and age-matched healthy volunteers participated in this study. EEG data was recorded from 19 scalp locations of the International 10/20 System from. Global Field Power (GFP) of spectral amplitude was computed across electrodes to obtain a measure of total amplitude for seven independent frequency bands.
Results: There was tendency to increase absolute power in delta and beta1 frequency bands in FTD patients compared to control, but there was no significant difference between two groups.
Conclusions: The increase of absolute power in delta band in FTD may reflect decline of brain function accompanied by degeneration of brain. Then, the increase of absolute power in beta1 band may be interpreted as an expression of tense condition. Therefore, qEEG is supposed to be a useful tool of investigating characteristics of brain electric field in FTD.

P-24-013
The role of oxidative stress in Mild Cognitive Impairment and Alzheimer disease

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Objectives: Mild cognitive impairment (MCI) is a transitional stage between normal cognitive aging and mild dementia or clinically probable Alzheimer's disease (AD). There is a great interest in the relationship between MCI and the progression to Alzheimer's disease (AD). Several studies show the importance of oxidative stress in the pathogenesis of AD. The aim of this study was to determine the oxidative stress status in MCI and AD patients.
Methods: The patients were selected using Petersen criteria for MCI and NINCDS ADRDA criteria for AD. The cognitive performance was assessed using MMSE (Mini Mental State Examination), ADAS-cog (Alzheimer's Disease Assessment Scale- cognitive subscale), Clock Drawing Test and Verbal Fluency Test. We assessed the levels of some enzymatic antioxidant defences like superoxid dismutase (SOD) and glutathione peroxidase (GPX), as well as lipid oxidation makers like MDA (malondialdehyde), using chemiluminometric and spectrophotometric methods. The results were compared to an aged-matched control group.
Results: Alterations in the activity of the antioxidant enzymes (SOD and GPX) were found in MCI and AD peripheral blood compared to age-matched controls. Also, MDA levels were significantly increased in the AD and MCI patients, comparative with the control group. Moreover, in MCI patients, cognitive function positively correlates with antioxidant levels.
Conclusions: These results support the hypothesis that oxidative damage is an important event in the pathogenesis of neurodegenerative diseases. Also, it seems that some peripheral markers of oxidative stress appear in MCI with a similar pattern to that observed in AD, which suggest that oxidative stress might represent a signal of the AD pathology.

P-24-014
Creatine deficiency syndrome: Study of a cohort of 530 patients in the CHU of Rouen

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Objectives: Developmental delay and mental retardation are an important public health problem. Creatine deficiency syndromes identified in the last decade are inborn errors of metabolism responsible of mental retardation and/or behavioural disorder and/or epilepsy. Three creatine deficiency syndromes have been characterized: defect of ceratine biosynthesis (AGAT and GAMT) and creatine transporter (CRTR) deficiency. These syndromes are characterised by a decrease of creatine signal determined by brain proton magnetic resonance spectroscopy. Creatine synthesis deficiency can be treated by oral supplementation of creatine; response to treatment depends on its early introduction. In contrast, none useful treatment is available for the CRTR deficiency.
Methods: Developmental delay and mental retardation are an important public health problem. Creatine deficiency syndromes identified in the last decade are inborn errors of metabolism responsible of mental retardation and/or behavioural disorder and/or epilepsy. Three creatine deficiency syndromes have been characterized: defect of ceratine biosynthesis (AGAT and GAMT) and creatine transporter (CRTR) deficiency. These syndromes are characterised by a decrease of creatine signal determined by brain proton magnetic resonance spectroscopy. Creatine synthesis deficiency can be treated by oral supplementation of creatine; response to treatment depends on its early introduction. In contrast, none useful treatment is available for the CRTR deficiency.
Results: Two cases of creatine deficiency were formally identified: a GAMT and a CRTR deficiencies. In four others cases, the diagnosis was suspected on biochemical results but no mutations was identified by direct sequencing.
Conclusions: These results showed that in some cases, this diagnosis is difficult to establish; evaluation of central creatine concentration represents the key exploration to confirm the diagnosis of creatine deficiency syndrome.

P-24-015
Persistence of abnormal cortisol levels in elderly persons after recovery from major depression

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Objectives: Cortisol hypersecretion is characteristic of acute clinical depression, but little is known in fully recovered, non-treated elderly persons with a life-time history of depression. This study was designed to examine patterns of diurnal cycle of cortisol in an elderly cohort without current depression or treatment for depression according to whether the person has or has not experienced a previous episode of depression or co-morbid depression with anxiety.
Methods: Cortisol secretion was evaluated in 162 community-dwelling elderly on a stressful and a non-stressful day (basal level). Past depression and anxiety disorders were assessed using a standardized psychiatric examination based on DSM-IV criteria (the Mini International Neuropsychiatric Interview).
Results: Antidepressant-free persons with a history of non-comorbid major depression (6.8% of the sample) showed basal cortisol hypersecretion compared to those with depression and anxiety (8.6%) or controls. Several hours after exposure to a stressful situation, controls showed a sustained increase in cortisol secretion, which was not observed in persons with a history of depression. Persons with a history of depression with anxiety showed a similar cortisol secretion at baseline to controls but a heightened response to stressful situation; a pattern comparable to that observed in subjects with pure anxiety disorders (16.7%).
Conclusions: An abnormal hypothalamic-pituitary-adrenal response persists even after effective treatment for depression. A history of co-morbid depression and anxiety gives rise to changes characteristic of anxiety alone. Our findings suggest that cortisol abnormalities may be trait markers for vulnerability to depression and for the differentiation of depression and depression with co-morbid anxiety.

P-24-016
Tactile perception in children with intellectual disabilities

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Objectives: Touch differs from other exteroceptive senses in that the body itself forms part of the tactile percept. Tactile perception provides information about our environment and provide feedback. The aim of the paper is to determine the quality of development tactile perception in children with intellectual disabilities.
Methods: The sample consists of 93 junior grade students of elementary schools for children with intellectual disabilities, age: 8 years and 6 months to 12 years and 3 months. The test that we have used for ability tactile perception evaluation was C3 scall from Luria - Nebraska revision for children (LNNB-C).
Results: In the scale that we have used is applied quantitative scoring in three levels. The results indicate a very low percentage of successful children in the sample as well as to the best results achieved children about 9 / 10 years.
Conclusions: The focus of the treatment of children in this development area would be directed to specific exercises and activities that improve the quality of tactile perception.

P-24-017
Depression in Parkinson's disease: Serotonin mechanisms, response to SSRI antidepressants

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Objectives: Parkinson's Disease (PD) has mediators disturbances in its pathogenesis. Depression could be revealed in 35 up to 70 % of PD patient by the different data. The origin of the depression in PD is discussing.
Methods: We examined 68 PD patients (29 males, 39 females) with the mean age 62,5. The average duration of the disease was 6,3years. We assessed severity if the PD using UPDRS, Hoen and Yahr scale. We used Beck depression scale, Hospital Anxiety and Depression scale, Montgomery-Asberg depression scale for the emotional status assessment. We determined quantity of blood serum serotonin by the Immune Assay method (ELISA). 20 of depressed PD patients received SSRI antidepressant – fluoxetine 20 mg daily, another 20 – placebo (randomized, blind, placebo controlled study) for 8 weeks. All the results were analyzed statistically using nonparametric tests.
Results: 64% of PD patients had moderate or sever depression. Blood serotonin level was significantly lower in PD (189,14±80,63ng/ml) than in healthy controls (271,98±92,86 ng/ml) $p<0,05$. And it was even more low in depressed patients (166,75± 98,34 ng/ml) $p<0,05$. Level of depression did not correlate with the duration or severity of motor symptoms of PD, but clearly correlated with blood serotonin level. After the treatment it was found that depression level and even severity of motor symptoms are decreasing in the group of patients receiving fluoxetine versus placebo group. Blood serotonin level decreased even more after the treatment by fluoxetine and had no significant changes in the placebo group.
Conclusions: Concerning some animal and PET studies blood serotonin can reflect the serotonin metabolism in the brain. Serotonin level has strong correlation with the level of depression in PD patients. Thus depression in PD is just partly reactive and more endogenous, serotonin-dependent. Both depression and motor symptoms of PD can be successfully modified by SSRI (fluoxetine).

P-24-018
Copper binding effect on amyloid peptide aggregation in Alzheimer's disease

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Abstract: A major source of neurodegeneration observed in Alzheimer's disease (AD) is believed to be caused by the toxicity (oxidative stress) from reactive oxygen species produced in the brain by amyloid-β-peptide (Aβ and copper species. Accurate details on the mechanism of copper Cu (II) binding with Aβ may be critical to the aetiology of AD. This work presents the investigation of the interaction of Cu (II) with Aβ (1-40) and Aβ (1-28) under different conditions, using intrinsic tyrosine fluorescence, ThT aggregation assays and transmission electron microscopy. Our results demonstrate that: 1. Cu (II) accelerates the initial phase of Aβ (1-40) aggregation and inhibits the aggregation of Aβ (1-28). 2. Cu (II) binding to Aβ(1-40) and Aβ(1-28) results in varying degrees of tyrosine fluorescence quenching. 3. The absence of the characteristic tyrosinate peak in the absorption spectra of Aβ (1-40)-Cu(II) and Aβ (1-28)-Cu (II) provides evidence that Cu (II) does not bind directly to the tyrosine residue in Aβ peptide but remains close to the metal binding site. 4. Tyrosine fluorescence is sensitive to the copper oxidation state, which is influenced by the aggregation of amyloid. In conclusion, our results contribute to understanding of Aβ aggregation into a variety of structures under different conditions, buffer, pH values and measurement techniques applied to study the state of the Aβ-Cu (II) complex.

P-24-019
Memory performance in patients with obstructive sleep apnea before and after positive airway pressure

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Objectives: The aim of the study was to examine if positive airway pressure improve memory performance in patients with obstructive sleep apnea after 6 months treatment
Methods: 10 patients with sleep apnea were administered neuropsychological memory tests before airway pressure treatment and at 6 months following up the first testing
Results: Results showed on the first testing that patients with sleep apnea showed memory deficits that were similar to those of depressed patients: working memory deficits, retrievial verbal episodic memory deficits and encoding visuo-spatial memory deficits
Conclusions: These preliminary findings allow to better characterize the memory deficits of patients with obstructive sleep apnea

P-24-020
Psychosis in Parkinson's disease patients: The relevance of dopaminergic drugs and of their mode of application

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Objectives: More than a third of patients with Parkinson's disease (PD) experiences psychotic symptoms (PS) in the course of the disease. Since dopaminergic drugs are the most potent triggers of PS, they have to be reduced, which results in a worsening of the parkinsonian symptoms. Additionally the use of neuroleptics is limited by their extrapyramidal side effects and therefore often insufficient. Eventually, the occurrence of PS is accompanied by early nursing home placement and increased morbidity.
Methods: The course and development of PS were examined in seven patients with advanced PD whose therapy was switched from an oral levodopa therapy to a new therapy with levodopa continuously administered intestinally by a portable pump. Four of the seven patients had had severe preceding PS under all available antiparkinsonian therapies combined with quetiapine, which is together with clozapine, the only neuroleptic without extrapyramidal side effects.
Results: After starting the intestinal levodopa therapy, PS was absent in those patients who had had PS before and did not occur in the three other patients despite much higher daily doses of levodopa. Later, psychiatric symptoms were only observed when tube dislocations from the intestinum into the stomach occurred or a concomitant dopamine agonist therapy had to be used.
Conclusions: Our observations indicate that the "unphysiological" pulsatile stimulation caused by the quick resorption and short half-life of orally administered levodopa is a more potent trigger for PS than the substance itself or the dose used. These observations are underlined both by the recurrence of psychiatric symptoms when levodopa is accidentally applied into the stomach resulting in the same absorption as oral administration, and by the fact that an additional oral therapy of a pulsatile nature can induce psychiatric symptoms.

P-24-021
Switching strategy involving Galantamine in the treatment of patients with mild to moderate Alzheimers disease

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Objectives: The aim of this study is to evaluate the clinical effectiveness of a switching strategy involving galantamine in patients with Alzheimer's disease(AD) who showed a lack of efficacy to another acetylcholinesterase inhibitor(AChEI).
Methods: Seventy patients with probable AD of mild-to-moderate severity were recruited. A total of 66 patients satisfied the criteria for the Intent-to-treat (ITT) population and were classified into two groups, the drug-naïve group (n=42) and the switched group (n=24). The primary cognitive outcomes were measured using the response rate after 26 weeks of treatment and a Korean version of the Alzheimer's Disease Assessment Scale-cognitive subscale (K-ADAS-cog). Secondary outcomes were measured using a Korean version of the Mini-Mental State Examination (K-MMSE), Seoul-Activities of Daily Living (S-ADL), Seoul-Instrumental Activities of Daily Living (S-IADL) and Korean version of the Neuropsychiatric Inventory (K-NPI).
Results: There were no significant between-group differences in the response rate to galantamine (71.4% for the naïve group vs. 58.3% for the switched group; $\chi 2=1.178$, df= 1, p= 0.277) or the adjusted change on the cognitive scales (K-ADAS-cog and K-MMSE) and non-cognitive scales (S-IADL, S-ADL, and K-NPI) at each efficacy evaluation. Stratification analyses by severity showed that if the duration of illness is constant, the probability of response is much higher in the naïve group than in the switched group of patients with AD of moderate severity ($\chi 2 = 4.09$, df= 1, p-value= 0.043), but not in those with AD of mild severity.
Conclusions: This study shows that previous exposure to an AChEI does not limit the efficacy of future treatment with galantamine on cognition, function, and behavior in the treatment of patients with mild-to-moderate AD, while a switching strategy involving galantamine may be more effective in patients in the earlier stages of AD.

P-06
Psychotic Disorders I

P-06-001
Compliance therapeutic adhesion over 8 year of follow-up in first psychotic episodes

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Objectives: The objective of this study is to asses compliance in a sample of patients with a first psychotic episode and to compare prognosis after 8 years of follow-up between patients with good and bad compliance.
Methods: 70 patients were evaluated at index episode and over the 8 years after their first hospitalization in the Santiago Apóstol Hospital (DSM IV). Psychosis was defined as the first time that the patient had positive psychotic symptoms (delusions/ hallucinations). A protocol that included demographic and clinical data was used. Prognosis was measured by GAF, ICG and Scale of Strauss – Carpenter. Number of relapses, substance consumption, and information about treatment adherence (Morisky - Green Test) were also evaluated.
Results: 2 patients had died by suicide behaviour (one man and one woman). The patients had 3. 19 (SD 4.35) hospitalizations during follow-up. At 8 years of follow-up cannabis was the most used substance (26. 8%), followed by alcohol (18.8%) and cocaine- amphetamines (10.9%). In relation with adherence, 47.2% frequently forgot to take the medication, 43. 4% of the sample stopped treatment when they felt well and 39.6% left medication when they felt bad. Comparing patients with bad and good adherence, the first ones, had worse functional adaptation measured by t GAF (U; p = 0.013), a more severe disorder (U; p = 0.015), greater number of hospitalizations (p=0.004) and more symptoms during follow-up measured by the Strauss Carpenter (p=0.003). Over the follow-up, the 21.7% of patients had made suicide attempts. Of these, the 75% have displayed bad adherence (F; p= 0.047).
Conclusions: The most important finding of this study is the low therapeutic adherence to treatment, and the risks associated with it as bad functional outcome and suicide risk. However, adherence is modifiable with psychotherapeutical techniques.

P-06-002
Impact of methamphetamine use in first episode psychosis

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Objectives: To examine the effects of methamphetamine use in first-episode psychosis
Methods: We are conducting a prospective, longitudinal study of first-episode psychosis in Cape Town, South Africa. Patients were included if they met the Diagnostic and Statistical Manual of Mental Disorders, Fourth Revision (DSM-IV) diagnosis of schizophrenia, schizophreniform disorder or schizo-affective disorder. Patients with a current DSM-IV diagnosis of substance abuse were excluded. This report discusses the baseline characteristics and early treatment response of patients with a history of methamphetamine use compared to patients without previous use. Clinical variables were measured using the Positive and Negative Syndrome Scale (PANSS), Clinical Global Impression Severity Scale (CGI-S), Calgary Depression Scale for Schizophrenia (CDSS), Social and Occupational Functioning Assessment Scale (SOFAS) and Extrapyramidal Symptom Rating Scale (ESRS).
Results: Of the 52 patients, 28 patients had used methamphetamine and 24 patients had not. We found significant differences between the two groups in the following demographic variables: age (mean 20.8 vs. 26 yrs; p = 0.00), gender (males 82.14% vs. 41.67%; p = 0.00), highest level of education (tertiary 3.57% vs. 33.33%; p = 0.03) and marital status (married 0% vs. 20.83%; p = 0.02). There were no significant differences in language, ethnic group, residential area and employment status. In terms of clinical variables, we found significant differences with baseline PANSS Total (mean 106.18 vs. 94.75; p = 0.01) and SOFAS (mean 39.46 vs. 45.29; p = 0.02). There were no differences in CGI-S, CDSS, ESRS, weight and BMI. At 3 months there were significant differences with PANSS Total (65.89 vs. 55.88; p = 0.01), CGI-S (3.61 vs. 3.04; p= 0.02) but no differences in CDSS, ESRS, weight and BMI.
Conclusions: Methamphetamine use significantly influences the presentation and early treatment response of first-episode psychosis.

P-06-003
Greek translation and reliability of the Psychotic Symptom Rating Scales (PSYRATS)

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Objectives: The PSYRATS are designed to assess the subjective characteristics of hallucinations and delusions. The objective of the present study is the presentation of the Greek translation of the PSYRATS and of their inter-rater reliability.
Methods: The scales were translated and back-translated, after taking permission from its writer, by three psychiatrists. The inter-rater reliability was assessed by the ratings of four psychiatrists who delivered them in 9 patients, 4 men and 5 women, with a mean age of 45 years old.
Results: The reliability co-efficient for the total rating of the auditory hallucinations subscale (AHS) is 0.972, while for 10 out of 11 items of the subscale co-efficient ranges from 0.731 to 1. For the item "controllability of voices" it is 0.555. For the four investigators' rates, Cronbach' s alpha ranged from 0.7 to 0.8. The reliability co-efficient for the total rating of the delusions subscale (DS) is 0.967, while for the 6 items of the subscale co-efficient ranges from 0.872 to 0.944. For the four investigators' rates, Cronbach' s alpha ranged from 0.7 to 0.8.
Conclusions: There is an excellent inter-rater reliability of the Greek translation of the AHS and the DS of the PSYRATS, regarding their total score as well as the scores of 11 out of 12 items of the AHS and the score of all the items of the DS. There is also consistency in the assessment of the two subscales between investigators.

P-06-004
Heart rate variability and Antrieb (drive, impulse) in catatonic schizophrenias – affection of the autonomic nervous system as a possible link between neurophysiological and psychopathological variables

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Objectives: German psychopathology uses the rather brought term "Antrieb" (drive, impulse) that in our view should be differentiated in three sub-categories (quantitative and qualitative disorders of higher Antrieb and disorders of basal Antrieb, Hohl-Radke 2008). The most bodily sensed part of this sub-categorization, the "basal Antrieb" is characterized as a continuum between "feeling lazy, lame and lacking energy" and "feeling fidgety, impelled and strained". We examined a possible association between this psychopathological sub-category and heart rate variability (HRV). We compared the relationships between HRV and ratings of "basal Antrieb" in catatonic versus non-catatonic schizophrenia patients.

Methods: 55 inpatients, suffering from schizophrenia spectrum disorders (9 catatonics, 46 other) were included. HRV was recorded in a 10/min clock-pulse-breathing trial of five minutes' duration. "Basal Antrieb" was appraised by a self rating and a clinicians rating on a 10cm-visual analogue scale. We compared log-transformed HRV total power levels (l-HRV) with visual analogue scales results.
Results: Comparing relationships of observer ratings of the "basal Antrieb" and l-HRV, we did not find any significant correlation. The same was true for patients' self ratings and l-HRV in the non-catatonic schizophrenias. However, in our 9 patients suffering from catatonic schizophrenia, we found a significant correlation between l-HRV and the "basal Antrieb"-self-rating-levels (Spearman's rho= 0,683, two-tailed p=0,042).
Conclusions: Our findings may emphasize that in catatonic schizophrenias a disturbed autonomic nervous system is more often recognized by the patients themselves than in other schizophrenia spectrum disorders. The autonomic nervous system may therefore constitute a link between psychopathological and neurophysiological measurements. A better self-awareness of a disturbed "Antrieb" in catatonia patients might be a key to insight into illness in these patients.

P-06-005
Two days treatment of auditory hallucinations by high frequency rTMS guided by cerebral imaging: A 6 months follow – up study

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Objectives: Auditory hallucinations are a common and disabling problem for many patients with schizophrenia that often fail to respond to optimal antipsychotic therapy. Repetitive transcranial magnetic stimulation (rTMS) has recently been suggested as an alternative treatment for these patients. Until now, rTMS has been used at low frequency and has been most commonly applied to the left temporoparietal cortex. In order to improve the efficiency of this treatment, we conducted a pilot longitudinal study using high frequency rTMS guided by anatomical and functional magnetic resonance imaging (MRI).
Methods: Eleven patients with schizophrenia (DSM-IV) were treated with high frequency (20 Hz) rTMS delivered over 2 days with a 6 months follow-up. The anatomical target was identified by MRI as the highest cluster activation along the posterior part of the left superior temporal sulcus from the BOLD signal contrast map of each subject (listening to French vs Tamil story).
Results: A significant reduction in the global severity and frequency of auditory hallucinations between baseline and post-treatment day 12 was observed. For 2 patients, auditory hallucinations disappeared entirely and persisted at 6 months of follow-up. High frequency rTMS was well tolerated in all patients.
Conclusions: This is the first study reporting the successful treatment of auditory hallucinations with 20 Hz rTMS. The efficacy at short term, the strengh of the therapeutic effect at 6 months for certain patients, the safety and short duration of treatment present a considerable therapeutic gain compared to low frequency rTMS.

P-06-006
Glutathione redox system and lipid peroxidation in patients with schizophrenia

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Objectives: The aim of the present study was to investigate glutathione redox system and lipid peroxide in plasma levels in schizophrenic patients.

Methods: 30 patients with paranoid schizophrenia (ICD-10 criteria) were enrolled to examine before and after 6 weeks of antipsychotic treatment. The glutathione (GSH) redox system is important for reducing oxidative stress. GSH, a radical scavenger, is converted to oxidized glutathione (GSSG) through glutathione peroxidase, and converted back to GSH by glutathione reductase. Serum levels of GSH and GSSG were examined by spectrofluorimetry, serum malondialdehyde (MDA) levels, a marker of lipid peroxidation were examined by spectrophotometric assays simultaneously. Results were compared to those of 34 age- and sex- status-matched controls.
Results: As a result, malondialdehyde, was found to be increased significantly in patients' group ($p<0.0001$) as compared with control group. Serum levels of GSH were significantly lower in schizophrenic patients as compared with control group (105,59±14,62 mkg/ml, 141,26±19,21 mkg/ml – in healthy persons, ð<0,05) and trend toward increase of oxidized glutathione concentration was observed. Moreover, GSH levels were significantly correlated to negative symptoms of schizophrenic patients. After treatment, level of MDA was significantly decreased than previously. At the same time neuroleptic treatment did not influence on levels of glutathione redox, oxidized glutathione and its ratio.
Conclusions: These results demonstrate increase production of reactive oxygen and decrease antioxidant protection in schizophrenic patients. Our study confirms the literary data that oxidative stress may be implicated in the pathophysiology of schizophrenia and GSH metabolism dysfunction is as one of the vulnerability factors for schizophrenia.

P-06-007
‚Theory of mind' in ultra high risk and first episode psychosis cohorts: Preliminary findings on degree of impairment

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Objectives: Theory of Mind (ToM), the mental capacity to infer one's own and others' mental states, is a key aspect of social cognition and is significantly impaired in schizophrenia (Brune 2005) and first episode psychosis (FEP; Bertrand et al 2007). ToM has also been found impaired in an at-risk population relative to healthy controls (Chung et al 2008), but whether the degree of impairment is parallel to FEP has yet to be explored. Therefore, the aim of this study was to investigate whether individuals at Ultra High Risk (UHR) of developing psychosis and FEP patients are equally impaired in ToM.
Methods: Nine UHR (M age =20.2, sd =3.3) and 11 FEP (M age =21.7, sd =2.3) clients have been recruited from ORYGEN Youth Health. Participants were administered the Hinting Task (score range =0-20; requires the ability to infer the intentions behind indirect speech), the Global Functioning: Social/Role Scales, and demographic and psychopathology questionnaires.
Results: Preliminary analysis using independent samples t-tests showed there were no differences in performance of the Hinting Task between groups (UHR M =16.0, sd =3.6; FEP M =15.9, sd =2.3 ;$t(17) = .07$, $p = .94$, Cohen's d =.03). Performance was below that of normal controls (M =18.1, sd =1.5), based on previous research (Bertrand et al 2007).
Conclusions: This study is still underway and has now begun to recruit healthy age and gender-matched controls. Participants in this study will also be followed-up after 12 months. It is expected that ToM of UHR participants will be as impaired as the FEP group, regardless of whether or not UHR participants convert to full-threshold psychosis. However, impairment is expected to be less severe than that observed in chronic schizophrenia. Future research should determine whether deficits in social cognition are vulnerability markers for psychosis and how such deficits impact on social functioning.

P-06-008
Risperidon, right choice of treatment for schizophrenia? Experience obtained through practice

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Objectives: The aim of the work is to represent the results of the replacement of typical anti-psychotics with risperidon, applied in the Centre for Mental Health in Kotor in the last two years, to patients that have been cured of chronical schizophrenia for a longer period. It offers data on to which extent introduction of risperidon improves the quality of patients' lives, whether and to which extent it jeopardizes the former level of remissions, whether and to which extent it improves the quality of remissions, how much it influences on frequency of undesired effects of anti-psychotic therapy and with which patients it proves necessary to include some alternative anti-psychotic therapy.
Methods: The examination has encompassed three groups of volunteers. The first group is made of 32 patients with a ten-year-old diagnosis of schizophrenia, both genders, the age between 35 and 6o, the second group consists of 21 patients with a diagnosis of sch from 1 to 1o years old, both genders, the age between 23 and 35. All these patients had been permanently treated with different combinations of typical anti-psychotics which always contained haloperidol or fluphenazin. All of them had a distinct " negative" sch syndrom. The third group includes 6 patients with the first psychotic episode whose cure had commenced with haloperidol. When EPS occurred, it was necessary to introduce a-typical AP. They are evaluated on PANSS and CGI scales every 15 days along with the use of the auto-anamnestic data, as well as the hetero-anamnestic data obtained from the family or a social service.
Results: The research is expected to last until may 2009

P-06-009
Abnormalities in the spontaneous and steady-state EEG activity of schizophrenics

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Objectives: Abnormalities in spontaneous and steady-state EEG oscillations, particularly in the alpha range, have been reported in schizophrenia patients by several recent studies. Here we investigated the topography and other characteristics, including specificity and relation to medications, of these EEG abnormalities.
Methods: Schizophrenic subjects (N=5), nonschizophrenic patients taking antipsychotics (N=5), and healthy controls (N=5) were recruited. A 256 channel hd-EEG system was employed to collect spontaneous waking (eyes closed) and several steady-state visual stimulation sessions in each participant. EEG sessions were 2 minutes long, and a strobe light flashed at different frequencies (7, 10 and 15 Hz) was used as visual stimulus.
Results: Schizophrenics had a significant increase in spontaneous EEG theta (4-8 Hz) activity as well as a reduction in the alpha power band (8-12 Hz) compared to both healthy and medicated controls ($p<.05$, unpaired t-test, Panel A). Schizophrenics also showed higher steady-state visual evoked potential (SSVEP) power at 7 Hz and a lower SSVEP activity at 10 Hz (Panel C and D). Furthermore, SSVEP at harmonic frequencies (15 Hz and 20 Hz) were respectively increased and decreased in schizophrenics relative to normal and psychiatric controls. Topographic analysis revealed that these effects were maximal in prefrontal and parieto-occipital regions (Panel B, C' and D').
Conclusions: These preliminary results confirm previous findings of deficits in the spontaneous and steady-state alpha oscillations of schizophrenics, and suggest that these deficits are possibly specific, medication independent, involve both sensory (parieto-occipital) and higher-order (prefrontal) cortical areas, and are associated with an increase in theta and its first harmonic oscillatory activity.

P-06-010
Effects of Selegiline on negative symptoms in schizophrenia: A double-blind, placebo-controlled, study

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Objectives: Introduction: It has been suggested that schizophrenic negative symptoms may be manifestations of regionally deficient CNS dopaminergic activity. We sought to test this hypothesis by openly treating patients on chronic antipsychotic medication who showed prominent negative symptoms with low-dose selegiline (5 mg b.i.d.), a monoamine oxidase-B inhibitor that selectively enhances dopaminergic activity.
Methods: Methods: Eighty patients meeting DSM-IV-TR criteria for chronic schizophrenia with prominent negative symptoms (Positive And Negative Symptoms of Schizophrenia-Negative (PANSS-N) subtype>15) were studied. Subjects had been kept at their current antipsychotic medication dose levels for at least a month before the study, which was continued unchanged throughout the trial. Over 6 weeks of selegiline treatment, subjects were divided into two groups, 39 patients received clozapine and while 41 patients received risperidone and each group was randomlydivided into three subgroups (for one group Selegiline 5 mg/day, for the second 10 mg/day, and for the third placebo was added to the regimen). Patients were assessed through and after 6 weeks by PANSS.
Results: Results: Eight subjects (5 patients in risperidone group and 3 patients in clozapine group) had significant increase in their positive symptoms and were excluded from the study and 4 patients could not continue the study because of severe side effects. Mean age of patients was 47.62 and mean duration of hospitalization was 8.94 years. In both clozapine and risperidone groups, No significant improvement was seen in three subgroups (Selegiline 5 mg/day, 10 mg/day, or placebo). (P=0.684 for risperidone and P=0.479) in clozapin subgroups) No significant difference between clozapine and risperidone groups was observed. (P=0.893).
Conclusions: Conclusions: Selegiline was not effective on negative symptoms of schizophrenia for inpatients. This inadequacy was true when seligiline was added to risperidone, or clozapine. Key Words: Selegiline, Schizophrenia, Negative symptoms.

P-06-011
The schizophrenia silent shout: The apathy

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Objectives: The schizophrenia scales are not designed to reflect a specific value of apathy, as the items for measuring these are sometimes from different subscales, with no solid specificity.Our goal was to measure the level of apathy in schizophrenia with specificity and clinical/statistical strong.
Methods: Twenty patients with schizophrenia, and receiving antipsychotic treatment, were assessed with the Apathy Inventory (IA), Test of Interest (TOI) and The Road test (Iniciative measure). Besides, SAPS, SANS, Calgary Scale Depression for Schizophrenia.
Results: Apathy was more highly associated with functional outcome than were other symptom measures, and it was independently associated with functional outcome above and beyond other negative symptoms.
Conclusions: The need to incorporate this discrete clinical symptomatical cluster in the clinical study of psychosis as its core, and consequently the clinical and functional monitoring in daily care for our patients.

P-06-012
Deficits in the inhibition of Gamma Oscillations in the Dorsolateral Prefrontal Cortex of patients with schizophrenia compared with Bipolar Disorder and healthy controls

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Objectives: Previous studies have shown that patients with schizophrenia (SCZ) and bipolar disorder (BD) have deficits in cortical inhibition (CI). Previously, CI could be measured through paired transcranial magnetic stimulation (TMS) of the motor cortex and recorded through surface electromyography (EMG). Through the combinations of interleaved TMS and electroencephalography (EEG), we have recently reported on methods in which CI can be measured from the dorsolateral prefrontal cortex (DLPFC), a cortical region that is more closely associated with the pathophysiology of SCZ and BD. Further, it is possible to index CI of specific cortical frequencies including the gamma (γ)-band (30-50Hz) frequency, whose modulation is suggested to be responsible for higher order cortical processing. In this study, therefore, we aimed to measure inhibition of γ oscillations (CIγ) in DLPFC in patients with SCZ compared with patients with BD and healthy subjects.
Methods: Long interval cortical inhibition (LICI) is a TMS paradigm that was used to index CI in the motor cortex and DLPFC.
Results: Patients with SCZ showed no deficits of CIγ in motor cortex (p=0.47) but significant deficits of CIγ in the DLPFC compared to healthy subjects (p=0.029) and patients with BD (p=0.029).
Conclusions: As inhibition of γ oscillations in the DLPFC may relate closely with higher order cognitive processing, these results suggest that in SCZ the lack of modulation of γ oscillations in the DLPFC may be a key perturbation of a neurophysiological mechanism that is responsible for frontal cognitive deficits in this disorder.

P-06-013
Implication of cryoglobulins in term of schizophrenia-associated immune system alterations

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Objectives: Several lines of evidence, including immunological and epidemiological, suggest a key role for upregulated immune response in the pathogenesis of schizophrenia, since alterations in both the innate and adaptive immunity were described in this pathology. However, the molecular pathomechanisms responsible for these alterations remain unclear. Cryoglobulins (Cgs) has been associated with a number of diseased conditions and considered as a nonspecific marker of the stimulation of the immune system, inflammation and autoimmune sensitization. Also Cgs may activate complement cascade that is a major effector system of innate immunity. This study aims to investigate of the quantitative and qualitative characteristics of Cgs in the blood of schizophrenia-affected subjects.
Methods: Eighty schizophrenic patients (55 medicated, 25 drug-free) and age, sex matched 40 healthy volunteers were recruited. Cgs were isolated by exposure of blood serum samples to precipitation at low temperature followed by extensive washings of Cg-enriched pellets. The immunochemical composition of Cgs was analyzed using different electrophoretic and immunoblotting systems. For data analyses Mann-Whitney U-test were applied and Spearman's rank correlation coefficient was calculated.
Results: The results obtained demonstrate the elevated levels of type III Cgs in the blood of schizophrenia-affected subjects as compared with healthy controls. Western blot analysis revealed the presence of key complement proteins and their activation products in Cgs isolated from the blood of schizophrenia-affected subjects. There were no significant differences in the levels of Cgs between medicated and drug-free schizophrenic patients, as well as significant correlation between serum levels of Cgs and clinical-demographic characteristics of the investigated subjects.
Conclusions: Our results suggest a possible role of Cgs in the pathogenesis of schizophrenia in term of schizophrenia-associated immune system alterations and linked aberrant apoptosis.

P-06-014
Recognition of positive and negative emotions in schizophrenic patients: A experimental paradigm with faces

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Objectives: In this exploratory study sought to observe whether the schizophrenic patients were able to make a paradigm attention modulated by spatial recognition with emotional stimuli, and showed a different pattern of responses for each condition.
Methods: In this study was used a simple task of spatial attention, which displayed faces with gestures (emotional, neutral and deictic gestures). During the task, persons had to give answers about the special localization of faces. Reaction time (RT) and accuracy of response (Acc) were registered.
Results: The main results show a different pattern of recognition between normal people and patients with schizophrenia. The axis of this difference is in negative emotions recognition where it was found a significant difference (p=0,01).
Conclusions: These results give an opportunity to gain comprehension about emotional substrate in schizophrenia, to generate a neurocognitive model and to think in new forms for treatments.

P-06-015
Atypical side effects of Antipsychotics – risk factor for noncompliance in first episode of schizophrenia

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Objectives: The correlation between the side effects of atypical antipsychotics (AA) and loss of compliance in the patients with first episode of schizophrenia.
Methods: 137 patients diagnosed with first episode of schizophrenia according DSM-IV criteria were treated with AA and they were somatic, biochemical and cardiac (ECG, BP, AV) assessed at baseline, 6 and 12 months.
Results: The sample was segregated in six groups of which patients number and mean dose of treatment are: 22 in amisulpride group (525 mg), 22 in aripiprazole group (23,75 mg), 23 in olanzapine group (13,15 mg), 24 in quetiapine group (573,25 mg), 23 in risperidone group (5,4 mg) and 23 in ziprasidone group (109,4 mg). After one year of treatment the most important side effect was weight gain caused by olanzapine (6,9 kg; 31%). Abnormal glucose level was observed only in olanzapine group (2,18%). High levels of prolactin were presented in risperidone (21,74%) and amisulpride (18,19%) groups. Hypotension was the most frequent cardiac side effect in quetiapine (54,17%), olanzapine (39,13%) and risperidone (30,44%) groups. Extrapyramidal side effects were only in 13,14% of all cases. The loss of compliance was correlated with weight gain (18,25%), clinical features of hiperprolactinemia (14,60%), extrapyramidal side effects (12%) and hypotension (6,57%).
Conclusions: Weight gain, clinical features of hiperprolactinemia and extrapyramidal side effects can be the principal reason of loss of compliance in first episode of schizophrenia during the first year of treatment with AA. The elevated values of cholesterol, glucose and triglyceride did not represent a reason for patient's loss of compliance but for psychiatrist they must represent a reason for therapy switching. It is important to acknowledge this not only in the acute treatment of schizophrenia but especially during maintenance and prophylactic treatment.

P-06-016
Cognitive impairment profile in schizophrenia

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Objectives: The longitudinal assessment of cognitive impairment in same patients who presented initials first psychotic episode (FE) and, after this, multi episode (ME) of schizophrenia treated with atypical antipsychotics (AA).

Methods: 39 patients (17 female, 12 male, average age 24,8 years) diagnosed initials with FE and after one year with schizophrenia according DSM-IV criteria were five years of psychiatric (PANSS,CGI-S, CGI-I) and neurocognitive (Trial Making Test A+B, Verbal Fluency Test, Rey's Auditory Verbal Learning Test) monitoring. In the first year all assessment were done on baseline, 6 and 12 months. After this period, the patients were neurocognitively assessed annually. Also, the patients were psychiatrically assessed when they presented relapses.
Results: In the first year of schizophrenia treatment there were no significant differences between type of antipsychotic treatment and the results of the neuropsychological test; no correlation between type of atypical antipsychotic treatment, intensity of symptoms (PANSS score), severity of disease (CGI-S) and neurocognitive results. For the patients who presented multi episodes of schizophrenia during 5 years we found a correlation between the severity of the illness and the number of episodes and the cognitive deterioration and no correlation with the type of schizophrenia or AA treatment.
Conclusions: There is no correlation between type of AA treatment and the course of cognitive functioning during the first years of treatment. The relative stable cognitive impairment in schizophrenia is correlated with a lower number and a reduced severity of relapsing episodes. The progressively deteriorating cognitive functioning is correlated with a higher number and severity of episodes.

P-06-017
Efficacy of aripiprazole vs quetiapine for the treatment of hostility in acute patients with schizophrenia

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Objectives: To compare the efficacy of aripiprazole and quetiapine in reducing hostility during the initial 7 days of treatment.
Methods: 32 acutely patients (14 female, 18 male, average age of 37.8 years) with chronic schizophrenia diagnosed according to DSM IV criteria were included based on their hostility factor score ≥ 20 derived from Positive and Negative Syndrome Scale (PANSS) and Clinical Global Impression-Severity (CGI-S) score ≥5. The sample was segregated in two groups according to antipsychotic treatment: quetiapine (17 patients) and aripiprazol (15 patients). The antipsychotic treatment was in flexibile doses (quetiapine up to 750mg/day; aripiprazole up to 30mg/day) which can be increased or decreased based on clinician judgment during the initials 7 days of treatment. It was permitted lorazepam,as rescue treatments, as needed to a maximum total dose of 4 mg/day. Efficacy measures were: mean change from baseline to end point in: PANSS–hostility factor, CGI-S and CGI-I scores. The safety measures were: mean change in Agitation Calmness Evolution Scale (ACES) score.
Results: 70.50% of quetiapine group compared to 60% of aripiprazole group completed 7 days treatment. The mean dose for aripiprazole group was 26,32 mg (SD 5.28) and for quetiapine group was 675.25 mg (SD 20.65). PANSS hostility factor, CGI-S and CGI-I measures showed the improvement of hostility by day 3, continuing up to end point for both group of treatment. There was a parallel reduction in hostility and agitation for both groups. The sedation was more frequent in quetiapine group (29.41% vs 13.33%) compared to aripiprazole group. By comparison to quetiapine group more patients in aripiprazole group received rescue lorazepam treatment (22,64% vs 37,22%).
Conclusions: Aripiprazole and quetiapine, despite their different receptor affinity profiles, decreased hostility and agitation rapidly and efficiently and had positive symptoms in acutely patients with schizophrenia during the initials 7 days of treatment.

P-06-018
Parametric variation in working memory demand in patients with schizophrenia: A behavioral and neuroimaging pilot study

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Objectives: Patients with schizophrenia exhibit serious and clinically relevant deficits in working memory (WM). However, investigations of WM in patients with schizophrenia using functional Magnetic Resonance Imaging (fMRI) have failed to reveal a consistent abnormality in brain activation in patients. One hypothesis is that patients exhibit a disordered relationship between the extent of activation of dorsolateral prefrontal cortex (DLPFC) and WM demand. However, existing WM tasks do not provide sufficiently fine-grained variation in WM demand to closely characterize the relationship between DLPFC activation and WM demand. Consequently, we have been developing a version of the self-ordering task that will allow for gradual increases in WM demand throughout a trial.
Methods: Ten patients with schizophrenia and nine matched control participants completed a behavioral version of the self-ordering task, and nine unmatched control participants completed the task while undergoing an fMRI scan. In each trial of the self-ordering task, participants are presented with 8 line drawings of 3D objects in a 3 x 3 array. On each step of the trial, participants must select any object that they have not previously selected. Thus, WM demand increases parametrically with each step of the trial.
Results: Both patients and controls performed the task significantly ($p < 0.05$) above chance accuracy from steps 3 through 8. Patients also performed significantly worse than controls ($p < 0.05$) from steps 3 through 8. The fMRI data indicate that healthy subjects increase activation of DLPFC as step number increases.
Conclusions: The self-ordering task is a valid means of assessing the effects of various levels of WM demand on DLPFC activation in functional imaging studies, and elicits substantial deficits in performance in patients with schizophrenia relative to control participants. This makes it a promising technique for elucidating the nature of WM deficits in patients with schizophrenia.

P-06-019
Disturbance of metacognition of agency in patients with schizophrenia

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Objectives: This study investigated metacognition of agency--people's assessments of when they were and were not in control--in patients with schizophrenia. Our central question was: Would the schizophrenics give evidence of consciously monitoring objective distortions in their control?
Methods: Patients were 22 medicated inpatients with DSM-IV-TR schizophrenia (mean age=42.3; 13 male) who were stabilized under treatment. Twenty controls with no history of psychiatric or neurological disorder were age and SES matched to patients (mean age=35.1; 11 male). Participants performed a task in which randomly positioned X's and O's scrolled down the computer screen. They moved a mouse to have an onscreen cursor touch the X's and avoid the O's. On some trials participants were, objectively, in perfect control: the cursor moved where they moved the mouse. On other trials computer-generated psuedo-random noise introduced Turbulence into the cursor movement, or the cursor position was Lagged 250-500ms from the mouse movements. At the end of each 20s trial participants made judgments of performance (JOPs) about the preceding trial, and assessments of how in control they had been, that is, judgments of agency (JOAs).

Results: Control participants' JOAs reflected the Turbulence and Lag manipulations, (F(1,19)=4.63, p=.001) indicating appropriate metacognition of agency (consistent with Metcalfe & Greene, 2007). In contrast, patient JOAs were insensitive to the Turbulence and Lag manipulations (F(1,21)=.10, p=.92). Both a mixed ANOVA (F(1,40)=4.56; p=.04) and a second-level multiple regression (t(40)=3.48; p=0.001) confirmed that the two groups differed on metacognition of agency.
Conclusions: The lack of monitoring of an objective loss of control indicates an impairment of metacognition of agency in patients with schizophrenia. This experimental finding is consistent with clinical observations of misattributions about the source of their own actions seen in patients with schizophrenia.

P-07
Psychotic Disorders II

P-07-001
Epileptic psychosis: A report of three cases

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Objectives: Patients with epilepsy have an increased risk of suffering from psychotic symptoms. Epileptic psychosis reflect a fundamental disruption in the fidelity of mind. The psychotic syndromes associated with epilepsy have generally been classified as preictal, ictal and postictal psychosis. The aim of this poster is to describe three cases of ictal, postictal and preictal epileptic psychoses.
Methods: We present three cases epileptic psychoses with a good response to antiepileptic treatment. Case 1. Preictal psychosis: A 42-year-old man with temporal lobe epilepsy who developed paranoid ideas and aggression against neighbours preceded his habitual seizure. It was repeated in three times before increased carbamazepine dosis (1200 mg /24h). Case 2. Ictal psychosis: A 50-year-old woman developed auditory hallucinations and persecutory delusions. An electroencephalography (EEG) study with left frontal lobe acute activity was obtained. After treatment with levetiracetam (2000mgr iv/ 24h) the patient was free of symptoms. Case 3. Postictal psychosis: A 39-year-old man with refractory temporal lobe epilepsy treated with left temporal lobectomy who developed a mystic and religious delusional picture 12 hours after of a focal complex seizure. The case had proper evolution after treatment with lamotrigine (500 mg /24h), levetiracetam (3000 mg/ 24h) and clonazepam (2 mg/ 24h).
Results: Our cases show some of the several risk factors known which may contribute to develop epileptic psychosis; such as temporal epilepsy, abnormal interictal electroencephalographic activity, history of encephalitis or status epilepticus, duration of epilepsy, family histories of psychiatric disorders or some anticonvulsant drugs. Nevertheless, the relationship between psychosis and epilepsy remains unclear and further research is needed.
Conclusions: It is important to recognize epileptic psychosis syndromes which respond readily to pharmacological treatment in order to avoid significant morbidity and mortality.

P-07-002
Enhanced cortisol suppression in response to dexamethasone administration in first episode psychosis patients

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Objectives: This study investigated hypothalamic-pituitary-adrenal (HPA) axis sensitivity in 18 first-episode psychosis (FEP) patients and 22 healthy controls using the low dose (0.25mg) Dexamethasone Suppression Test (DST).
Methods: Blood samples were obtained at 9:00 a.m. for the determination of baseline cortisol. Participants ingested 0.25mg of dexamethasone at 11:00 p.m. and blood samples were obtained at 9:00 a.m. the following day for determination of cortisol and dexamethasone. Suppression was defined as a cortisol level <5ug/dL.
Results: Six out of 18 (33%) FEP patients suppressed cortisol following ingestion of dexamethasone compared to two out of 22 (9%) healthy control participants ($\chi 2=3.37$; p=0.112). There was a moderate, positive correlation between childhood physical neglect and percent cortisol suppression within the FEP group (r=0.396; p=0.161).
Conclusions: These preliminary findings show for the first time that a subset of FEP patients display enhanced feedback inhibition of the HPA axis. Furthermore, enhanced suppression may be associated with childhood traumatic experience, such as physical neglect. Enhanced negative feedback of the HPA axis has also been described in patients with post-traumatic stress disorder (PTSD). Future studies should investigate the relationship between neuroendocrine dysfunction, prior exposure to childhood trauma, and development of PTSD symptoms in FEP patients using a larger sample size.

P-07-003
Inflammatory component in pathogenesis of schizophrenia and post-traumatic stress disorder

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Objectives: The present report overview our recent data on assessment of the involvement of deregulated immune response in pathogenesis of schizophrenia and post-traumatic stress disorder.
Methods: The research included large-scale studies of inflammatory mediators in the blood of drug-free patients affected with paranoid schizophrenia and post-traumatic stress disorder. Methodology was based on hemolytic assays, Western blot, ELISA, immunochemical assays and flow cytometry.
Results: In both diseased conditions marked changes in functional activity of the complement cascade, including its all three pathways, the classical, the alternative, and the lectin, have been detected. These changes associate with alterations in the levels of the complement components, C1q, C2, C3, and C4, expression patterns of the complement CR1 receptors on erythrocytes and leukocytes, and levels of different sub-populations of immune complexes.
Conclusions: The results obtained underline the important role of the inflammatory reactions in pathogeneses of psychiatric disorders.

P-07-004
Circadian melatonin rhythm in paranoid schizophrenic patients

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Objectives: Reported Melatonin (MLT) levels in schizophrenia are controversial. Our objective consists of studying daytime and nighttime MLT levels in a sample of schizophrenic patients.
Methods: The study was carried out in accordance with the Helsinki Declaration. All subjects or their families, in case of a transitory disability of the patient, signed the consent form before being included in the study. The sample comprises 43 patients with paranoid schizophrenia, meeting DSM-IV criteria, which were hospitalized in The University Hospital of the Canary Islands because of an acute exacerbation. The period of study was six months, from January to June 2006. At admission and at discharge, blood samples were drawn from the antecubital vein at 12:00 and 24:00 hours. MLT levels were determined by ELISA techniques. Clinical state was measured with the Clinical Global Impression scale (CGI) at admission and discharge. Psychometric evaluation was carried out by the same psychiatrist and biochemical analyses were performed by the same biochemist. MLT levels and the CGI results were contrasted with the t-Student statistics.

Results: The sample comprises by 33 women and 10 men, with mean age of 37.6±10.8. Comparison of diurnal and nocturnal MLT levels at admission reveals that there are significant differences (6.44±7.92 vs. 48.89±40.65, p<0.001) being nocturnal MLT levels higher than diurnal levels. At discharge this difference was significant too, persisting higher nocturnal MLT levels (6.86±9.74 vs. 49.98±40.10, p<0.001). CGI scores decreased significantly at discharge compared to CGIS scores at admission (4.4±0.8 vs. 3.0±0.7, p<0.001) showing a significant clinical improvement at discharge.
Conclusions: Patients in the acute episode of the disease present a circadian rhythm of MLT formation, showing a higher MLT nocturnal level than diurnal ones, this pattern persists when the patient is stabilized.

P-07-005
Do patients with auditory hallucinations have auditory processing deficits?

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Objectives: Recent studies have shown that patients with auditory hallucinations (AH) have significant affective prosody deficits. However, the potential contribution of auditory processing deficits to AH and affective prosody difficulties has not been investigated. This study aimed to investigate whether AH patients have auditory processing deficits using established auditory tasks focusing on pitch judgment, auditory streaming and affective prosodic identification.
Methods: A community sample meeting DSM-IV criteria for schizophrenia or schizoaffective disorder (18 with current AH, 11 with no significant history of AH (NAH)) and a matched healthy control group (n = 12) has completed the auditory tasks and measures assessing current psychiatric symptoms.
Results: An ANOVA on preliminary data has established that AH patients showed significant pitch judgment deficits. Mean accuracy scores for the three groups were as follows; AH 69.2% (SD = 12.2%), NAH 79.7% (SD = 9.1%), and Control 80.4% (SD = 10.0%; significance level p < 0.05). Analyses of all auditory task data will be presented in this paper.
Conclusions: Even at this preliminary stage of testing, our data supports the hypothesis that auditory processing deficits are part of the cognitive profile of AH patients. Analyses of the full data set will provide evidence on the extent to which bottom-up, perceptual anomalies contribute to the genesis of auditory hallucinations and affective prosody difficulties.

P-07-006
Environmental Supports Improve Negative Symptoms in Schizophrenia

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Objectives: Negative symptoms associated with schizophrenia include restricted affect, poverty of speech, decreased motivation, interests, emotional range, sense of purpose and social drive; all major contributors to lost productivity, poor quality of life, and generally poor outcomes. There is no sufficient evidence to recommend any pharmacologic agent for the treatment of negative symptoms in schizophrenia necessitating the investigation of psychosocial interventions in conjunction with pharmacology.
Methods: Our research group has used Cognitive Adaptation Training (CAT - a psychosocial treatment using environmental supports such as signs, checklists, alarms and the organization of belongings to bypass cognitive deficits and to cue and sequence adaptive behaviors in the home) to improve functional outcomes. During three studies totaling over 245 patients, subjects were randomized to CAT, an active control group, or standard care (TAU) for 9 months. Measures of negative symptoms were obtained each three months using the Negative Symptom Assessment (NSA) or a brief 4-item measure of negative symptoms.
Results: With respect to negative symptoms we found improvements in CAT relative to the other groups on the motivation factor of the NSA. This factor measures initiation, engagement in daily activities, interests and self-care. The average effect size was in the moderate range. Similarly in an effectiveness study with 100 participants, we found improvements on a brief negative symptom measure for those in CAT compared to the matched comparison group.
Conclusions: Results of these 3 studies provide evidence that CAT interventions may be effective for improving negative symptoms in schizophrenia. Negative symptoms are thought to be related to disruptions in ventral striatal reward systems. It is possible that by using external cues and environmental supports, CAT bypasses motivational systems typically needed to initiate behavior. A test of the efficacy of this intervention in a study of individuals specifically selected for persistent and clinically meaningful negative symptoms is necessary.

P-07-007
Reduced early auditory evoked gamma band response in patients with schizophrenia

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Objectives: There is growing evidence about abnormalities of certain GABAergic interneurons and their interaction with glutamatergic pyramidal cells in schizophrenia. These interneurons also appear to play an important role in the generation of neural activity in the gamma band (30–100 Hz) of the electroencephalogram (EEG). Synchronous high frequency gamma activity has been proposed to play an important role in integrating parallel neuronal activity and is now in the focus of research as a correlate of the interneuron dysfunction in schizophrenia. One example of such gamma oscillations is the early auditory evoked gamma band response (GBR). Although some studies showed alterations in auditory elicited gamma activity in patients with schizophrenia generally, so far there is no direct evidence providing a reduced early auditory evoked GBR. It was the aim of the present study to address two questions: (1) Is the early auditory evoked GBR decreased in schizophrenic patients? (2) Is this possible decrease a result of a reduced activity in the anterior cingulate cortex and/or the auditory cortex identified as sources of the GBR previously?
Methods: We investigated the early evoked GBR and its sources in the anterior cingulate and the auditory cortex in 90 medicated patients with schizophrenia and an age-, gender- and educational-level-matched healthy control group using an auditory reaction tasks.
Results: To our best knowledge, this is the first study reporting a significant reduction of the early auditory evoked GBR in schizophrenia (Z = 2.9; p = 0.004). In the LORETA analysis performed for the early evoked GBR, this effect was due to a reduced activity in the a priori defined regions of interest in the auditory cortex and the anterior cingulate cortex / medial frontal gyrus region in patients with schizophrenia.
Conclusions: These findings are in line with other reports of an impaired ability of schizophrenic patients in generating gamma activity and support the hypothesis of a disturbed GABAergic interneural modulation of pyramidal cells in schizophrenia.

P-07-008
Autoimmunity in bipolar and schizophrenic disorders

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Objectives: To study laboratory and clinical evidence of autoimmune disease in psychiatric patients with bipolar or schizophernic disorders
Methods: Screening for autoantibodies namely ANA, anti-DNAds antibodies, anti-thyroid antibodies in addition to other non specific laboratory tests (PCR, Sedimentation rate, VDRL, protein electrophoresis etc.) of psychiatric patients in inpatient and outpatient units
Results: The study is under way but has not yet been completed
Conclusions: Awaiting completion of study to determine conclusions

P-07-009
Single trial P3a/P3b deficits discriminate cognitive deficits in borderline personality disorder from schizophrenia

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Objectives: Both Borderline Personality Disorder (BPD) and schizophrenia have been associated with reduced P300 amplitude in the auditory oddball paradigm using conventionally averaged event related potentials (ERPs). However, P3a and P3b identification from single trial ERPs may allow a more comprehensive comparative analysis of the differences in cognitive deficits in BPD and schizophrenia. The aim of this study was to investigate the specifics of single trial P3a and P3b abnormalities in age and sex matched people with BPD, and schizophrenia in comparison with normal controls.
Methods: Electroencephalographic (EEG) data was acquired from age and sex matched people with BPD (N=17), schizophrenia (N=17) and normal controls (N=17) while performing an auditory oddball task. Late component ERPs were identified in single trial ERPs using a fragmentary decomposition (FD) method (Melkonian et al. 2003 Journal of Neuroscience Methods). P3a and P3b amplitudes were compared between groups using non-parametric statistics.
Results: P3a and P3b identification from single trial analysis revealed that the reduced P300 amplitude (conventionally averaged) in BPD was associated with increased P3a amplitude compared to controls and people with schizophrenia. This pattern was not found in people with schizophrenia where the P3a amplitude did not differ significantly from controls and BPD and the reduced P300 amplitude (conventionally averaged) reflected both fewer and reduced amplitude single trial peaks in P3b compared to controls and BPD.
Conclusions: These results indicate the value of single trial analysis in understanding the differing mechanisms underlying similar P300 amplitude deficits in these two clinical disorders. The increased P3a amplitude in BPD may reflect a disturbance in habituation to novelty, while the P3b deficits found in schizophrenia may reflect a failure to make use of context in information processing.

P-07-010
Electroconvulsive Therapy (ECT) in schizophrenia associated with violence: A case series

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Objectives: The Royal College of Psychiatrists (UK) recommends Electroconvulsive therapy (ECT) as fourth-line option while the National Institute of Clinical Excellence (NICE) guidance does not recommend use in treatment-resistant schizophrenia. Cochrane review evidence indicates ECT-antipsychotic combination as an option, particularly for rapid improvement and those with limited medication response. Our objective is to present a case series of patients with schizophrenia who responded to ECT in a forensic setting.
Methods: Five patients suffering from treatment-resistant, chronic schizophrenia and persistent & severe violent behaviour were managed with a combination of antipsychotics-ECT in a high-secure inpatient forensic setting (Broadmoor Hospital, UK) that manages patients deemed as posing the highest level of risk.
Results: 5 patients received ECT aged between 23 and 49 years old, with onset of illness between 15 and 20 years, and duration of illness between 8 to 30 years. All patients had diagnosis of schizophrenia and violent offences ranging from grievous bodily harm to homicide and persistent violence in a hospital setting. One patient was treated with Clozapine whilst others were managed on a combination of typical/atypical antipsychotics; and all the patients were treatment-resistant. All patients had sustained periods of improvement ranging from 10 months to 20 months following ECT characterised by improvement in psychotic symptoms and cessation of serious violence. Three patients received maintenance ECT treatment and the courses of ECT ranged between 1 and 4.
Conclusions: ECT, in combination with antipsychotics, can be a useful treatment option for a specific sub-group of schizophrenia characterised by treatment-resistance and persistent violence. However, a careful and considered decision-making process is equally important. In view of the lack of robust evidence (and the negative stigma) for ECT in schizophrenia (and in general), there is an urgent need to evaluate the efficacy of ECT in the difficult to treat patients of schizophrenia with a forensic history.

P-07-011
Latency classification of the frontal MMN responses to the pitch deviants in schizophrenic patients

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Objectives: The mismatch negativity (MMN) has been considered as a potential marker of schizophrenia, because of a reduction of the MMN amplitude in schizophrenics. However, MMN-latency effects are not clear.
Methods: A passive auditory oddball paradigm was applied to schizophrenics (N=67) and healthy subjects (N=55). Frontal response (Fz) was analyzed in the theta - low alpha frequency range The MMN-like components of the differential waveform were evaluated in the post-stimulus time period 50-250ms. In order to be classified, latencies of the negative peaks dEP were recalculated relative to four principal EP components of the correspondent "deviant" response (P30-50, N100, P150, N200).
Results: Three types of the negative dEP waves were identified: two types of 1-peak responses: N1-like (130-140ms), N2-like (170ms), and the 2-peaks responses with 1-st peak at 90-100ms and 2-nd peak at 180-200ms. The N1-like response was obtained in controls and patients with the same percentage (33 % vs 29%). The N2-like responses were obtained significantly more frequently in healthy subjects (47 % vs 19%), while the 2-peaks responses were obtained more frequently in patients (20% vs 52%). The schizophrenics had significantly lower peak dEP amplitudes only of the N1-like response. Latencies dEP were significantly prolonged in schizophrenics only in the 2-nd peak of the 2-peaks responses. In the contrary to the N1-like and 2-peaks responses, latency of the N2-like responses could not be linear predicted by the latencies of the response to deviant in both groups of subjects.
Conclusions: It is suggested that the three types of MMN-response (5-10Hz) defined are related to different types of cortical activity elicited in response to the pitch deviant stimuli and these differ in healthy subjects and schizophrenics.

P-07-012
Efficacy of haloperidol and quetiapine combination in refractory schizophrenia: A case report

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Objectives: To describe the long-term efficacy and safety of haloperidol and quetiapine combination.
Methods: We describe the case of a patient with refractory schizophrenia.
Results: Mr. A, a 30-year-old man, was diagnosed chronic paranoid schizophrenia in 1995. He had a history of psychotic disorder since age 15. The patient had been hospitalized on two occasions in 1195 and 1996. He has been treated with loxapine, risperidone and olanzapine, at therapeutic doses, without good response. Clozapine was not tried during hospitalizations because he had a history of specific phobia, blood-injection type. The patient was referred to our service in 2002, from his psychiatrist. During examination, the patient displayed bizarre delusions, persecutory ideas, auditory hallucinations and inappropriate affect. The patient was started haloperidol 15 mg and biperidine 6 mg and, then, increased to 30 mg with good response. Two months later, haloperidol decreased to 20 mg because of Parkinsonian side effects and he deteriorated. Ziprasidone and aripiprazole were tried in combination with haloperidol in an attempt to treat the patient's persisted bizarre delusions, but without significant response.

Ziprasidone and aripiprazole were discontinued and a low dose of quetiapine was started in combination with haloperidol 20 mg/day. The dose of quetiapine was increased to 300 mg in the morning, 200 mg in the noon and 500 mg in the evening. Within 4 weeks, the patient reported feeling much better, his auditory hallucinations had subsided, his affect had improved and he was no longer experiencing bizarre delusions. To date, the patient has been taking haloperidol 20 mg and quetiapine 1000 mg combination for 4 years and he continues to respond very well to his treatment in term of both efficacy and tolerability.
Conclusions: This case illustrates the efficacy of haloperidol and quetiapine combination treatment for refractory schizophrenia.

P-07-013
Gamma-interferon and interleukin-4 levels in the process of treatment of schizophrenic patients

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Objectives: Objectives: Aim of research was study of spontaneous and mitogen-induced production and concentration of serum gamma-interferon (γ-IFN) and IL-4 in dynamic of treatment of schizophrenics.
Methods: Methods: Spontaneous and mitogen-induced (phytogemagglutinin) production and serum concentration γ-IFN and IL-4 in entire blood have been studied in dynamic of treatment of 37 schizophrenic patients (1st point – during admission in hospital, 2nd point – by week 6 of appropriate treatment). Levels of γ-IFN and IL-4 were identified with sets for immune-enzyme analysis and counted with account for absolute number of mononuclear cells. Control group – 10 mentally and somatically healthy persons.
Results: Results: In 1st point spontaneous production and concentration of serum γ-IFN significantly exceeded values in control. In control group spontaneous production and serum γ-IFN were equal zero. In 1st point we have identified low level of mitogen-induced production of IL-4 as compared with control. Spontaneous production and serum concentration of IL-4 significantly exceeded values in control, because these indices in healthy persons were near zero. In the process of treatment level of spontaneous production of γ-IFN of patients increased by two times as compared with 1st point. Serum concentration of γ-IFN has a trend toward lowering in the process of the therapy. Mitogen-induced production of IL-4 increased: spontaneous by 1,2 times, induced by 1,8 times as compared with 1st point. Serum level of IL-4 lowered in the process of the therapy by 3,4 times.
Conclusions: Conclusions: It has been shown that schizophrenic process is accompanied by disturbances of production of γ-IFN and IL-4 by leukocytes of schizophrenic patients. Heightening serum level of γ-IFN and IL-4 testifies to activation of the immune system and enforcement of mediated Th2-cells of humoral immune response.

P-07-014
Substance use disorder comorbidity in Latinos with schizophrenia

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Objectives: The aims of this study were to estimate the frequency and course of substances use disorders in Latino patients with schizophrenia and to ascertain risk factors associated with substance use disorders.
Methods: We studied 518 subjects with schizophrenia recruited for a genetic study from the Southwest United States, Mexico, and Central America (Costa Rica and Guatemala). Subjects were assessed using structured interviews and a best estimate consensus process. Logistic regression, x2, t- test, Fisher's exact test, Yates' correction, as appropriate, were performed to assess the sociodemographic variables associated with dual diagnosis. We defined substance use disorder as either alcohol or substance abuse or dependence.
Results: Out of 518 patients with schizophrenia, 121 (23.4%) had substance use disorders. Comorbid substance use disorders were associated with male gender (88.4%, p: 0.001), resident in the USA, history of depressive syndrome or episode, and being unemployed. The rates of dual diagnosis among Latino patients were into the range of those reported in other countries. The substance most frequently used was alcohol either alone or with other substances.
Conclusions: This study provides data suggesting that depressive episode or syndrome, unemployment and male gender were factors associated with substance use disorder comorbidity in schizophrenia. Binary logistic regression showed that country of residence was associated with substance use disorder in schizophrenic patients. The percentage of subjects with Comorbid substance use disorders was higher in the Latinos living in the USA compared with subjects living in Central America and Mexico.

Characteristics	*Substance Use Disorder and schizophrenia*		*Schizophrenia only*		All Subjects	
Demographic characteristics	N	%	N	%		
Count	121	23.4	397	76.6	518	
Male	107	31.5	233	68.5	340	
Female	14	7.9	164	92.1	178	
	Mean	SD	Mean	SD	Mean	SD
Age at Interview	38.2	10.5	37.7	10.9	37.8	11.3
Years of education	9.1	3.6	8.9	3.8	8.9	3.8
Determinism *	3.2	0.8	3.1	0.9	3.1	0.8
Depressive Syndrome/Episode	N	%	N	%		
YES	64	52.9	161	40.5	225	43.4
NO	57	47.1	236	59.5	293	56.6
Living Situation *	N	%	N	%		
Alone	7	6.0	19	4.9	26	5.1
With family or other people	102	87.2	355	91.7	457	90.7
In residential treatment facility	3	2.5	10	2.6	13	2.6
Other	5	4.3	3	0.8	8	1.6

P-07-015
New-onset psychosis associated with HIV infection treated with HIV antiretroviral medications and inclusion of HIV medication in involuntary mental health treatment

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Objectives: New-onset psychosis associated with HIV infection has a prevalence varying between 0.23 and 15.2%. The psychosis is suggested to be secondary to HIV encephalopathy as it occurs in the later stages of HIV disease, is associated with cognitive impairment and is more likely in patients not taking antiretroviral therapy. This poster describes 4 cases of new-onset psychosis associated with HIV successfully treated by the addition of central nervous system (CNS) penetrating HIV antiretroviral therapy to antipsychotic medication.
Methods: Four cases of new-onset non-iatrogenic psychosis without delirium or current substance abuse in HIV positive patients and their management are described.
Results: All 4 patients had an onset of psychosis late in the course of their HIV illness and later in life than is usual with functional psychoses. All psychoses were associated with cognitive impairment of a pattern typically seen in HIV encephalopathy. The psychoses were initially successfully treated with antipsychotics. All patients were prescribed CNS penetrating antiretroviral therapy and cognitively improved. Antipsychotic treatment was successfully withdrawn after a number of months in the context of well-suppressed HIV virus without a recurrence of psychosis. In 2 patients a relapse of psychosis was associated with non-adherence to antiretroviral therapy. In 3 patients antiretrovirals were included in ongoing involuntary mental health treatment orders.
Conclusions: Optimal suppression of the HIV virus is important in the management of psychosis in HIV-positive patients. A HIV antiretroviral regimen with CNS penetrance should be part of the management of new-onset psychosis in HIV-positive patients and part of ongoing maintenance treatment - involuntarily if necessary.

P-07-016
The effect of cigarette smoking on prepulse inhibition and P50 suppression in Japanese patients with schizophrenia

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Objectives: The prevalence of cigarette smoking is known to be higher in patients with schizophrenia than general population. Though it is a serious problem for their health, some have suggested that smoking may be an attempt to self-medicate. To our knowledge, no group has investigated the effect of cigarette smoking in Asian patients with schizophrenia. This study investigated the effect of cigarette smoking on prepulse inhibition (PPI) and P50 suppression of startle response in Japanese patients with schizophrenia.
Methods: PPI and P50 suppression was assessed at baseline, after overnight smoking cessation and after smoking reinstatement in nicotine-dependant schizophrenics (n=15) and control smokers (n=15).
Results: PPI and P50 suppression were significantly smaller at baseline in patients with schizophrenia than controls. PPI and P50 suppression were reduced by overnight cessation, and the reduction by overnight cessation were improved after smoking reinstatement. However, smoking cessation and reinstatement didn't alter PPI and P50 suppression in controls.
Conclusions: In Japanese patients with schizophrenia, cigarette smoking improved PPI and P50 suppression impaired by smoking cessation.

P-07-017
Influence of infections on schizophrenic patients

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Objectives: Increasing evidence supports infections as a risk factor for schizophrenia. Recent studies discuss the influence of viruses, bacteria and protozoans on the pathogenesis of psychiatric disorders. It is suggested that prenatal infections can cause schizophrenia later on. Buka et al showed that maternal exposure to herpes simplex virus is associated with an increased risk of psychoses among offspring. The findings may be explained by reactivated infections or an alteration of the immune status. Also postnatal exposure to infectious agents can provoke schizophrenia. So far, Chlamydophila infections represent the highest risk factor for schizophrenia. This study investigates the association between schizophrenia and infectious agents that can invade the brain parenchyma.
Methods: A total of 31 patients with schizophrenia and 30 healthy matched individuals were included. For each individual antibody titers of CMV, HSV, EBV, Chlamydia and Toxoplasma gondii were evaluated with ELISA. For statistical analysis we used Fisher's exact test and Mann-Whitney-U Tests.
Results: Significantly elevated antibody titer within the schizophrenic group were found for Chlamydia trachomatis (p=0.005) and herpes simplex virus (p=0.05). There was a tendency for higher antibody titers in the schizophrenic group for Toxoplasma gondii (p=0.09) and Epstein-Barr virus (p=0.08). Also a tendency for different positive antibody titers for infectious agents was present at the same time within the group of schizophrenic patients (p = 0.07).
Conclusions: The higher prevalence of infections within the schizophrenic group emphasized the important role of infectious agents in the pathogenesis of psychiatric disorders. Because none of these agents have been consistently linked with schizophrenia, one hypothesis is that infections could initiate schizophrenia either by direct brain lesions or by triggering an immune response. It still remains unclear whether these consequences are due to the infection or to the changes in the immune balance caused by the infection.

P-07-018
Types of transaction in the family as they are expressed in space arrangements and the habits in the house with schizophrenic

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Objectives: Aim of research was to study, quantitatively and qualitatively, the boundaries in the relations of members of families with member with diagnosis schizophrenia, in the context of their daily operation in the spaces of use and residence
Methods: A questionnaire, with the form of structured interview, created by the inquiring team was granted in three teams of 40 individuals, that examined in the outpatient service of Psychiatric department of General Hospital Athens "G.Gennimata's. a) In patients with diagnosis schizophrenia b)patients with emotional disorders c) Adults without psychiatric disturbance that arrived in the outpatient service for issuing of health certificate. The diagnoses were made according the ICD -10. The ages of the examinined were 20-44 years. The statistical analysis of data was made with the SPSS.
Results: Families with members with diagnosis schizophrenia and emotional disorders had vaguer boundaries b) In the team with diagnosis schizophrenia existed higher percentages, of lack of personal space, and personal objects or they did not define their personal space and objects, than the team with the emotional disorders and the team without psychiatric disturbances. c)Ta vague limits and the lack of personal space in the families with schizophrenic member existed during at the childhood and adolescence
Conclusions: This data can used for therapeutic interventions.

P-07-019
Antineuronal Antibodies in a schizophrenic patient and his family

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Objectives: We present a schizophrenic patient with various immunological diseases (Insulin Dependent Diabetes Mellitus (IDDM), autoimmune Thyroiditis, Psoriasis Vulgaris), who comes from a family with autoimmune diseases, with characteristic organ specific autoimmunity (Rheumatoid Arthritis). Because immunological parameters have been proposed to be involved in schizophrenic process, we search for antineuronal antibodies in the schizophrenic patient and other family members.
Methods: Western-Blot analysis of serum of the schizophrenic patient and other family members, with LAN 5 human Neuroblastoma cell line as source of antigen and also human CNS homogenates.
Results: There were antibodies detected to neuroblastoma proteins, molecular weight 20 to 150 kDa including bands at 30, 60 and 90 kDa approximately most of them co-migrating with human CNS proteins. There are differences between the family members and the schizophrenic patient which seems to have a unique antibody profile.
Conclusions: Immunological mechanisms may be involved in some patients with schizophrenia.

P-16
Psychotic Disorders III

P-16-001
Adjunctive Aripiprazole: A good strategy for Clozapine induced metabolic syndrome

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P-16-002
The effect of weight loss on obesity-related quality of life and body image in obese schizophrenic patients

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Objectives: The purpose of this study was to assess the effect of weight loss on obesity-related quality of life, emotional and physical well-being, and body image of the patients.
Methods: Total 51 patients were enrolled in a 12-week, randomized weight reduction program. Thirty-two patients were randomly assigned to an intervention group in which they received weight management program. Nineteen patients were allocated to a control group in which they received usual clinical inpatient treatments. Body weight, body mass index (BMI) and quality of life scales such as Short Form of Medical Outcome Study (SF-36), Korean version of Obesity-related Quality of Life Scale (KOQOL) and Korean version of Body Weight, Image and Self-Esteem Evaluation Questionnaire (B-WISE-K) were evaluated during 12-week period. All assessment were done at baseline, week 4, week 8 and week 12.
Results: Sixteen of 32 (50%) patients in intervention group and 12 of 19 (69.4%) patients in control group completed this study. We found significant differences in weight and BMI changes from baseline to endpoint between intervention and control groups. After completion of the weight management program, there were significant differences on the Physical Component Summary of SF-36, and total scores, Psychosocial Heath, Physical Health, and Diet on the KOQOL, and total scores of B-WISE-K between intervention and control group.
Conclusions: The results show that the weight reduction program was effective for weight loss in schizophrenic inpatients. In addition, weight loss might positively improve health-related and obesity-related quality of life, and weight-related body image in schizophrenic patients.

P-16-003
Hypersensitivity to MK-801 – induced hyperlocomotion in a neurodevelopmental model for schizophrenia: Reversal by antipsychotics

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Objectives: It is now well established that embryonic day 17 (E17) exposure to methylazoxymethanol (MAM) in the rat is a promising model for schizophrenia. Indeed, this model is with face validity, in particular for mimicking behavioural abnormalities and deficits in PFC network in a similar way to that seen in schizophrenia. The validation of this model as a predictive pharmacological screening tool has never been investigated before. In this study, we investigated for the first time the predictive validity of this model by testing the capacity of acute neuropleptic and second generation antipsychotics to reverse abnormal behaviours observed in MAM rats.
Methods: E17 MAM-exposed female rats were tested in spontaneous locomotor activity and MK-801-induced hyperactivity tests in an open-field at adulthood. In addition, the capacity of haloperidol, clozapine and risperidone to reverse both spontaneous hyperactivity and hypersensitivity to the locomotor activating effects of MK-801 observed in MAM rats was investigated.
Results: At adulthood, female MAM-exposed rats showed more pronounced spontaneous locomotor activity. They were also hypersensitive to the locomotor activating effects of MK-801 as well as to its adverse effects on locomotion. In addition, we found that all tested antipsychotics were able to reverse both spontaneous hyperlocomotion and hypersensibility to the locomotor activating effects of MK-801 observed in MAM rats.
Conclusions: E17 MAM-exposed rats showed more MK-801-induced hyperlocomotion, possibly due to developmental alteration of glutamatergic and/or dopaminergic systems in mesocortico-limbic circuitry. Both neuroleptic and second generation antipsychotics were effective in blocking this hyperactivity. Further validations are needed but these findings add to the heuristic value of this animal model, which may be useful in testing new therapies in schizophrenia.

P-16-004
Effects of olanzapine-treatment on cell mitotic activity in the hypothalamus and adipose tissue of mice

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Objectives: Olanzapine, an atypical antipsychotic drug, has been used to treat schizophrenia. Weight gain is one of the side effects of olanzapine treatment in schizophrenic patients. Mechanisms underlying the weight gain remain unclear. A recent study has shown that neurogenesis occurs in the hypothalamus in addition to the well known neurogenic regions such as the subventricular zone and the dentate gyrus of the hippocampus. These newborn neurons in the hypothalamus are involved in controlling body weight and energy metabolism. This study also demonstrated newborn oligodendrocytes in the hypothalamus. We hypothesized such newborn glial cells or glial progenitors in the hypothalamus might also be involved in controlling body weight.
Methods: Female C57BL/6J mice, 10 weeks of age, were fed with olanzapine or haloperidol mixed with food for 8 weeks and administered with BrdU (1mg/ml, p.o.) for subsequent 10 days. After the administration of BrdU, mice were sacrificed for histological examinations. Brains were cut with a cryostat and stained with anti-BrdU antibody using ABC kit and DAB. Double immunofluorescence labeling was performed to detect colocalization of BrdU with lineage markers for cell differentiation, such as Olig2, NG2, APC, NeuN, and GFAP.
Results: It was 6 weeks after olanzapine-treatment onset until body weight change of olanzapine-treated mice became greater than that of control mice. In this experimental condition, the number of BrdU-positive cells, which co-express glial cell marker, in the hypothalamus was significantly higher in olanzapine-treated mice than in haloperidol-treated mice or in control mice.
Conclusions: These results suggest that possible link between gliogenesis in the hypothalamus and weight gain by olanzapine-treatment. The adipose tissue of olanzapine-treated mice was increased to a greater extent than that of control mice. The sizes and numbers of adipocytes are now under investigation to assess the role of olanzapine.

P-16-005
A randomized controlled study of cognitive remediation in schizophrenia (RECOS: Cognitive Remediation in Schizophrenia vs CRT: Cognitive Remediation Therapy)

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Objectives: The RECOS Hospital Program for Clinical Research (PHRC), coordinated by Nicolas Franck, aims to validate the RECOS cognitive remediation program, developed by Pascal Vianin and designed to rehabilitate specific cognitive functions impaired in schizophrenia by proposing individual care specific to each patient. The program, which uses various exercises and specifically designed software, will be compared to the already validated Cognitive Remediation Therapy developed by Ann Delahunty and Til Wykes.

Methods: 2 comparative study groups of 140 stabilized patients with schizophrenia (DSM-IV) will be treated respectively by RECOS and CRT. The Behavioral Assessment of the Dysexecutive Syndrome (BADS) and other neuropsychological tasks will be carried out both prior to and immediately after treatment and then 6 months later. The program will also assess the effects of remediation on social life, by using the MRSS (Morning Rehabilitation Status Scale); self esteem with the Rosenberg self esteem scale; subjective cognitive complaints, using the SSTICS (Subjective Scale to Investigate Cognition in Schizophrenia); insight scale symptoms, using both the BPRS (Brief Psychiatric Rating Scale) and the PANSS (Positive and Negative Syndrome Scale). Statistical analysis of the results will include the Student t test, the khi-2 test and ANOVAS.
Results: Preliminary results will be presented. Also an attempt to link clinical symptoms, social insight assessments and the effect of cognitive remediation will be made.
Conclusions: The results are expected to show that the RECOS program can significantly reduce cognitive-related problems and help improve social behavior in schizophrenia. The design of this study could possibly determine the specificities of both programs, taking into account the symptom profiles of the patients.

P-16-006
Apathy and cognition in schizophrenia

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Objectives: Apathy is a common negative symptom in schizophrenia that has been associated with poor treatment outcome. The purpose of this study was to investigate the relationship between the level of apathy and other symptoms as well as neurocognitive deficits in schizophrenia
Methods: Twenty-nine patients with schizophrenia were assessed with the Apathy Evaluation Scale (AES). Positive, negative, and other symptoms of schizophrenia were assessed with the PANSS. Depressive symptoms were separately assessed with the Calgary Depression Scale for Schizophrenia (CDSS). Patients also underwent a neuropsychological battery assessing attention, verbal and visual memory, and executive functions. Mentalizing capacity was assessed with the Faux Pas Recognition Test. Correlations between clinical and neuropsychological variables were calculating using Spearman's rho.
Results: The mean score on AES was 47.04 (range 31-69, S.D. = 10.61). Apathy was associated with age (r = -0.481, p = 0.010) and duration of illness (r = -0.490, p = 0.008). AES score was not correlated with the PANSS subscale and total scores as well as the CDSS score. There was also no correlation between AES score and the scores on WAIS, Babcock Story Recall Test, Rey Auditory Verbal Learning Test, Rey Complex Figure Test, Stroop Test, Verbal Fluency Test, and Wisconsin Card Sorting Test. Apathy was correlated with low scores on Trail Making-A Test (r = 0.402, p = 0.047) as well as the Correct Rejection dimension of the Faux Pas Recognition Test (r = 0.514, p = 0.009).
Conclusions: Although preliminary, our findings support the hypothesis that apathy is a relatively separate syndrome in schizophrenia associated with deficits in specific cognitive domains, such as concentration, visuomotor processing, and mentalizing capacity.

P-16-007
Mentalizing and awareness of illness in schizophrenia

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Objectives: There is a substantial body of evidence that Theory of Mind (ToM), the ability to correctly interpret and predict the mental states of other people, is impaired in people with schizophrenia. The aim of the study was to investigate the relationship between mentalizing capacity and poor insight in schizophrenia.
Methods: Twenty-nine patients with schizophrenia were assessed with the Faux Pas Recognition Test (Faux Pas), a task for advanced ToM functioning. The Scale of Unawareness to Mental Disorder (SUMD) was used to assess the level of insight of the patients. Positive, negative, and other symptoms of schizophrenia were assessed with the PANSS. Patients also underwent a neuropsychological battery assessing attention, verbal and visual memory, and executive functions. Correlations between clinical and neuropsychological variables were calculating using Spearman's rho.
Results: There was no correlation between Faux Pas score and the PANSS subscales and total scores. Faux Pas scores – detection scale and total score – was correlated with "awareness of the response to medication" item of SUMD (r = -0.461, p =0.027, and r = -0.423, p = 0.039, respectively). There was no correlation between performance in Faux Pas and the remaining items of SUMD – awareness of having a mental disorder, awareness of social consequences, awareness and attribution of symptoms. Moreover, there was no correlation between the items of SUMD and the scores on WAIS, Babcock Story Recall Test, Rey Complex Figure Test, Trail Making Test, Stroop Test, Verbal Fluency Test, and Wisconsin Card Sorting Test.
Conclusions: Our results are consistent with a previous study that reported association between ToM deficits and poor insight in schizophrenia. Taking into account that insight and mentalizing are distinct phenomena, we can hypothesize that patients with impaired mantalizing capacity tend to underestimate their clinical improvement and thus the need of medication.

P-16-008
Effect of carbamazepine on behavioral troubles with schizophrene patient

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Objectives: the addition of carbamazepine to the neuroleptic treatment entailed the disappearance of the violence episodes among schizophrenics.
Methods: The authors report on the case of 4 schizophrenic patients treated in hospitalization at the Department of psychiatry of the CNHU of Cotonou, and who present paroxysmal episodes of violences in spite of a very well conducted neuroleptic treatment.
Results: carbamazepine is efficient on the paroxysmal unrests of behavior among schizophrenics
Conclusions: the addition of carbamazepine to the neuroleptic treatment entailed the disappearance of the violence episodes among schizophrénics,

P-16-009
Synaptosomal-associated protein (snap-25) polymorphisms and response to olanzapine in schizophrenia patients

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Objectives: Genetic factors may influence response to antipsychotic treatment in patients with schizophrenia. The synaptosomal-associated protein of 25 kDa (SNAP–25) gene may be an interesting candidate gene regarding clinical outcome with antipsychotics. SNAP–25 is a presynaptic plasma membrane protein and an integral component of the vesicle docking and fusion machinery mediating secretion of neurotransmitters. Muller et al. reported that Mn1I T/G, Tail T/C polymorphisms in the SNAP-25 gene were associated with both antipsychotic drug response and drug induced weight gain. We aimed to evaluate the association of SNAP-25 (Mn1I T/G and DdeII T/C) polymorphisms with response to olanzapine in our study.
Methods: Our study comprised 86 unrelated subjects who strictly met DSM-IV criteria for schizophrenia and all were of Turkish origin. Genetic analyses were performed and patients were evaluated with rating scales.
Results: When we compare the groups TT with TG+ GG patients with T/T genotype had better response to olanzapine for SANS scale in SNAP-25 Mn1I polymorphism. Also patients with TC+ CC genotype were responded better than patients with TT genotype for SNAP-25 DdeII polymorphism.

Conclusions: Despite the fact that significant associations between three variants (DdeII, MnlI, TaiI) of the 3-UTRregion of the SNAP-25 gene and schizophrenia could not be detected in a family based association study. Muller et al. reported that MnlI and TaiI polymorphisms (but not DdeI polymophism) were associated with response to olanzapine. Interestingly we found an association between SNAP-25 DdeII T/C polymorphism and response to olanzapine treatment. SNAP-25 gene polymorphisms might be related to antipsychotic response but further studies were needed.

P-16-010
Changes in oxy – hemoglobin during emotionally loaded shiritori task in schizophrenic patients evaluation by NIRS

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Objectives: Shiritori is popular cognitive task in Japan. In this study, we analyzed the Oxy-hemoglobin (Oxy-Hb) during the emotionally loaded Shiritori task in schizophrenic patients to study the characteristics of cognitive function in schizophrenic patients and the effects of affective stimuli.
Methods: Oxy-Hb was measured from 18 schizophrenic patients and age matched healthy paid volunteer. Written informed consent was taken from all subjects before study. The Ethics Committee of Kurume University approved this study. The changes in Oxy-Hb were observed using Hitachi EEG 4100 with 46 channels (left: 22 channels, right: 12 channels, front: 12 channels). In the present study, all subjects were asked "Please say a-i-u-e--o " when viewing the crying or smiling baby faces were used as rest condition, and were asked "Please continue Shiritori following me" when viewing the same baby faces as task condition. The grand averaged of Oxy-Hb from five times trial was taken for data.
Results: In schizophrenic patients, the increase in Oxy-Hb when viewing crying baby was significantly smaller than when viewing smiling baby in left recording channels. However, in healthy controls, the increase in Oxy-Hb when viewing crying baby was significantly larger than when viewing smiling baby in left recording channels. There was significant negative correlation between the negative symptom scores and the concentration of Oxy-Hb.
Conclusions: These results indicated that the cognitive function was influenced by affective stimulus. Schizophrenic patients cause mismatch for affective stimuli during cognitive performance. Changes in Oxy-Hb evaluated by NIRS during Shiritori task can be useful psycho-psysiological parameter of cognitive functions.

P-16-011
Characteristics of emotional charged P300 component in patients with schizophrenia: Comparison with healthy controls

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Objectives: We analyzed the P300 component of the emotional charged visual event-related potential in patients with schizophrenia and also performed LORETA analysis to study the characteristics of cognitive function in schizophrenic patients and the influences of affective stimuli.
Methods: The subjects were 40 patients (26.9±6.3 years) who had been diagnosed as having schizophrenia by 2 psychiatrists according to ICD-10. Written informed consent was taken from all subjects before study. The Ethics Committee of Kurume University approved this study. The visual event related-potential was measured using NeuroFax (Nihon Koden), and oddball tasks (target stimulation: photograph of crying or smiling baby face, non target stimulation: photograph of a neutral baby face) were used. Brain waves were recorded at 18 sites (F3, F4, C3, C4, P3, P4, O1, O2, F7, F8, T3, T4, T5, T6, Fz, Cz, Pz, and Oz). LORETA analysis was performed using the LORETA explorer by the paired t test. Positive and negative symptom scores (PANSS) were taken from all patients.
Results: There were no significant differences between the P300 amplitude for the crying face and for the smiling baby in schizophrenic patients. But, the P300 amplitude for the crying face was significantly larger than for the crying face in healthy controls. LORETA analysis demonstrated that there were significant differences between task and non-task in the activity at the medial frontal, the superior parietal lobe areas and amygdala in patients when viewing smiling baby. But, significant differences in the activity at the medial frontal, the superior parietal lobe areas and amygdala were obtained in controls when viewing crying baby.
Conclusions: Emotional charged visual event-related potential and LORETA analyses is useful psycho-physiological markers of cognitive dysfunction in schizophrenia, and it is important to diagnose such cognitive disorder secondarily and to determine the therapeutic strategy.

P-16-012
Omega-3 fatty acids reduce serum triglyceride levels in individuals at ultra-high risk for psychosis

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Objectives: Schizophrenia patients represent a patient population with a high prevalence of metabolic syndrome. The correlation between metabolic disturbances and schizophrenia has been consistently demonstrated in drug-naive patients with first-episode schizophrenia. Omega-3 polyunsaturated fatty acids (n3PUFA) have been shown to be an effective and well-tolerated treatment for dyslipidemia. Higher n3PUFA dose is associated with greater reductions in serum triglycerides (TGL). In a recent review, n3PUFA were demonstrated to be effective in reducing TGL by approximately 30% (mean baseline TGL value of 150-500 mg/dl). We aimed to investigate the effectiveness of n3FA in reducing TGL in a patient sample of young individuals at ultra-high risk (UHR) for psychosis.
Methods: 33 subjects (mean age 17.1, SD 2.4) meeting UHR criteria assessed with the CAARMS (Yung et al., 2005), received 1.2 g/day of n3PUFA (eicosapentanoic acid (EPA) and docosahexaenoic acid (DHA)) over a period of 12 weeks. Blood samples were taken at baseline (prior to the intake of n3PUFA), and at 12 weeks.
Results: Statistical analysis of the effect of n3PUFA on serum triglyceride levels (TGL) revealed a non-significant trend (mean=14.364, SD=42.891, p=0.063) of reduced TGL after a 12 week intake period. After splitting the group (median split at TGL=81 mg/dl), the effect in the high-TGL group was significant (mean=38.867, SD=47.038, p=0.006); in the low-TGL group no effect was shown.
Conclusions: This study demonstrated the effectiveness of n3PUFA in reducing triglycerides in individuals at ultra-high risk for psychosis. This patient group had no clinically significant hypertriglyceridemia at baseline, but was at risk of developing an illness highly associated with metabolic disturbances and cardiovascular risk. It has been demonstrated that n3PUFA are effective in preventing psychosis in UHR individuals; a relationship of the TGL-reducing effect to the etiology of psychosis merits further investigation.

P-16-013
Inspection time, intelligence and cognition in schizophrenia

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Objectives: Cognitive impairment is a core feature of schizophrenia, separate from psychotic symptoms of the illness and predictive of functional outcomes. Individuals with schizophrenia show deficits in a number of cognitive functions including attention, memory and executive functioning. The accurate assessment of and remediation of these deficits is an important issue, with implications for practice, research, treatment and rehabilitation. Some theorists suggest that cognitive deficits in schizophrenia are discrete. Others argue that they can be accounted for by a common underlying variable, speed of cognitive processing. The present study aimed to investigate whether the cognitive dysfunction associated with schizophrenia can be explained in terms of speed of information processing, measured with a brief visual Inspection Time task (IT).

Methods: Fourteen adults aged 29 to 56 years (mean age 41.3 years, S.D. 8.6) with a diagnosis of schizophrenia were assessed on an IT task, a concise measure of intelligence (IQ) and the Brief Assessment of Cognition in Schizophrenia (BACS). Data were analysed using Pearson product-moment correlation and standard multiple regression.
Results: There was a weak association between IT and IQ (r=-.04, p=0.89), whereas in healthy individuals, IT and IQ are more highly correlated (r=-0.5: Nettelbeck, 1987). IT and IQ accounted for a significant proportion of variance in overall BACS performance (adjusted R2 = .47), and that IT predicted BACS performance slightly better than IQ did. The contributions of IT and IQ to performance on the individual BACS subtests were also explored.
Conclusions: Our findings indicate that a deficit in cognitive processing efficiency is an important feature of cognitive impairment in schizophrenia, and that IT is a useful means of assessing cognitive dysfunction in people with this disorder.

P-16-014
Source monitoring seems to be more affected in paranoid than in non-paranoid schizophrenia

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Objectives: A specific deficit in source monitoring has been advanced as explanation in psychotic phenomena. However, contradictory results have been reported regarding the performance of source monitoring and the level o f positive symptomatology in schizophrenia.
Methods: In the present study, we contrasted with healthy male volunteers (n=50) two groups of remitted medicated male schizophrenics, simple (n=24) or paranoid (n=32) (based on DSM-IV criteria), all groups being equivalent in respect to usual demographic and clinical parameters.
Results: The status of their theory of mind – based on Gardner tasks (Marjoram et al., 2005) have been considered common to all types of schizophrenia (and independent from history of positive symptomatology), and have been found similarly affected in patients as compared with healthy subjects; the performance on source monitoring – based on Henquet et al., 2005, on the other hand, placed non-paranoid schizophrenics more closely to healthy volunteers than to paranoid schizophrenics.
Conclusions: Despite similar levels of neurocognitive deterioration as proved by the theory of mind performance it seems that source monitoring is specifically more affected in paranoid as opposed to non-paranoid schizophrenics. The results are finally interpreted in the frames of different neurocognitive theories of schizophrenia.

P-16-015
Translational modeling of the asenapine plasma concentration dopamine D2 receptor occupancy relationship in rats and humans

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Objectives: Asenapine is under development for the treatment of schizophrenia and bipolar disorder. Optimal antipsychotic efficacy of antipsychotics has been associated with dopamine D2 receptor occupancy levels in the range of 60%–80%. Here, we describe a pooled analysis of in vivo D2 occupancy in rats and humans; from this analysis, we determine the in vivo potency of asenapine using a single pharmacokinetic-pharmacodynamic (PK-PD) model, and then compare the in vivo potency of asenapine with its in vitro receptor affinity.
Methods: Asenapine plasma concentrations and D2 occupancy data were obtained after administration of asenapine to rats (0.003–0.3 mg/kg), healthy human volunteers (0.1 mg QD or 0.3 mg BID), and patients with schizophrenia (2.4–4.8 mg BID). Asenapine plasma concentrations resulting in 60% and 80% D2 occupancy were determined using the parameter estimates of an Emax model.
Results: Asenapine plasma concentrations producing 50% D2 occupancy were 0.58 ng/mL (range, 0.35–0.81 ng/mL) in rats and 0.66 ng/mL (range, 0.38–0.93 ng/mL) in humans (P=NS), which are comparable to the in vitro affinities of asenapine for the rat (pKi, 8.5) and the human (pKi, 8.9) D2 receptor. Asenapine plasma concentrations producing 60% and 80% D2 occupancy were 0.87 and 2.32 ng/mL, respectively, in rats, and 0.98 and 2.62 ng/mL in humans.
Conclusions: Asenapine plasma concentrations producing in vivo D2 occupancy in the range of 60%–80% are comparable in rats and humans, suggesting that, for asenapine, in vivo D2 occupancy in rats is a good predictor of D2 occupancy in humans. Further, the results of this analysis indicate that, for asenapine, PK-PD relationships for D2 occupancy can be translated from preclinical models to the clinical setting. This research was supported by Schering-Plough.

P-16-016
Aripiprazole and its human metabolite OPC14857 reduce, through a presynaptic mechanism, glutamate release in rat prefrontal cortex: Possible relevanceto neuroprotective interventions in Schizophrenia

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Objectives: Aripiprazole is a novel atypical antipsychotic drug with neuroprotective properties. As excessive glutamate release is now considered to be part of the pathophysiology of schizophrenia, the objective of this study was to investigate the effect of aripiprazole and its human metabolite OPC14857 on the release of endogenous glutamate
Methods: to use an in vitro assay system to investigate the effect of aripiprazole and its human metabolite OPC14857 on the release of endogenous glutamate from isolated nerve terminals (synaptosomes), freshly prepared from rat prefrontal cortex.
Results: Both aripiprazole and OPC13857 potently inhibited 4-aminopyridine (4-AP)-evoked glutamate release in a concentration-dependent manner. Inhibition of glutamate release by aripiprazole and OPC13857 was associated with a reduction of 4AP-evoked Na1 influx and depolarization, as well as downstream elevation of cytoplasmic free calcium concentration mediated via N- and P/Q-type voltage-dependent Ca21 channels (VDCCs). Release induced by direct Ca21 entry with Ca21 ionophore (ionomycin) was unaffected by aripiprazole or OPC13857, indicating that the inhibitory effect of aripiprazole or OPC13857 is not due to directly interfering with the release process at some point subsequent to Ca21 influx. In addition, the dopamine D2 receptor antagonist haloperidol and the 5-HT1A receptor antagonist WAY100635 all effectively blocked the aripiprazole or OPC13857-mediated inhibition of 4-AP-evoked glutamate release. Moreover, aripiprazole or OPC13857 modulation of 4-AP-evoked glutamate release appears to involve a protein kinase A (PKA) signaling cascade, insofar as pretreatment of synaptosomes with the PKA inhibitor H89 suppressed the inhibitory effect of aripiprazole or OPC13857.
Conclusions: Together, these results suggest that aripiprazole and its human metabolite OPC14857 inhibit glutamate release from rat prefrontocortical nerve terminals, likely by the activation of dopamine D2 and 5-HT1A receptors, which subsequently results in the reduction of nerve terminal excitability and downstream VDCC activation through a signaling cascade involving PKA. These actions of aripiprazole may contribute to its neuroprotective effect in excitotoxic injury.

P-16-017

Niacin sensitvity different in people at risk to develop psychosis and in first-episode schizophrenia patients

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Objectives: Attenuated flush response to local methylnicotinate (AMN, niacin) skin stimulation represents a well-established finding in schizophrenia. As deficient flush response relates most likely to an innate depletion of polyunsaturated fatty acids (PUFA) and disturbed prostaglandin formation, AMN challenge has been considered as possible endophenotype marker of disturbed membrane lipid repair/remodelling, occurring in schizophrenia. An important general criterion of endophenotype markers is their state-independency. Having previously observed a flush deficit only in first-episode (but much less pronounced in multi-episode) patients, we now assume a state dependency also during the transition to psychosis phase of disorder.
Methods: AMN (0.1M, 0.01M, 0.001M and 0.0001M) was applied to the skin of the volar forearm in 81 ultra high-risk (UHR) patients, 31 neuroleptic-naïve first-episode patients (FEP) and 31 healthy controls. Skin flushing was visually assessed in 5 min intervals over 20 min according to the well-established 7 point Berger-Rating Scale. Digital photographs (Nikon Coolpix) of skin response at all concentrations and measurement intervals were stored for later independent assessments and supervision. Data analysis was controlled for effects of demographic co-variates.
Results: Flush response in UHR subjects was significantly increased as compared to healthy controls. In contrast, flush response in FEP was significantly decreased as compared to controls and UHR subjects. There was no effect of gender but a significant effect of age on the intensity of skin response. However, age did not affect the group effects.
Conclusions: The results further support the "phasic", state-dependent character of AMN flush response and corroborate rather the idea of a process marker, than of an endophenotype marker. Due to the involvement of PUFA derivates in inflammation/immunomodulation, we consider the flush deficit as possible activity marker of inflammatory response, immunactivation and anti-oxidative defense.

P-16-018

Niacin sensivity, membrane fatty acids and phospholipase A2 activity: Associations in people at rist to develop psychosis

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Objectives: Attenuated flush response to local methylnicotinate (AMN, niacin) skin stimulation represents one of the most commonly replicated biological parameters in schizophrenia. As proposed by the "membrane lipid hypothesis", impaired skin response was related to a depletion of polyunsaturated fatty acids (PUFA) in cell membranes and disturbed prostaglandin formation. While some studies supported associations between niacin sensitivity and both, PUFA levels and Phospholipase A2 (PLA2) activity (key regulating enzyme of membrane remodelling and PUFA availability), others failed to show any associations. Assuming that processes leading to the flush deficit are active and changing during the at risk and initial acute state of disorder, we investigated niacin sensitivity, PUFA profiles and PLA2 activity simultaneously in ultra high-risk (UHR) subjects before and after transition to psychosis.
Methods: AMN (0.1M, 0.01M, 0.001M and 0.0001M) was applied to the forearm skin in 81 UHR patients (13 transitions/first follow-up year). Skin flushing was visually assessed in 5 min intervals over 20 min using the 7-point Berger-Rating-Scale. In all subjects PUFA in erythrocyte membranes were assessed using gas chromatography. Calcium-independent PLA2 activity was measured in blood serum using a fluorometric HPTLC-based assay.
Results: Significant associations were found between niacin skin flushing and those (n-6)-PUFA acting as prostaglandin precursors. Only levels of these PUFA were also correlated with PLA2 activity. During the transition to psychosis phase there was a shifting pattern of these associations.
Conclusions: Our results further support the "precursor deficiency assumption" of niacin subsensitivity in schizophrenia. PLA2 activity could be increased to compensate the membrane deficiency of special PUFA. Physiological functions of the lacking PUFA indicate an association with inflammatory/immunmodulatory processes. The changing result pattern pre and post transition to psychosis indicates a state dependency of the underlying pathophysiology.

P-16-019

Frontal lobes MRI-peculiarities and auto antibodies to nerve growth factor (NGF) in families of patients with schizophrenia

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Objectives: Analysis of interrelations between brain structures abnormalities and objective biological characteristics of ongoing disease process can help to discover the nature of neuropathology in schizophrenia. From this point of view impairment of frontal lobes and level of auto antibodies (AAb) to NGF in schizophrenia patients` families should be studied. Both these factors are involved in pathogenesis of schizophrenia
Methods: To study correlations between MRI-peculiarities of frontal lobes and AAb to FRN, 70 subjects were examined (19 patients with schizophrenia, 25 their first degree relatives and 26 controls matched by the age). 3 mm coronal T1-weighted 3D magnetic resonance images were acquired on a 0.5 Tesla magnet Tomikon S50, Bruker (Germany). Volumes of frontal lobes (total) were calculated. AAb level to FRN in the blood serum was estimated by the immunofermentative analysis.
Results: Decreasing of frontal lobes volume in patients with schizophrenia ($p=0.03$) and their relatives (tendency) in comparison with controls was demonstrated. Correlation between AAb level to FRN and frontal lobes volume was revealed only in patients (Spearman: $r= - 0.59$; $p<0.01$).
Conclusions: The data hypothesize that morphological abnormalities in patients with schizophrenia are being formed both as a predisposition and in the disease process which is accompanied by autoimmune component to nerve growth factor.

P-16-020

Schizophrenia-specific health-related quality of life: A conceptual framework for research and clinical assessments

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Objectives: Although recognized that health-related quality life (HRQOL) assessment in schizophrenia is the most relevant patient-reported outcome, it is still elusive how to organize it. This study is a part of an ongoing project aiming to develop directions for and a schizophrenia-specific measures that shall be used in research and clinical assessments. Here, it was provided a conceptual framework.
Methods: It was hypothesized that the concept of schizophrenia-specific HRQOL should be multidimensional, with domains interacting dynamically with each other. It was assumed further that there are domains perceived by the patients that affect HRQOL and those indicate on a level of HRQOL. Within different subdomains, the former should contain multiple causal variables and the later multiple effect indicators.
Results: Within one side of the framework, named the schizophrenia impact core, there are at least two domains influencing HRQOL as perceived by the patients – the schizophrenia and the treatment-specific one. The first would include the symptoms and signs of schizophrenia with impairment and disability (e.g. negative symptoms) and the second its treatments (e.g. side effects). On the other side, named the schizophrenia-related quality of life core, there are subjective and objective domains as perceived by the patients indicating on HRQOL. The subjective domains indicate on different aspects of well-being, while the objective on daily functioning. Additionally, the domains of importance are possible to differentiate as the being, belonging, and becoming ones. Between the cores, a dynamic relationship is considered.

Conclusions: Considering HRQOL in schizophrenia with two separated parts, the influencing and indicating one, it would be possible to assess it more comprehensively. This concept is now examined qualitatively to evaluate its characteristics and to discover the domains of importance, namely how people with schizophrenia perceived quality of life.

P-17
Psychotic Disorders IV

P-17-001
Psychological and neuropsychological similarities and discrepancies of triplets suffering from atypical schizophrenia

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Objectives: To compare findings from the psychological and neuropsychological assessment of a set of male triplets suffering from atypical schizophrenia.
Methods: Three male triplets had developed a symbiotic relationship by the end of high-school and manifested almost identical psychotic symptomatology at least 4 years before their admission for inpatient treatment at the age of 23. Their psychopathology comprised of trichotillomania in the context of an elaborate pseudo-philosophical world view that led them to grandiose self-perception, withdrawal, social isolation, decline in every aspect of functioning and, finally, physical aggressiveness. All three men also had G6PD deficiency and Gilbert syndrome. The neuropsychological assessment included: General Verbal and General Performance Ability, Executive Functions, Complex Attention Functions, Verbal Fluency, Motor Speed, Perceptual Organization, Visuospatial Constructional Ability, Visuospatial Memory, Verbal Learning and Verbal Memory. The psychological evaluation included the Minnesota Multiphasic Personality Inventory (MMPI) and the Eysenck Personality Questionnaire (EPQ).
Results: Verbal I.Q, Performance I.Q, Full Scale I.Q. and Verbal Memory were in the normal range for all three subjects. All three subjects showed impairment in Complex Attention Functions, one subject showed impairment in Executive Functions and one subject in Verbal Fluency and Visual Memory. In the EPQ all three subjects showed a low or medium degree in the personality dimensions of Extraversion, Psychotism and Neurotism. In the MMPI all three subjects showed psychopathological profiles.
Conclusions: In a set of triplets suffering from schizophrenia of a very similar psychopathological presentation, the majority of Neuropsychological and Psychological tests are found not to differ substantially among them, while Executive Functions, Verbal Fluency and Visual Memory were the main areas of difference.

P-17-002
Study of schizophrenia

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P-17-003
The impact of smoking on the schizophrenic relapses

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Objectives: Premisis: Nicotine has great affinity towards the nicotinic receptors alpha 7 (1.2) and the addiction and the general pleasure generated by legal or illegal drug consumption are in relation with the doping ways (3). Purpose: The assessment of smoking impact on the schizophrenia relapses on a lot of schizophrenic patients.
Methods: A random lot of 134 schizophrenic patients diagnosed according to CIM X have been observed according to the quantity of cigarettes smoked, association with other legal drugs, heredocollateral history, sex and somatic comorbidities.
Results: 53.7 % of the lot were smokers and 46.3% were non smokers. The relapses on time unit in smokers are more frequent than in non smokers. The schizophrenic patients who smoked before the onset of the illness experience significantly more relapses than the smokers who started smoking after the onset of the disease and than non smokers. Smokers who started smoking after the onset of the disease have less relapses than non smokers (p=0.0021). In regard to the quantity smoked, those under a packet a day have less relapses than non smokers (p=0.046). Those who smoke more than a packet a day have a higher number of relapses than the first two categories (p=0.022; 0.0462). On sexes, smoking men have more relapses than non smokers (p=0.045) and is the other way around for women (p=0.046).
Conclusions: 1. Men are negatively influenced while women, positively. 2. Starting smoking before the onset of the disease is a negative prognosis factor. 3. Smoking less than a packet is a positive prognosis factor, especially in women. 4. These tendencies remain even if the lot is compliant or noncompliant

P-17-004
Hypofrontality and the frontal-striata-thalamic pathway during varied attentional tasks in schizophrenia

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Objectives: Two separate cohorts of patients with schizophrenia and healthy controls were studied with fluorodeoxglucose (FDG) positron emission tomography (PET) to examine whether decreased activity in the frontal-striatal-thalamic pathway was present across disparate attentional activation tasks with known performance deficits in patients.
Methods: Nineteen unmedicated patients with schizophrenia (13 men and 6 women, mean age=30.1 years) and 38 healthy comparison subjects (24 men and 14 women, mean age=30.6 years) had FDG uptake while they performed the Flanker task, requiring attention to stimuli embedded in a background. Twenty-five different unmedicated patients with schizophrenia (20 men and 5 women, mean age=33.4 years) and 25 healthy comparison subjects (15 men and 10 women, mean age=35.6 years) performed the Startle-Blink task requiring judging of tones accompanied randomly by loud clicks.
Results: Patients with schizophrenia had significantly lower FDG uptake in the dorsolateral prefrontal cortex for both tasks and this was most marked for Brodmann area 44. Differential activity was also seen in the mediodorsal nucleus (MDN) of the thalamus, with patients showing lower FDG uptake than healthy controls in the ventral-most portion. No group differences were observed in the caudate nucleus.
Conclusions: These results suggest a broad attentional modulation deficit in schizophrenia involving the prefrontal-thalamic circuit.

P-17-005
Olanzapine orally disintegrating tablets cause no moresedation than standard tablets in a small outpatient sample

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Objectives: The aim of this short observational study was to investigate whether patients receiving olanzapine in a single daily dose feel more morning sedation than those receiving the same mgs in divided daily doses.
Methods: 28 outpatients (16 men 12 women) receiving Olanzapine were categorized in two groups: 1st orally disintegrating tablets 20mg once daily (n=11), and 2nd standard tablets in 3 times daily divided dose of 20mg (n=17). Patients were carefully selected not to be under any other neuroleptics, but those taking mood stabilizers (5), antidepressants (4) and anxiolytics (11), were eligible. They should be for at least 1 week in the above dose. Their diagnoses were schizophrenia (n= 20) and bipolar disorder in manic phase (n= 8). Mean age was 36.55 and the two groups did not differ significantly (t=2.78). BPRS scale was given at the evaluation time (mean 53.26) and the two groups' score did not differ significantly (t = 3.31). Morning sedation was checked (yes or no) after their own report. A total of 13 patients reported morning sedation.

Results: 7 patients out of 17 under standard tablets reported sedation, compared to 6 out of 11 under orally disintegrating tablets. This result proved not significant statistically (chi-square=0.47).
Conclusions: In our sample, Olanzapine orally disintegrating tablets once daily, cause no more sedation than ordinary tablets in divided doses.

P-17-006
Traumatic brain injury and secondary psychosis

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Objectives: Estimates suggest that approximately 10% of patients who have experienced a traumatic brain injury (TBI) go on to develop psychotic symptoms. These result in significant patient distress and disability, and can complicate broader aspects of rehabilitation, yet, our understanding of psychosis following TBI remains in its infancy. This poster reviews the current literature and summarises the common features of psychotic experiences following traumatic brain injury.
Methods: The literature on psychosis following TBI was reviewed.
Results: Existing literature indicates that the precise relationship between TBI and the presence of psychotic symptoms is extremely complex and perhaps individually unique; studies show a highly variable range of psychosis onset, progression and course. There is some suggestion that certain individuals may be at a higher risk of developing psychosis following TBI relative to others.
Conclusions: Symptom trends that are distinctive of psychosis secondary to TBI may indicate the potential for a separate diagnostic category. Identification of potential risk factors may aid the detection of those at a higher risk for psychosis and allow management strategies to be implemented early, prior to the onset of advanced symptoms.

P-17-007
Relation of 18F-fallypride binding potential and antipsychotic treatment response in patients with schizophrenia

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Objectives: While numerous antipsychotic medications are available to people with schizophrenia, their efficacy rates are limited to ~ 50-60%, highlighting the tremendous need for objective biomarkers that predict general and, most importantly, differential treatment response. Herein we report associations between the binding of a high-affinity D2/D3 dopamine PET ligand, 18F-fallypride, and subsequent response to antipsychotic therapy with ripseridone or aripiprazole in a pilot cohort of unmedicated subjects with schizophrenia. This is an early report of our efforts to characterize potential biomarkers predictive of antipsychotic treatment response.
Methods: We acquired 18F-fallypride PET images from 9 unmedicated patients (6 medication naïve) with schizophrenia. Dopamine D2/D3 receptor levels were measured as binding potential (BP). MRI images in standard Talairach position and segmented into gray and white matter were coregistered to fallypride images. A stereotaxic atlas of 40 Brodmann areas (BA) was applied, allowing calculation of BP in each BA. Subjects were then randomized into a 16 week double-blind aripiprazole or risperidone trial. Baseline vs. end-of-trial PANSS change scores were compared to BP values in an intent-to-treat analysis.
Results: 18F-fallypride BP in the parahippocampal gyrus (BA27 and 35), putamen and caudate had correlations above r=0.5 ($p<0.05$) with PANSS change scores (total plus positive, negative, and general subscale scores). Further, correlations above r=0.4 ($p<0.05$) were noted in related temporal areas 28 and 36, in orbitofrontal area 12, and in the medial dorsal nucleus of thalamus.
Conclusions: Dopamine receptor affinity and density estimated by BP appears to be an effective means to identify a testable biomarker associated with antipsychotic treatment response, particularly in temporal and subcortical regions of corticolimbic and corticostriatothalamic circuits previously implicated in the pathophysiology of schizophrenia. Clearly a larger sample is needed to extend these results, and importantly, to determine whether 18F-fallypride PET might constitute a biomarker predictive of differential treatment response to pharmacologically distinct antipsychotic drugs.

P-17-008
The effect of ketamine on behavior and quantitative EEG – an animal model of psychosis

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Objectives: Many quantitative EEG (QEEG) abnormalities have been described in schizophrenia e.g. increased power in delta and theta bands in frontal regions, decreased alpha power and increased beta power, decreased as well as increased EEG coherence. With respect to the glutamatergic hypothesis of schizophrenia, NMDA antagonists represent the most reliable pharmacological models of this disease. Thus in our experiments we have analyzed the behavioral action of ketamine in rats and its correlates in QEEG. We focused on changes in locomotion, prepulse inhibition (PPI) of acoustic startle reaction (ASR), and on EEG spectra and EEG coherence.
Methods: Locomotion and PPI were analyzed after ketamine 9 and 30 mg/kg i.p. (Ethovision and SR-Lab systems). In EEG experiments, rats were stereotacticaly implanted with 14 electrodes on the frontal, parietal and temporal cortices. EEG recordings were performed 7 days after surgery in conscious rats. After the first 10 minutes of baseline recording the rats were administered with ketamine 9 or 30 mg/kg i.p. and the EEG was recorded for another 30 min with a 21 channel amplifier (BrainScope). Artifact-free epochs were selected by visual inspection form the baseline records as were three temporal regions for each dose. The EEG power spectra and coherence were analyzed using Neuroguide Deluxe software v. 2.4.6. Each epoch after administration was compared to its corresponding baseline record.
Results: Ketamine 30 mg/kg significantly disrupted PPI in rats and there was a trend to increase locomotion. The lower dose of 9 mg/kg was without any effect. Ketamine in both doses led to a massive cortical excitation by means of an overall increase in absolute EEG power. Similarly, ketamine increased almost all coherences thorough the spectrum.
Conclusions: Our results indicate that ketamine induces significant alterations in QEEG. These are present even when no behavioral changes are observed, indicating a greater sensitivity to the method. This work is supported by projects CNS MSMT1M0517 and MZ 0PCP2005

P-17-009
Public mistrust of DNA biobank studies in Malaysia

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Objectives: For the past 25 years, scientists have been carrying out research to identify potential biomarkers for schizophrenia. However, this effort has been hampered by a lot of reasons, among which non-participation or non-compliance is one great hindrance. As in most designs of neuroscience study to identify and thus further develop chemical, biological or genetic markers, the collection of appropriate and sufficient samples often pose as a primary obstacle to overcome. While biological samples can be obtained with consent, in tandem with medical procedures from psychiatric patients, control samples being contributed on a voluntary basis can be a slow and painstaking effort. Therefore, in this study, the first stage in our investigation included the administration of questionnaires to reveal the reasons of non-participation as controls.

Methods: A total of 255 non-participants of both sexes responded, in which 12 of them went on further as to give their extra comments. Eleven reasons were suggested in the questionnaire to which four alternatives were to be chosen, given scores of 1 to 4. Mean and median scores were used in order to assess the relevance of each alternative, with the lower score indicating a higher relevance.
Results: The results showed that in most cases, the unwillingness to participate was due to perceived lack of information given to them about the study. The second reason for non-participation stemmed from the expectation of some sort of payment as a token of appreciation in return for their contribution of blood samples.
Conclusions: This part of study was able to dissect the public attitude in showing lack of enthusiasm to participate in a psychiatric study. This study further suggests the need for efficient public information and the importance of bioethical explanation pertaining to public participation as normal healthy controls in medical studies.

P-17-010
Where does evidence from new trials for schizophrenia fit with the existing evidence: A case of the Emperor's new clothes?

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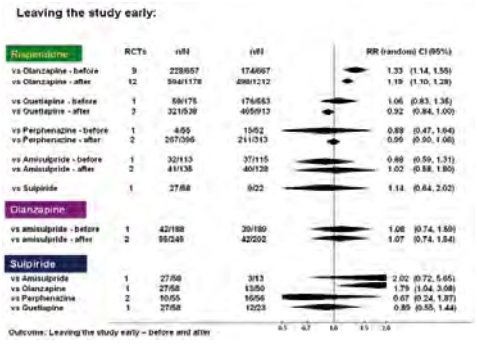
Objectives: To compare the evidence that existed for treatment of schizophrenia prior to 2005 with results from large scale pragmatic trials.
Methods: To compare the evidence that existed for treatment of schizophrenia prior to 2005 with results from large scale pragmatic trials.
Results: For the outcome of leaving the study early, data from the two new independent studies only increased precision and decreased the risk of Type II error. In no case did they materially change the impression already available from existing evidence. There were no differences between the antipsychotics for this outcome as noted in figure 1. The only place where this increase in precision seems powerful is in the comparison including perphenazine. This is because perphenazine has been largely ignored by the research community and the addition of CATIE's data hugely increases the precision. CUtLASS compared sulpiride with newer drugs and found no clear differences.
Conclusions: For the outcome of leaving the study early, data from the two new independent studies only increased precision and decreased the risk of Type II error. In no case did they materially change the impression already available from existing evidence. There were no differences between the antipsychotics for this outcome as noted in figure 1. The only place where this increase in precision seems powerful is in the comparison including perphenazine. This is because perphenazine has been largely ignored by the research community and the addition of CATIE's data hugely increases the precision. CUtLASS compared sulpiride with newer drugs and found no clear differences.



P-17-011
HPA axis functioning in schizophrenic patients

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Objectives: The aetiology and pathophysiology of schizophrenia are not yet known. Many reports describe neuroendocrine differences between groups of patients with schizophrenia and groups of control subjects. In the Diathesis-stress models of schizophrenia, the stress exposure is an environmental risk factor, in a pre-existing abnormality. Walker and Diforio (1997) in their review of the role of cortisol in schizophrenia established a causal role for cortisol in schizophrenia. This review examines the recent scientific findings on the role of the hypothalamic-pituitary-adrenal (HPA) axis related to schizophrenia.
Methods: review of the literature
Results: Hypothalamic- pituitary-adrenal (HPA) axis hipereactivity and larger pituitary volume had been demonstrated in schizophrenia. Therefore, the genetic risk for schizophrenia may seem to be characterized by an enhanced sensitivity to stress. In the same way, antipsychotic medication reduces HPA activation
Conclusions: In this review we explore and discuss the role of cortisol in schizophrenia as an etiological factor and pathophysiological factor.

P-17-012
Association between the leukemia inhibitory factor gene and schizophrenia and cognitive functions

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Objectives: Leukemia inhibitory factor (LIF) is a member of the interleukin(IL)-6 cytokine family, comprised of IL-6, oncostatin M, IL-11, ciliary neurotropic factor and cardiotropin-1, that signals via binding to a heterodimeric glycoprotein 130 / LIF receptor complex. LIF is known to regulate neuronal phenotype and coordinate the astrocyte, oligodendrocyte, microglia, and inflammatory cell responses. Many studies suggest that LIF is involved in neurobehavioral development. Recently, Watanabe et al. reported that the LIF-treated rats displayed decreased motor activity. In the present study, we investigated the association between the LIF gene and the patients with schizophrenia in a Japanese population. A possible association of the LIF gene with memory and intelligence in healthy subjects was also examined.
Methods: Subjects were comprised of 884 patients with schizophrenia and 923 age- and gender-matched healthy controls. We genotyped the three single nucleotide polymorphisms (rs929271, rs737812, rs929273) of the LIF gene with TaqMan technology on an ABI7500 system.
Results: We found an association in the frequency of the allele at rs929271 (P = 0.04). As to subcategories of schizophrenia, hebephrenic type, but not paranoid type schizophrenia was significant different from controls in genotype and allele distributions at rs929271 (genotype, P = 0.04; allele, P = 0.01), and in allele distribution at rs929273 (P = 0.02). At rs929271, we also found significant differences in Wisconsin Card Sorting Test total errors between those who carried the T-allele (carrier, T/T or T/G) and those who did not (non-carrier, G/G).
Conclusions: The present study suggested that the LIF gene associated with susceptibility to schizophrenia and cognitive function.

P-17-013
Neurocognitive deficits in schizophrenia measured by the Cambridge Neuropsychological Test Automated Battery

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Objectives: It is well known that severe cognitive deficits are present in schizophrenia and there is a wide variety of neuropsychological tests to measure these. In this study Cambridge Neuropsychological Test Automated Battery (CANTAB) was used to assess different aspects of cognition in 27 schizophrenic patients compared to the control sample of CANTAB.

Methods: Executive functions were measured by Intra-Extra Dimensional Set Shift (IED) and Stockings of Cambridge test (SOC). Delayed Matching to Sample (DMS) and Spatial Span test (SSP) were also carried out to assess visual and working memory capacity.
Results: Patients performed significantly worse than control population on all but two tasks. The errors related to perseveration of actions on IED signify deficits in rule learning and in the ability to react to the changing feedbacks. This may indicate that the flexibility of attention related to fronto-striatal areas are not working properly. The difference between the performance on frontal lobe sensitive SOC's Mean initial thinking time (P = 0,781) and Mean subsequent thinking time (P = 0,04) indicates that patients planned their moves as long as the control group did, but made significantly more steps to reach the sample arrangement. Weaker working memory performance on SSP and specific difference on DMS was observed: in the presence of visual sample while picking the exact match, their performance did not differ from the controls (P = 0,085), but a short delay between the sample and the possible matches resulted in worse scores (P<= 0,001). These sets of data referring to the deficit in the maintenance of visual information are related to the medial temporal lobe and frontal areas.
Conclusions: In conclusion, CANTAB is a sensitive indicator of the impairments in working memory capacity, planning actions, flexible thinking and visual memory of schizophrenic patients.

P-17-014
Auditory mismatch negativity deficits in long-term heavy cannabis users

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Objectives: Mismatch negativity (MMN) is an auditory event-related potential indicating auditory sensory memory and information processing. Deficient MMN generation is a robust finding in schizophrenia. Based on the close relationship between cannabis, the endogenous cannabinoid system and schizophrenia, the present study tested the hypothesis that chronic cannabis use may be associated with deficient MMN generation as well.
Methods: MMN was investigated in age- and gender-matched chronic cannabis users (n=30) and nonuser controls (n=30). The cannabis users were divided into two groups according to duration and quantity of cannabis consumption. The MMNs resulting from a pseudorandomized sequence of 2 x 900 auditory stimuli were recorded by 32 channel EEG. The standard stimuli were 1000 Hz, 80 dB SPL and 90 ms duration. The deviant stimuli differed in duration (50 ms) or frequency (1200 Hz). Statistical calculations were based on nonparametric tests.
Results: Chronic cannabis users showed reduced MMN amplitudes at central electrodes in the frequency deviance condition compared to controls. With regard to subgroups, reduced amplitudes of frequency MMN at frontocentral electrodes were found in long-term (≥ 8 years of use) and heavy (≥ 15 joints/week) users compared to short-term and light users.
Conclusions: The results indicate that chronic cannabis use may cause a specific impairment of auditory information processing, similar to the deficits observed in schizophrenia. Moreover, duration and quantity of cannabis use could be identified as important factors of deficient MMN generation.

P-17-015
The conscious mind and quantum mechanics

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Objectives: To propose an explanation about the possible mechanisms underlying the conscious experience in humans as a result of brain function, considering histological structure of brain tissue and using quantum mechanics as a reference frame.
Methods: Review of the literature concerning functional correlates of the conscious experience and an alternative explanation considering histology, electrophysiology and quantum mechanics.
Results: The gap junction unions between neurons could explain in part, the simultaneous processing information of different regions of the brain. This type of junction works like a cable delivering information at a very high speed. Nowadays is controversial the precise physiological mechanism underlying conscious experience and explanations not considering quantum mechanics may result insufficient.
Conclusions: Considering the characteristics of brain tissue, particularly the structure and function of gap junctions, and quantum mechanics, it is proposed a mechanism which explains how the brain process simultaneously information and how the conscious experience emerge.

P-17-016
Water poisoning with SCH patients in conjunction with psychotic perceptions

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Objectives: This case study is to point the attention of a doctor-psychiatrist to unpredictability of a clinical course of psychotic process.
Methods: The research paper introduces a patient who, as a part of his psychotic perceptions, drank a large quantity of water within a short time period.
Results: The patient (A. B. born in 1988) has been experiencing psychic difficulties since the age of fifteen, for which he was treated on several occasions under the diagnoses F23.0 and F20.1. Notwithstanding the regular check-up examinations and the prescribed therapy, the patient's mental condition deteriorated and included intense psychotic perceptions ("a fungus in his stomach which is growing and killing him") and within two hours time he consumed around 10 liters of water. Nausea, vomiting, uncontrolled twitches of the entire body, a series of epileptic attacks of grand mal type, as well as loss of consciousness ensued.
Conclusions: Despite the regular checkups and prescribed therapy, the patient had a worsening psychological status followed by intensive psychotic perceptions, where he consumed large quantities of water. It led to polymorphic-somatic problems, which ultimately might have led to patient's death.

P-17-017
Neuropsychological functioning and plasma levels of homocysteine in early - onset schizophrenia forensic patients compared with adult - onset - schizophrenia forensic patients and normal controls

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Objectives: The primary purpose of this preliminary study is to compare the profile and severity of cognitive impairments in white, Caucasian early onset schizophrenia patients (EOS defined as onset before the age of 18 years) with patients who received the schizophrenia diagnosis after the age of 20 years, who are treated in a forensic psychiatric hospital. A healthy control group was included, matched on age and education.
Methods: Neuropsychological testing was conducted using the CANTAB automated test battery (Stockings of Cambridge, SOC; Intra/Extradimensional Set Shift, IED; Simple Reaction Time, SRT; Paired Associates Learning, PAL, Stop Signal Task, SST) evaluating cognitive performance independently of language and culture. To allow for the use of premorbid IQ as a co-variable the Multiple Vocabulary Choice Test (Mehrfachwahl-Wortschatz-Test) was also employed. In addition plasma levels of homocysteine are currently under investigation.
Results: As expected, our preliminary data show, that normal controls (matched on age and education) had a better cognitive performance than schizophrenia forensic patients. On all tests patients were significantly poorer than controls. Moreover, EOS-patients showed significantly lower episodic memory, response inhibition and attentional set shifting performance than patients who received the schizophrenia diagnosis after the age of 20 years.

Conclusions: Early onset schizophrenia forensic patients are a very rare collective and their cognitive deficits are still not well investigated. This study demonstrates that early onset schizophrenia forensic patients may have more cognitive deficits than adult onset schizophrenia forensic patients. In addition plasma levels of homocysteine are currently under investigation. Because it is unclear, whether such deficits are stable (trait deficits) during the course of the illness or if they fluctuate (state deficits) a 3-month follow up will be carried out.

P-17-018
Preliminary study of ABO blood group distribution in schizophrenia

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Objectives: Blood grouping in modern haematology utilises ABO antigens to reflect genetic differences and is linked to the study of personality. Different blood groups account for the variation in individual personalities and are often associated to mental disorders. This study investigated possible relationship between blood group distributions amongst schizophrenic patients and their subtypes compared to healthy controls. The relationship between gender and schizophrenia was also studied.
Methods: A total of 489 schizophrenic subjects aged between 16 to 80 years were recruited from Ulu Kinta Mental Hospital, Malaysia, and subdivided into five different subtypes. Another 210 healthy control subjects were also recruited. Subjects were tested for their blood group, and differences in blood group distribution between schizophrenic and healthy subjects were estimated by Chi-square test with $P<0.05$ significance.
Results: To date, our preliminary results showed significant difference between schizophrenics and healthy controls in blood group distribution ($P=0.035$), and marked a significant higher incidence of blood group O in schizophrenics, suggesting blood type O individuals have higher risk of developing schizophrenia. However, analysis on sex ratio suggested that blood type A females have higher risk of schizophrenia, although the association was not statistically significant. Subdivision of subjects into the five subtypes showed no statistical significant trend.
Conclusions: The overall observations were encouraging, suggesting association of specific blood groups to schizophrenia. However, it is important to have a large sample size and equal ratio of male and female to ascertain the relevance of blood group distribution to schizophrenia.

P-17-019
Role of carotenoid level in schizophrenia

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Objectives: Free radicals are produced as part of the body immune response triggered by exogenous oxidants. In excess, they impaired antioxidant defense system and cause oxidative stress. Antioxidants are hypothesized in schizophrenia as antidotes to counteract oxidative stress and improve immune function. Carotenoids serve as reliable indicators of overall antioxidant level in human. This study investigated the possible relationship of carotenoid antioxidant levels and schizophrenia.
Methods: A total of 489 schizophrenic subjects were recruited from Ulu Kinta Mental Hospital, Malaysia and another 223 healthy control subjects were also recruited. Subject skin carotenoid levels were measured using a non-invasive technique, Raman spectroscopy, to detect the vibration energy of carotenoids in human skin.
Results: The results showed a reduced carotenoid level in patient compared to healthy control, indicating higher level of oxidative stress in schizophrenic patients. This is contributed by excessive free radicals generated from high neuronal activity in human brain, producing deleterious effects on signal transduction.
Conclusions: Further research on diet and smoking is needed to ascertain the relevance of antioxidant defense system to schizophrenia. This will provide theoretical bases for new strategy in the treatment of schizophrenia, such as antioxidant supplement.

P-25
Psychotic Disorders V

P-25-001
Reaction time to sound and light in schizophrenic patients and normal people

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Objectives: Based on clinical observations individuals with schizophrenia have deficits in a large number of functional domains, including social skills, social cognition, difficulties in perceiving, understanding, anticipating and reacting to social cues and deficient in social networks that are crucial for normal social interaction. (Yager and Ehmann, 2006). Disturbances and disorders in the domains are thought to explain impairments in social functioning that potentially have an direct link to social behavior, social function and interaction with others. In this field and for better and more understanding about schizophrenia, the study aims to investigate reaction time to stimuli in the field of light and sound attention and perception in schizophrenic patients and comparison with normal people.
Methods: Method of the research is experimental. 20 schizophrenic subjects were randomly selected from three psychiatric hospitals and compared with 20 normal subjects. An apparatus named Chronoscope was used to assess reaction time to light and sound stimuli. The apparatus assesses the light and sound stimuli in 0/001 seconds. Independent T test was used to analyze and compare means of schizophrenic subjects with normal subjects.
Results: Analysis of means showed differences between groups. Normal subjects were much more rapid in reaction and responding to light and sound than schizophrenic subjects.
Conclusions: Results indicated schizophrenics people with problems in mood,affect, emotion and depressed mood and temper are unable in rapid response to light and sound that lead to them low abilities and functions than normal group.

P-25-002
Reasons for adherence to antipsychotic treatment: The patient's perspective

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Objectives: To examine patient-reported attitudes toward antipsychotic medication and their relationship with clinical outcomes and adherence to pharmacotherapy.
Methods: The clinical development archive for olanzapine was examined for all studies with ≥50 patients and involving use of the Positive and Negative Syndrome Scale (PANSS) and Drug Attitude Inventory (DAI-10). Four randomized, double-blind studies were identified, which included adult patients (18–65 years) with DSM-IV schizophrenia, schizoaffective disorder, or schizophreniform disorder who were receiving randomly assigned treatment with olanzapine (5–20 mg/day), another antipsychotic (haloperidol, 2–20 mg/day; risperidone, 2–10 mg/day; ziprasidone, 80–160 mg/day), or placebo.
Results: Patient-reported improvements (DAI-10) were significantly greater for olanzapine ($n = 712$) than for the other treatments (haloperidol, $n = 145$; risperidone, $n = 158$; ziprasidone, $n = 271$; placebo, $n = 102$) on most of the DAI-10 items. For example, significantly fewer patients felt "weird" during olanzapine treatment than with haloperidol ($P = .025$) or ziprasidone ($P = .037$), significantly more reported feeling relaxed with olanzapine than with haloperidol ($P = .008$) or risperidone ($P = .046$), and significantly more patients receiving olanzapine considered their medication's benefits to outweigh its risks than was the case for risperidone ($P = .036$). Positive attitude toward medication reported by patients was associated with greater clinical improvement on the PANSS, as well as with lower discontinuation rates.
Conclusions: Patients' perceptions of treatment benefits can be associated with corresponding differences in objective clinical measures, including reduction of symptom severity and lower discontinuation rates. These findings may contribute to a better understanding of reasons for treatment adherence from patients' own perspectives.

P-25-003
Plasma homocysteine, folate and B12 levels in Tunisian patients with schizophrenia

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Objectives: We aimed to determine plasma homocysteine, folate and B12 levels in patients with schizophrenia and to investigate the association between homocysteine and clinical features of schizophrenia and its relationship with plasma folate and B12 levels.
Methods: It was a case-control study carried out on 61 (54 males and 7 females, mean age= 33.3 years) patients with chronic schizophrenia recruited in the psychiatry department in the University Hospital of Monastir (Tunisia) and 54 (25 males and 21 females, mean age= 45.9 years) healthy controls recruited from the blood bank in the same hospital. Total homocysteine levels were determined quantitatively by fluorescence-polarization immunoassay (FPIA). Differences between patients and controls were tested using an ANCOVA with gender and group as independent variables, adjusting for age.
Results: Patients with schizophrenia had higher plasma homocysteine and lower plasma folate than controls (respectively mean=16.1 µmol/l in cases versus 10.9 µmol/l in controls: p=0.028 for homocysteine and 8.2 ng/ml in cases versus 4.2 in controls: p<0.001 for folate). Patients and controls did not differ in B12 levels. Both male and female patients had increased plasma homocysteine compared to controls. In patients with schizophrenia, plasma homocysteine was not correlated with age and duration of illness and was not significantly differ between clinical sub-types and type of antipsychotic treatments. Moreover, plasma homocysteine was higher in patients without family history of psychiatric disorders (19.2 µmol/l) versus 12.7 µmol/l in patients with family history of psychiatric disorders (p=0.03). Finally, a negative correlation was found between plasma homocysteine and B12 levels (p=0.04).
Conclusions: These findings suggest that increase in plasma homocysteine in schizophrenia is not limited to young male patients and is associated with absence of family history of psychiatric disorders and with low B12 levels.

P-25-004
Niacin skin flush response in schizophrenia linked to soluble interleukin 2 receptor serum levels

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Objectives: Attenuated skin flush response to local methylnicotinate (niacin) stimulation represents a robust parameter in schizophrenia. There is also major evidence for involvement of immunological processes in schizophrenia. Skin response is mediated by vasodilatory prostaglandins. However, the underlying pathomechanism of attenuated skin flushing in schizophrenia is not clarified. We investigated possible correlations to the inflammation response system.
Methods: We present preliminary results of an ongoing study. Skin flush response to different niacin concentrations was assessed over 15 minutes by optical reflection spectroscopy. Serum concentration of different cytokines were measured by means of commercially available ELISAs. So far 10 persons (unmedicated schizophrenic patients and healthy controls) were included.
Results: We found a significant correlation of soluble interleukin 2 receptor (sIL-2R) and niacin skin flush response (R=0.84; p=0.002).
Conclusions: Reduction of sIL-2R may indicate an elsewhere proposed imbalance of TH-1/TH-2 immune responses in schizophrenia. Blunted flush response to niacin has been considered to reflect a dysfunction of prostaglandin-mediated processes. Since prostaglandins induce sIL-2R production, both, reduced sIL-2R serum concentration and correlated attenuated skin flushing in schizophrenia may be secondary to processes leading to a prostaglandin deficiency.

P-25-005
TH-1/TH - 2 cytokine imbalance more pronounced in neuroleptic - naïve first episode schizophrenia

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Objectives: There is major evidence for the involvement of immunological processes in the pathophysiology of the disorder. Especially alterations of T-cell function and activation of the inflammatory response system appear to be linked to schizophrenia. We investigated serum levels of TH1 and TH2 related cytokines in unmedicated schizophrenic patients.
Methods: We investigated 17 schizophrenic patients and 25 healthy controls. Subjects with medical history of chronic inflammatory or autoimmune disease were excluded from the study. To account for different stages of disorder we divided patients into first episode (FEP) and recurrent episode patients (REP) for subgroup analysis. All investigated patients were unmedicated at time of investigation and suffered an acute psychotic episode. First episode patients were naïve in terms of neuroleptic medication. Serum levels of following cytokines were measured by means of commercially available ELISAs: interleukine (IL)-2, sIL-2R, IL-4, IL-6, IL-13 and soluble intercellular adhesion molecule (sICAM)-1.
Results: We present preliminary results of an ongoing study. In patients we found increased IL-13 levels(p= 0.009) and decreased sICAM-1 levels (p= 0.03). The same constellation was found in FEP subgroup when compared to controls. Additionally, in FEP subgroup we found elevated IL-4 (p=0.02) and decreased sIL-2R (p=0.04).
Conclusions: The finding of decreased sICAM-1, a signalling molecule required for the activation of TH-1 helper cells and therefore a marker of the cellular immune system is in line with previous studies. Also, decreased sIL-2R in drug naïve FEP may refer to a relatively reduced TH-1 response. On the other hand there is an increase of TH-2 system cytokines IL-13 and IL-4 (latter only significant in FEP). Differences between patient groups may refer to stage of disorder but also to previous neurolepetic medication in REP. These findings support the hypothesis of a TH-1/TH-2 imbalance in schizophrenic patients, more pronounced in first episode patients.

P-25-006
Expressiveness and recognition of self-generated facial emotions are impaired in schizophrenia

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Objectives: Several studies demonstrate that patients with schizophrenia are impaired in the recognition of expressions and in facial expressiveness of emotions. The aim of our study was to demonstrate that the emotion recognition deficit is not specific to expressions produced by others and exists for self-generated expressions, to our knowledge there is no published report about those original conception of self-impaired recognition in schizophrenia.
Methods: Nineteen patients with schizophrenia (DSM-IV criteria) and nineteen non-patient comparison subjects were filmed while producing six facial expressions, either by imitation (watching facial photography) or by mime (reading contextual emotion). Two months later, each subject viewed his own films and was asked to rate the intensity and the nature of its expressions as well as the certainty of his answers. Films were also shown to twelve independant raters (in ecological conditions) who had to evaluate the same parameters as filmed subjects.
Results: Patient group was impaired for the recognition of their own expressions, whether they were mimed or imitated. Independent raters less recognised patients' expressions and rated their expressions as less intense than controls, which indicates a diminished capacity to imitate and mime expressions in schizophrenia. Moreover, patients were not fully aware of their deficits as they over-rated the intensity of their expressions and were sure of their answers even when they didn't recognise correctly their expressions.
Conclusions: Deficits in recognition of their own expressions can be a core symptom in schizophrenia.

P-25-007
Addition of aripiprazole improves antipsychotic-induced hyperprolactinemia and reverses amenorrhea: Two cases

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Objectives: Hyperprolactinemia is an important adverse effect of antipsychotic medication. From the second generation antipsychotics amisulpride, risperidone and paliperidone cause marked elevation in serum prolactin levels. Aripiprazole as an adjunctive treatment has been shown, though not consistently, to improve antipsychotic-induced hyperprolactinemia. A pharmacodynamic interaction at dopamine receptors has been proposed. Aripiprazole may bind to the dopamine receptor more robustly and act as a dopamine receptor agonist in an antipsychotic-induced hypodopaminergic state
Methods: We report two cases of successful treatment of risperidone- and amisulpride-induced hyperprolactinemia and amenorrhea by addition of aripiprazole. This strategy was chosen over administration of an adjunctive dopamine agonist or discontinuation of treatment and a switch to a different antipsychotic agent to avoid clinical deterioration.
Results: Case1: a 35-year-old schizophrenic woman, who was successfully treated for her third and very severe episode with 800mg of amisulpride and which was gradually reduced to 400mg after 6 months of treatment, developed amenorrhea. It was the patient's decision not to discontinue amisulpride as it was very effective for her psychiatric symptoms. Gradually 10mg of aripiprazole were added and after 12 weeks she regained menstruation and prolactin levels fell (50%). Case 2: a 30-year-old schizophrenic woman was effectively treated with risperidone 4.5mg, after two trials with other antipsychotics. She developed amenorrhea and aripiprazole 10mg was gradually added. After 13 weeks she regained menstruation and prolactin levels fell (65%).
Conclusions: Our subjects were clinically stable and there was a high potential risk for relapse due to their history. This led us to the addition of aripiprazole which successfully improved hyperprolactinemia. Treatment was safe and well-tolerated. Both patients regained their menstrual periods in more than 8 weeks, a time frame that was previously reported. It appears that aripiprazole is effective in normalizing prolactin in some patients and this could become a treatment of choice.

P-25-008
Fugue and aphonia as first and foremost presentations of a case of psychosis

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P-25-009
Self-other discrimination in schizophrenic patients

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Objectives: Self-face recognition has been suggested to be an indicator of higher-order self-awareness. Recent studies into the neuronal network indicate that the visual pathway of recognising one's own face differs from the one involved in recognising others. Self-face perception activates cortical areas that are also involved in other self-related tasks. These processes involve parietal and frontal regions mainly in the right hemisphere. It is assumed that self-face processing is dysfunctional in schizophrenia and this deficit could be related to altered self-awareness in schizophrenia. Here, we investigate how schizophrenic patients, whose self-awareness is compromised, differ in a self-other discrimination task from healthy subjects.
Methods: Our behavioural task consisted of videos where the own, a familiar or unfamiliar face transform into each other. The participants were instructed to press a button when they recognize the face the video is transforming into. We combined behavioural testing with EEG, expecting a deeper understanding of the neural network involved in self-recognition in patients.
Results: Behavoiural results indicate that schizophrenic patients differ less between self-other discrimination and other-other discrimination tasks. In contrast, healthy subjects show an advantage over patients to recognize faces during a self-other discrimination task compared to other-other discrimination. Notably, patients respond to more trials when their own face is included in the video, while they often do not even recognize that the video is changing during an other-other discrimination task. Further analyses will focus on differences between healthy subjects and schizophrenic patients in EEG activation in parietal regions. Given the known importance of inferior parietal lobule (IPL) function in self-awareness, it is predicted that IPL function is impaired in individuals with schizophrenia with altered self-awareness.
Conclusions: On a behavioural level, we could demonstrate that schizophrenic patients have problems with self-other discrimination tasks. How this is reflected in brain activation will be discussed.

P-25-010
Suicide attempts in schizophrenic patients

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Objectives: Approximately 10% of schizophrenic patients die by suicide. Decreasing suicide among patients who suffer mental diseases is a priority of the international mental health services.
Methods: Research took place at the Psychiatric Department of Asklepeion General Hospital of Voula in Athens, during the study of Liaison-Consultation Psychiatry cases of the last 20 years. 815 cases of complete suicide were examined of which 52 were diagnosed with schizophrenia (DSM-IV criteria). We investigated demographical risk factors such as: age, gender and marital status, as well as clinical factors such as: the presence of hallucinations, suicidal attempts in history, depressive disorders and alcoholism or alcohol abuse.
Results: In the general population most suicidal cases are over 40 years old, in contrast with the schizophrenic population where the age with the maximum suicidal risk is 20-30 years old. Thus, from the 52 schizophrenic suicide cases, 46 (88%) were between 20 and 39 years old and only 6 (12%) were over 40 years old. The schizophrenic suicide numbers differ between the sexes: 32 (61.54%) were males and 20 (39.46%) were females, 80% of females and 20% of males presented suicidal attempts in their history. The frequency of clinical risk factors was: 30 (57.7%) schizophrenic patients had attempted suicide in their history; 36 (69.23%) had comorbidity depressive disorders; 44 (84.61%) had hallucinations and in 40 (76.92%) cases the presence of alcohol was established at autopsy.
Conclusions: In reducing the risk of suicide in schizophrenic patients, we must reckon with the heterogeneity in predisposing mechanisms involved in suicide. The clinical risk factors had an important part in the suicidal behaviour of schizophrenic patients because these factors are not only predisposing mechanisms but can also be the cause of suicide.

P-25-011
A cognitive investigation of delusions: Are positive schizotypal symptoms associated with cognitive dysfunction and biases?

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Objectives: To date there has been no cognitive model to explain delusions independent of aetiology or phenomenological characteristics. This study investigated whether abnormalities in cognitive processes associated with delusions are independent of diagnosis and/or phenomenology by examining a nonclinical population with delusion proneness. We hypothesised that delusions are the consequence of poorly formed semantic memories and deficient emotion perception. This model was compared to others in the literature: reasoning, attributional bias and theory of mind (TOM) problems.

Methods: A community sample of people with high schizotypy (or delusion proneness; n=19) and low schizotypy (n=22) was recruited. Participants were given a task battery that included semantic memory, emotion perception, reasoning, attributional bias and TOM. Additionally, an assessment of symptoms, mood, levels of delusional thinking and general intelligence was undertaken. The data were analysed primarily with ANOVAs.
Results: The results supported the newly proposed model of delusions. While people with low schizotypy showed a decrease in reaction times to all emotions for the short stimulus presentation when compared to the long presentation, the high schizotypy group showed this decrease in reaction times to all emotions except for fear. For the emotion of fear, response times for people with high schizotypy were similar across the two stimulus presentation length. Additionally, accuracy levels for the emotion of anger were lower for people with high schizotypy. The high schizotypy group also showed greater levels of priming than those with low schizotypy on the semantic priming task for the longer stimulus onset asynchrony. No significant group differences were found on any of the other tasks.
Conclusions: Abnormal perceptual experiences and poorly formed semantic memories were related to unusual beliefs in a non-clinical sample. Further work in clinical samples is needed to examine the dependence of this model.

P-25-012
Serum proBDNF / BDNF ratio in patients with schizophrenia

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Objectives: Brain Derived Neurotrophic Factor (BDNF), a member of the family of neurotrophins (NTs), is central to many facets of CNS function. Several studies demonstrated that abnormal BDNF levels are involved in the pathophysiology of schizophrenia. Conversely, there are no studies investigating the role of BDNF's precursor (proBDNF) in humans. Indeed, proBDNF as well as the other pro-NTs is crucial in signalling pathways by interacting with the p75 neurotrophin receptor (p75NTR). Interestingly, proneurotrophins often have biological effects that oppose those of mature neurotrophins. Based on this evidence, we developed firstly an ELISA kit to quantify the proBDNF/BDNF ratio in human serum. Then we compared proBDNF/BDNF ratio between patients with schizophrenia and healthy controls.
Methods: 40 patients with a DSM-IV-TR diagnosis of schizophrenia and 40 aged and gender matched healthy volunteers were investigated. Total serum BDNF (ng/mL) was measured by using a specific ELISA kit (BDNF Emax imuunoassay system, Promega Co, USA). Subsequently western blotting was used to detect both mature and precursor form of BDNF. A two tailed statistical significance was set at $p<0.05$. A One-way ANOVA was conducted to detect the between group differences in total serum BDNF and proBDNF/BDNF.
Results: There were no statistically significant differences between patients with schizophrenia and healthy controls ($p=0.558$) in terms of total serum BDNF. Conversely, a significant reduction of serum proBDNF/BDNF ratio was found in patients with schizophrenia in comparison with healthy controls ($p<0.05$).
Conclusions: Firstly, this study demonstrated that proBDNF may be measured in human serum and that the proBDNF/BDNF ratio is altered in patients with schizophrenia. We hypothesized that abnormal proteolitic processes occurring in schizophrenia brains may lead to decreased proBDNF/BDNF ratio. We will further explore whether proBDNF/BDNF ratio correlates with cognitive performances; also we will investigate the effect of antipsychotics (typicals vs atypicals) on the serum proBDNF/BDNF ratio in patients with schizophrenia.

P-25-013
The efficacy of atypical and classical antipsychotic agents in the acute treatment of schizoaffective disorders

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Objectives: The aim of this research is to compare the efficasy of classical (CAP) and atypical antipsychotic (AAP) drugs in the acute treatment of schizoaffective disorders (SAD).
Methods: This prospective study enrolled 30 hospitalized patients of both sexes, aged 18-65 years, who met the criteria for SAD according to DSM-IV-R. The patients were treated with AAP or CAP along with mood-stabilizers. The efficasy of the therapy was evaluated using the Positive and Negative Syndrome Scale (PANSS) on 0., 7., 14. and 30. day of hospitalization. Statistical analysis was performed with application of Mann-Whitney Test, using SPSS 14.
Results: Analysis of difference in values at (0. – 30. day of treatment): PANSS-positive scale points out significantly higher difference in the group treated with AAP (mean17.70, Me = 17.00) in comparison with the group treated with CAP (mean 13.70, Me = 13.00) ($z= -3.419$, $p = 0.001$); PANSS-negative scale reveals significantly higher difference in the group of patients treated with AAP (mean 10.07, Me =8.50) in comparison with the group treated with CAP (mean 6.90, Me = 8.50) ($z= -1.853$, $p < 0.001$); PANSS-general psychopathology scale revealed significantly higher difference in the AAP group (mean 32.30, Me = 30.50) compared to the CAP group (mean 26.83, Me = 27.50) ($z= - 2.457$, $p <0.001$). Comparison of overall difference in values of the total PANSS score (0.-30. day) between AAP (mean 60.07, Me = 60.00) and CAP (mean 47.43, Me = 47.00) indicated high statistically significant difference in favor of the AAP group ($z = - 3.498$, $p < 0.001$).
Conclusions: Both, CAP and AAP are efficient in acute treatment of SAD but AAP revealed more rapid and more effective reduction of schizophrenic symptoms.

P-25-014
Neurobiological vulnerabitlity determinded by vascular factor in schizophrenia

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Objectives: The corellation of risk vascular factors with neurobiological vulnerability in schizophrenia with unfavorable evolution. There is few information about primar vascular factors in cortico-subcortical disconectivity or secondary factors induced by antipsychotics with hypotensor effect correlated with hypofrontal syndrome.
Methods: The retrospective study analize the risk factors for unfavorable evolution for 20 male patients, having the paranoid schizophrenia (DSM-IV), the age of onset over 18 years, the present age bellow 35 years, 10 years of illnes evolution and over 10 times hospitalized, presented importand cognitive impairment (CDR>1). All patients treated with medication with well-known hypotensor effect. At the cathamnestic time, we made transcranial doppler and CT evaluation.
Results: Possible correlation between hypofrontal syndrome and vascular factor at the level of anterior cerebral artery (ACA) and median cerebral artery (MCA) and unfavorable evolution:
- obstetrical trauma or cerebral hypoxia – 16 patients (80%)
- febrile seizure / irritative EEG – 8 patients (40%)
- following cortisonic therapy over 90 days in childhood – 7 patiens (35%)
- language and learning impairment – 14 patients (70%)
- EPS occured during antipsychotic therapy – 20 patients (100%)
- streptococical reccurent infections – 6 patients (30%)
- decrease of sanguine perfusion at the level of medial cerebral artery – 11 patients (55%), all these patients having frontal atrophy and important ventricular megalia releaved by CT;
- levomepromazine administered for a period longer than 7 years in a medium dose of 75mg/day (100%) – the neuroimaging is suggestive for the neuroaggresive role of hypotension.

Conclusions: The vascular factor in unfavorable evolution of schizophrenia can be suggested by: important cognitive impairment, obstetrical trauma, cerebral hypoxia, language and learning impairment, EPS, long-term treatment with medication with well-known hypotensor effect. The presence of these factors indicate also therapeutical resistance.

P-25-015
Neuroprotecion and cardioprotection for the antipsychotics with long - term action (animal model study)

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Objectives: The assesment of the neuro- and cardioprotective effect at the antipsychotics with long-term action on the animal mode (Common Winstar rat) may offer preliminary data on the treatment risks. The efficacy of the antipsychotics with long-term action therapy can be limited by the serious adverse events (cardiovascular, EPS, decrease of neuroprotection).
Methods: We studied on animal model (Common Wistar rats) using 3 antipsychotics with long-term action (haloperidole decanoate, flupentixol decanoate and rispolept consta). We formed 3 study lots and a control lot each constitued of 5 male adults rats, weighting 200-250 g, held through the study duration (14 days) in temperature, humidity, food and ambient stressless conditions. The studied substances were administrated intramuscular, in the 0- and 7-day, the equivalent to: N1 - haloperidole decanoate (0.50mg/kg/week), N2 - flupentixole decanoate (0.50mg/kg/week) and N3 - rispolept consta (0.50mg/kg/week). The study animals were sacrificed on the 15th day. We monitorized EPS and sudden death. The sample brain was histopathologically processed through specific colouring and fixation techniques and we evaluated the neuroprotection comparing the cytoarchitectural changes in frontal cortex, hippocamp, basal ganglia and cardiac tissue for cardioprotection.
Results: Important changes of the cytoarchitecture at the frontal cortex, dentate gyrus and the hippocampic zone (vacuolizations and pinocytosis) and important vascular changes (neoformation vessels, blood extravasation) were observed in N1 lot. The cytoarchitectural and vascular changes decrease at the N2 and N3 lot. At the cardiac tissue level we observed edema and vessels changes at N1 and N2 lot.
Conclusions: The decrease of neuro- and cardioprotection is important for haloperidole decanoate. Flupentixol decanoate may have a neuroprotector effect superior to haloperidole, but has a limited cardioprotection. Rispolept consta has a better neuro- and cardioprotection effect.

P-25-016
Negative symptoms in schizophrenia

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Objectives: Objetive: to analyze the evolution of the negative symptoms in patients with neuroleptic treatment
Methods: Methods the pursuit of 60 outpatients in attention took place, with the diagniose of paranioid schiziophrenia during one year. A clinical interview took place and it were administered the PANSS, every fifteen days at the beginning and each one month later. The interview were made by a psychiatrist, a psychologist and the same proffesinal carried out the pursuit of scales panss.
Results: Results it were observed that after a year 50% of the patients obtain an improuvement in the negative symptoms according to clinical examination and the PANSS. Patients were used aripiprazol, olanzapina, haloperidol and risperidone
Conclusions: Conclussion: negative symptoms of schizophrenia could improuved with neuroleptic treatment.

P-25-017
Assessment of risk factors in tardive dyskinesia

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Objectives: Tardive dyskinesia is a side effect that can lead to life-threatening problems for patients treated with neuroleptics and cause important medical, ethical and legal problems for physicians. Therefore, we aimed to assess the risk factors of tardive dyskinesia and evaluate prevention and early diagnosis strategies.
Methods: This study included 80 patients (50 psychiatric outpatients who had been using neuroleptics and had been followed-up at BakirkoyTraining and Research Hospital for Psychiatry, Neurology, Neurosurgery and 30 control patients who did not develop tardive dyskinesia despite a history of neuroleptic use for at least the previous three months). Sociodemographic and clinical characteristics were questioned via a form developed for this study. The Abnormal Involuntary Movement Scale was used to determine the presence and severity of dyskinetic movements, and cognitive ability was evaluated via the Standardized Mini-Mental State Examination (SMMSE). The results were compared with Student's t test, Mann Whitney U test, Chi-square and Fisher's exact test, and a p value of <0.05 was considered to be significant.
Results: The mean age of the dyskinesia group was significantly higher than the control group ($p<0.001$). A history of using depot (injectable) neuroleptics and a family history of psychiatric disorders were also significantly higher in the dyskinesia group ($p=0.049$ and $p=0.043$, respectively). Additionally, a significant difference was observed between the dyskinesia and control groups regarding the age of the first depot neuroleptic use (38.2 years and 27.8 years, respectively; $p=0.046$). The SMMSE scores were significantly higher in the control group ($p<0.001$).
Conclusions: Many risk factors influence the development of tardive dyskinesia. Since treatment options are limited, risk factors should be carefully assessed in the atypical neuroleptic treatment planning and early intervention is necessary.

P-25-018
Minor physical anomalies in schizophrenic and schizoaffective patients and non - psychiatric controls: Assessment of group - and sex - specific differences

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Objectives: Minor physical anomalies (MPAs) constantly show increased prevalence in schizophrenia subjects suggesting the presence of neurodevelopmental abnormalities that may be involved in the etiology of the disease. The role of sex in the incidence of MPA has not been well characterized.
Methods: We have investigated the differences in MPAs between groups and sexes. Several anthropometric measures of the head and face between schizophrenia and schizoaffective disorder patients (N=70) and non-psychiatric controls (N=46) were performed using modified Lane scale. Factor analysis has been applied to achieve data reduction, followed by analyses of variance and chi-square analyses in order to assess group and sex differences in our sample. Logistic regression analyses were performed to investigate the possible association between particular MPAs and PANSS subscales. Probability of $P<0.05$ was considered statistically significant.
Results: Significant group differences were found in horizontal and vertical facial asymmetries along midline, in all three facial arcs' measures, lobe attachment, and total MPA score. Sex differences revealed higher total MPA score in the male sex, and pointed to nasal features, frenulum, palate shape, and anterior hair margin variability. The presence of the particular MPA was also associated with illness severity in terms of PANSS negative sub-scale, general psychopathology, and total PANSS scores.

Conclusions: The results support the view of craniofacial MPAs being markers of the subtle brain abnormalities due to embryonic intimacy during development of the anterior face and brain, thus representing vulnerability for later development of psychotic disorders. Furthermore, significantly higher MPA score in males argue in favor of the higher proneness of the male sex to early embryonic maldevelopment.

P-25-019
Toluene exposure during adolescence produces long-lasting schizophrenia – like behaviors in mice

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Objectives: Abuse of toluene-containing volatile solvents by adolescents is a significant public health problem. However, the long-term behavioral consequences of toluene abuse during this key stage of development are not well established. The present study characterized the long-term behavioral and neurochemical consequences of toluene exposure during adolescence in young adult mice.
Methods: Male NMRI mice received one injection per day of either toluene (600 mg/kg) or oil during postnatal day (PN) 35-37 and (750 mg/kg) during PN38-39 and PN42-46. A variety of psychiatric disorder-relevant behavioral tests were examined at PN56-P84.
Results: The toluene-exposed mice were significantly deficient in the social interaction test, nesting behavior, social dominance tube test, and novel objective recognition test. However, toluene exposure did not affect locomotor activity and behavioral profiles in the forced swimming test, tail suspension test, emergence test and elevated plus maze. Neurochemically, the turnover rates of dopamine in the prefrontal cortex, striatum and nucleus accumbens were reduced in toluene-treated mice.
Conclusions: These results provide evidence to suggest that toluene exposure during adolescence is associated with long-lasting schizophrenic negative symptom-like behavors and cognitive impairment, as well as neurochemical dysfunction.

P-25-020
Effects of Risperdal Consta on psychosocial functioning in schizophrenia

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Objectives: Psychosocial functioning and its improvement is one of the main goals in schizophrenia treatment. The primary objective of this study is to compare patients on Riperdal Consta hospitalized in Mental Hospital to patient on Risperdal Consta who are users on Community Mental Health Center.
Methods: There were examined two groups of patients. The first group was 18 patients who are users of Community Mental Health Center, with diagnosis of schizophrenia and the second group was 18 patients hospitalized in Mental Hospital, with same diagnosis. The both groups of patient were treated with Risperdal Consta. On the both groups were applied BPRS (Brief Psychiatric Rating Scale) and GAFS (Global Assessment of Functioning Scale).
Results: The result showed differences in the psychosocial recovering between two groups. The results on the BPRS and GAF were lower (p>0, 01) in the first group of patients, treated in extra hospital conditions.
Conclusions: An extra hospital environment is significantly better supportive factor in the treatment in schizophrenia. The usage of Risperdal Consta and it combination with resocialization techniques, especially in extra hospital conditions is the treatment of choice in the present stage of knowledge.

P-35
Psychotic Disorders VI

P-35-001
Corpus callosum abnormalities in schizophrenia: Potential association to symptom cerebral substrate and age course of illness

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Objectives: Corpus Callosum (CC) size and interhemispheric communication have been found to be abnormal in schizophrenia.
Methods: We studied the CC morphology in schizophrenia patients (n=50) compared to healthy control subjects (n=50). Midsagittal CC linear and area MRI measurements were performed using a semi-automated segmentation approach subdividing the CC into seven segments. The study was restricted to right-handed male subjects, ageing 18-55 years. To investigate age-related differences, we stratified the two groups into age subgroups (18-25, 26-35, 36-45, 46-55). ANCOVA was performed to compare CC morphometric data among schizophrenia patients and healthy control subjects. One-way ANOVA and independent Student t test were performed to compare CC linear and area measurements among age subgroups (both in schizophrenia patients and healthy control subjects) plus, according to age subgroups, by diagnostic groups (schizophrenia vs control). Correlation analysis was finally performed to assess the relationship between CC morphology and variables such as age, age at onset, illness duration and psychopatology ratings.
Results: After controlling for midsagittal cortical brain area and age, ANCOVA revealed an overall effect of diagnosis on CC splenium width [F(2,96)=11,173, p=0,001] and CC anterior midbody area [F(2,96)=13,336, p<0,0001], and a diagnosis by age interaction [CC splenium width: F(2,96)=5,932, p=0,004; CC anterior midbody area: F(2,96)=5,662, p=0,005]. Independent Student t test revealed a smaller CC splenium width in the 36-45 age schizophrenia group compared with control (p=0,006), also with a smaller CC anterior midbody area in the 18-25 age schizophrenia group compared with control (p=0,006). Correlation analysis did not reach significance.
Conclusions: In line with previous reports, these findings suggest a significant difference in CC splenium and anterior midbody subregions in patients with schizophrenia compared with controls. They also suggest age-related differences in CC morphological changes among the two groups.

P-35-002
Factors associated with weight change in a 16-week randomized double-blind, double-dummy trial of sublingual orally disintegrating olanzapine vs. oral olanzapine in patients who gained weight during olanzapine treatment: The PLATYPUS Study

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Objectives: Weight gain has been very commonly reported during olanzapine treatment. Preliminary evidence suggests that patients treated with orally disintegrating olanzapine (ODO) may experience less weight gain than patients treated with standard olanzapine tablets (SOT). We report a post-hoc analysis of factors associated with weight change in the first double-blind comparison of weight gain in patients treated with SOT or ODO.
Methods: 149 patients with schizophrenia, bipolar disorder, and related psychotic disorders were randomly assigned to 16 weeks of treatment with either SOT plus orally disintegrating placebo, or ODO plus placebo tablets. To enter, patients must have either gained ≥5 kg or 1 kg/m2 increase in Body Mass Index (BMI) during olanzapine treatment over 1 to 12 months prior to study entry. Patients taking medications or having medical conditions that might impact weight control were excluded. Primary and secondary results are reported elsewhere. Factors examined included baseline BMI, pre-study weight gain on SOT, age, gender, duration of pre-study SOT treatment, appetite change, and Clinical Global Impressions (CGI) change.

Results: 115 patients completed the study. When baseline BMI was broken into subgroups of ≤25 kg/m2, between 25 and 30 kg/m2, and ≥30 kg/m2, the mean weight gain difference between ODO and SOT (ODO-SOT) was 0.26 kg, -1.06 kg, and -0.9 kg respectively. Further analysis is pending and results will be presented.
Conclusions: ODO may be a reasonable treatment option for some patients who gain weight with SOT. There may be subgroups that are more likely to benefit with less weight gain.

P-35-003
Disturbed prepulse inhibition in patients with schizophrenia is consequential to selective attention deficits

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Objectives: Prepulse inhibition (PPI) refers to the reduction in the magnitude of the startle reflex which occurs when a loud startling stimulus is preceded by a quieter non-startling stimulus (termed the prepulse). PPI has been shown to be decreased in patients with schizophrenia, which is suggested to reflect a deficit in 'sensorimotor gating', resulting from disrupted pre-attentive processing. However, recent studies have suggested that decreased PPI in patients may be secondary to deficits in selective attention. Thus, this study aimed to clarify the nature of PPI in schizophrenia using improved methodology.
Methods: PPI was measured in 44 patients with schizophrenia and 32 controls across a range of startling stimulus intensities, under two attention conditions, one whilst participants were attending to the auditory stimuli, and one whilst participants completed a visual task in order to ensure they were ignoring the auditory stimuli. Curves of best fit were fitted to the startle magnitudes, across the stimulus intensities, and a number of parameters were extracted from these logistic functions.
Results: Repeated Measures ANOVA, with planned pairwise comparisons, indicated that, relative to controls, patients with schizophrenia showed decreased PPI of RMAX (reflex capacity) ($p = 0.008$) and increased PPI of Hillslope (reflex efficiency) ($p = 0.023$) only when they were instructed to ignore the auditory stimuli and focus on the visual task. Furthermore, controls showed significant attentional modulation of all reflex parameters (RMAX, $p = 0.011$; ES50, $p= 0.015$; Threshold, $p= 0.002$; Hillslope, $p = 0.015$), but patients did not.
Conclusions: These findings suggest that disturbed PPI in patients with schizophrenia is secondary to deficits in selective attention, whereby patients are unable to ignore the distracting, attention-capturing auditory stimuli when instructed to do so. As such, disturbed PPI in schizophrenia appears not to result from a disruption to pre-attentive processing, but rather from dysfunctional top-down control of PPI.

P-35-004
Subjective experience with an antipsychotic treatment

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Objectives: Non-compliance of antipsychotic medication caused by distressing side effects of antipsychotics is a major problem in the treatment of schizophrenia, leading to relapses and frequent hospitalisations. Subjective well-being also interacts compliance and plays an important role in the quality of life of patients with schizophrenia. In our study we observed subjective well-being and quality of life of outpatients under the antipsychotic treatment in correlation with presence of side effects, seriousness of psychopatology and also with type of an antipsychotic treatment.
Methods: We examined 30 outpatients with schizophrenia. Severity of illness was measured by CGI-S and PANSS. Patients in remission fulfil consensus criteria of symptomatic remission (Andreasen et. al 2005). Presence of side effects of antipsychotics was considered by Structured Adverse Effects Rating Scale (SARS). Quality of life was measured by WHO-QOL-BREF, an attitude toward antipsychotic treatment was considered by Drug Attitude Inventory (DAI-30) and subjective well-being by Scale to Measure Subjective Well-being Under Neuroleptic Treatment (SWN, Naber 2005) Results were analysed with statistical programm SPSS.
Results: In scales DAI-30 and WHO-QOL there were not significant difference between patients in remission and patients with non-remission. The score of SWN was significant higher in remission group. Patients treated with atypical antipsychotics have higher SWN score than patients treated by conventional antipsychotics. Patients treated with atypical antipsychotics had significantly higher DAI-30 score. In the group with low PANSS score we have found statistical difference in SWN score, which is significantly higher than in the group with high PANSS score. The QOL score in group with low PANSS score is significantly higher than in the group with high PANSS score.
Conclusions: An measurement of subjective well-being of patients under the antipsychotic treatment is not only an academic problem, because it is one of the most important factors which directly interacts the final effect of treatment of schizophrenia.

P-35-005
Prepulse inhibition as a biological marker of at risk mental state of schizophrenia

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Objectives: Deficits in sensory gating as indexed by prepulse inhibition (PPI) of the acoustic startle response have been suggested as a potentially useful endophenotype for schizophrenia. Aim of this study is to clarify whether PPI abnormality is found in at risk mental state of schizophrenia (ARMS).
Methods: Sixteen ARMS subjects, diagnosed with comprehensive assessment of at risk mental state of Japanese version (CAARMS-J), were compared with 27 first-episode patients, 14 chronic patients and 43 healthy controls on the magnitude of startle habituation, startle-alone response, and inhibition of startle following a 60 or 120-ms prepulse. Cognitive functions were assessed using the Brief Assessment of Cognition in Schizophrenia (BACS) and treatment variables were recorded.
Results: Compared with healthy controls, ARMS subjects had significantly less PPI particularly with 120-ms prepulses, while first-episode subjects with both 60-ms and 120-ms prepulses, and chronic patients with 120-ms prepulses. Fifty four % of ARMS subjects and 77% of healthy controls were correctly classified by using PPI with 120-ms prepulses. There were not significant differences in startle reactivity and habituation among four groups. Mean composite Z-score of BACS in ARMS subjects and first-episode patients were -1.3 and -2.1, respectively, without significant difference. No significant correlation was found between PPI or BACS scores and medication dosages.
Conclusions: Current results suggest that sensory gating function is already impaired in ARMS subjects and that PPI may be a sensitive biological marker of early intervention.

P-35-006
Discriminant analysis in schizophrenia and healthy controls using prefrontal activation during frontal lobe tasks: A near-infrared spectroscopy study

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Objectives: While major psychiatric disorders such as schizophrenia are largely diagnosed on symptomatology, several studies have attempted to discriminates schizophrenia patients from non-schizophrenics using biomarkers. Studies using near-infrared spectroscopy (NIRS) to assess brain function have predominantly focused on prefrontal cortex function. We have evaluated prefrontal cortex activation related to five executive tasks in schizophrenia to assess the NIRS measurement as a suitable application for schizophrenia patients (SCH) and healthy controls (HC).

Methods: Sixty SCH and 60 HC underwent five frontal lobe tasks consisting of Verbal Fluency Test (VFT) letter, VFT category, Tower of Hanoi (TOH), Sternberg's Task and Stroop Task. We measured concentration change in oxygenated hemoglobin (⊿[oxy-Hb]) based on photon diffusion theory using 2ch NIRS during the frontal lobe tasks. SCH showed less prefrontal cortex activation and poorer task performance under some tasks than healthy subjects. We then applied discriminant function analysis using stepwise regression using ⊿[oxy-Hb] and task performance measures as independent variables. The first analysis was conducted to obtain the discriminant function which most correctly classified the original 30 HC and 30 SCH. A second analysis was then performed to prospectively validate the discriminant model by classifying a new cohort that consisted of 30 HC and 30 SCH.
Results: The better discriminant model was led by using not only task performances or ⊿[oxy-Hb] but both of them. The result was that 88.3% of the subjects were correctly classified by TOH and VFTs in the first analysis. When the discriminant function derived from the original cohort was applied to classify data from the second cohort, it correctly assigned 75% of the HC and SCH.
Conclusions: We showed the NIRS measurement could be acceptably applied to differentiate SCH from HC.

P-35-007
Mismatch negativity in schizophrenia and patients at risk

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Objectives: Recent studies have shown that the mismatch negativity (MMN), a change-related component of the auditory event-related potential (ERP) that can be understood as an index of automatic context-dependent information processing and sensory auditory memory, is altered in different clinical populations. The objective of our study was to display the magnitude of this deviation in dependency of the stage of schizophrenic illness.
Methods: We used an auditory oddball paradigm in combination with a visual vigilance control task. Control probands (n = 97) had no history of psychiatric disorders. Schizophrenia patients (n = 99) were inpatients of the UHC meeting the DSM-IV criteria for first-episode schizophrenia. Subjects in a putative prodromal stage of illness (n = 140) were outpatients of the Early Recognition Centre of the UHC meeting the criteria of BSABS and SPI-A. EEG acquisition used Cz as reference electrode (250 Hz sampling rate, < 5 kΩ of impedance). Stimuli were randomly presented via headphones. Off-line data were computed to a linked mastoid reference. Differences in the MMN amplitude between groups were tested by analysis of variance (ANOVA).
Results: We found significant differences between groups of control subjects, at risk and schizophrenia patients independent of medication ($p < .05$). Patients in early prodromal stages showed no significant differences from control subjects but in patients in late prodromal stages the MMN amplitude was significantly reduced ($p < .05$). We did not observe differences between controls and patients without later transition to schizophrenia. Prodromal patients with later transition to psychosis and first-episode schizophrenia patients showed a significant MMN amplitude reduction compared to controls ($p < .05$).
Conclusions: Our results suggest that the deviance of MMN indexes the stage of illness. The decrease of the MMN amplitude in late prodromal and first-episode stages seems to reflect the stage-dependent advance of a basal sensory information processing deficit underlying schizophrenia.

P-35-008
Hepatitis B in schizophrenia: Prevalence and comparison with healthy controls

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Objectives: Patients with severe mental illness are at higher risk of contracting blood born infections. In fact, Hepatitis B rates, for example, were estimated at five times fold among these patients compared to general population. However, prevalence of hepatitis B infection was not fully investigated in schizophrenia. The aim of this study was to assess the prevalence of Hepatitis B infection among Tunisian schizophrenic patients.
Methods: Over a period of 12 months, sera samples from sixty-nine patients meeting DSM-IV criteria of schizophrenia were analysed for the presence of Hepatitis B surface antigen (HBs Ag) by enzyme-linked immunosorbent assays (ELISA) commercial kits and controlled with automated microparticle enzyme (MEIA;AXSYM® HCV version 3.0, Abbott Laboratories). As controls, we used sera samples from 69 healthy blood donors, with matched age and sex.
Results: The prevalence of Hepatitis B infection in schizophrenic patients was 5.8% (N=4), whereas it was 2.9% (N=2) in healthy controls, without statistically significant difference. Nevertheless, we noticed that all of four seropositif patients were male and had a history of substance abuse and only one of them reported having irregular and multiple sexual partners.
Conclusions: Although the high prevalence of risk behaviours among schizophrenic patients indicates that they constitute a high-risk group for Hepatitis B infection, our data showed no association between Hepatitis B infection and schizophrenia.

P-35-009
Cariprazine (RGH-188), a potential antipsychotic with Dopamine D3/D2 functional antagonist properties, attenuates manic-like behaviors in animal models

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Objectives: Effects of cariprazine, a potent dopamine (DA) D3/D2 functional antagonist with "DA system stabilizing" activity being developed for the treatment of schizophrenia and bipolar mania, were evaluated on manic-like behavior in animals using the ouabain- (rats) and amphetamine/chlordiazepoxide (CDP)-induced hyperactivity models (mice).
Methods: In rats, IP cariprazine 0.06, 0.25, 0.5, or 1.0 mg/kg, IP lithium 6.75 mEq/kg (positive control), or IP artificial cerebrospinal fluid/saline (negative control) was administered 1 hour before intracerebroventricular injection of ouabain 5 µL 10-3 M. In mice, PO cariprazine 0.03, 0.10, or 0.30 mg/kg (60-min pretreatment), IP valproate 400 mg/kg (positive control; 30-min pretreatment), or water were administered before IP injection of amphetamine/CDP or water. Open-field activity assessment began immediately following administration of ouabain or amphetamine/CDP (assessment period: rats, 30 min; mice, 60 min). Comparisons were made using the Student-Newman-Kuels test (ouabain model), and ANOVA and Fisher PLSD (amphetamine/CDP test).
Results: Cariprazine significantly reduced hyperlocomotion in both models. In rats, oubain caused significant increase in open-field activity ($P<.01$); lithium significantly decreased oubain-induced hyperactivity ($P<.01$). Cariprazine 0.06, 0.25, 0.5, or 1.0 mg/kg significantly decreased oubain-induced hyperactivity ($P<.01$) (maximum response comparable to lithium). In mice, amphetamine/CDP resulted in significant increase of locomotor activity. Both cariprazine (0.10 and 0.30 mg/kg) and valproate significantly (($P<.05$) decreased d-amphetamine/CDP-induced hyperactivity versus vehicle. Potency and efficacy of cariprazine was greater than valproate.
Conclusions: Cariprazine significantly reduced ouabain- and amphetamine/CDP-induced motor hyperactivity in animal models of mania. Results suggest that cariprazine may have utility for control or prevention of mania in humans.

P-35-011
Rational for the use of neurofeedback as a rehabilitation tool to overcome neurocognitive impairments in schizophrenia

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Objectives: Over the past decades, there has been an enormous effort to develop various behavioral approaches for the rehabilitation of schizophrenia. Among these approaches, cognitive rehabilitation plays a key role, relying on the evidence that neurocognitive deficits are core features of the illness. The aim of this presentation is to discuss the feasibility and the rational for the use of neurofeedback as a bio-behavioural and rehabilitation tool to overcome neurocognitive impairments in schizophrenia.
Methods: Current literature on the efficacy of neurofeedback was reviewed. Studies focusing the neurophysiology and the use of neurofeedback in schizophrenia and disorders associated with similar neuro and social cognitive impairments (e.g., attention deficit/hyperactive disorder, Autism) were taken into account.
Results: Research shows that a variety of neurofeedback protocols have been used successfully in the treatment of several mental disorders. While it is clear that neurofeedback had a positive effect on behavioral and cognitive measures in different populations, few studies reported its use with schizophrenic patients. Moreover, neurophysiological abnormalities in schizophrenia are inconsistent, although some studies have shown reduction of alpha power, excessive theta and decreases on the P300 amplitudes concomitant with executive and attentional problems. These findings, as well as recent data showing the social cognitive correlates of Mu suppression, should be taken into consideration in the formulation of Neurofeedback protocol's for patients with schizophrenia.
Conclusions: Neurofeedback maybe a promising method for the rehabilitation of people with schizophrenia, given that it was shown to be effective improving attention, executive functioning, motivation and self-control in other neuropsychiatric disorders. This review highlights the need for controlled studies to investigate the replication of these cognitive and behavioral outcomes in schizophrenia.

P-35-012
Neurocognitive predictors of proactive coping in schizophrenia

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Objectives: Impairments in social/occupational functioning have been linked to impairments in neurocognition in schizophrenia. However, few studies attempted to analyse the impact of neurocognition on coping. In that sense, the aim of this study was to examine the predictive value of neurocognition for a variety of domains related to coping, focusing proactive coping in particular.
Methods: Sample consisted of 28 schizophrenic patients followed during a 30 months period. All participants were assessed for neurocognitive functions on the following domains: attention (d2 cancellation test), executive functioning (Wisconsin Card Sorting Test), processing speed (Digit Symbol – Coding and Symbol Search), working memory (Digit Span and Letter-Number Sequencing), calculation (Arithmetic), visuo-spatial organization and memory (Rey-Osterrieth complex figure test) and general intellectual ability (IA test). All patients completed the Proactive Coping Inventory to assess their coping skills 30 months post cognitive assessment. Data was analysed by stepwise multiple regressions with the neurocognitive measures entered as predictor variables and the Proactive Coping Inventory domains as dependent variables. A probability of 0.05 was used to enter a variable in the equation, while a probability of 0.10 was used to remove a variable.
Results: Several stepwise multiple regressions were performed after correlating variables in study. Visuo-spatial memory and working memory emerged as significant predictors of proactive coping (R2=0.43) and reflective coping (R2=0.39) domains; working memory was a significant predictor of the strategic planning (R2=0.34) domain; visuo-spatial memory was a significant predictor of the instrumental support seeking subscale (R2=0.20); and calculation significantly predicted the emotional support seeking subscale (R2=0,26). None of the neurocognitive functions were correlated to avoidance coping.
Conclusions: Neurocognitive status seems to play an important role on the use of proactive and strategic coping skills in patients with schizophrenia. The strengthening of cognitive skills by means of cognitive rehabilitation may be used as a way to promote adaptive coping.

P-35-013
A new tool to evaluate anxiety in schizophrenia: Anxiety Scale in Schizophrenia (ASS)

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Objectives: The aim of this study was to design a scale (ASS) to specifically measure anxiety in a hetero evaluation manner and to explore its nature and subtypes in schizophrenia.
Methods: Following a review of literature and examination of current theories in anxiety in schizophrenia, a selection of items was done. The item selected were reformulated and submitted along The Delphi method to further evaluate questionnaire's pertinence, reliability and limitations. The Delphi Expert Committee validate the construction of a twenty-nine items questionnaire in a Likert-formatted (ASS). Each item take into account the intensity, frequency and functional consequences of the symptom. The ASS, PANSS and HAMA were administered to patient with schizophrenia in a cross sectional, multicenter study.
Results: Two exploratory factor analysis conduct to an item selection reducing the 29 items ASS into a 22 item scale. Three factors have been described as "somatic anxiety","perceived and expressed anxiety", and "environemental anxiety". The 22 items ASS scale shows good reliability and validity.Cronbach's alpha statistics for each factor and the total ASS are good (respectively 0.87, 0.79, 0.71 and 0.89).. The two first factors showed high correlation with the 2 Hamilton anxiety subfactors ("physical" and "psychic" respectively), assessing a good concurrent reliability. Interrater fidelity has been evaluated for 17 patients: ICC are good (> 0.7).
Conclusions: ASS ,s reliability and validity have been established in a french schizophrenics sample. Future research using ASS will be needed to establish its responsiveness and stability.

P-35-014
Spectral karyotyping of schizophrenia populations in Tamilnadu, South India

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Objectives: The focal aim of the present investigation was to study the foremost chromosomal aberrations (CA) like deletion, translocation, inversion and mosaic in schizophrenic subjects of Tamilnadu, Southern India. Totally 65 blood samples were collected from various hospitals in Tamilnadu, Southern India. Equal numbers of physically and mentally healthy subjects were serve as a control.
Methods: In the present study chromosomal examinations were carry out by using the GTG banding technique on 65 schizophrenics and finally the results were ensured by spectral karyotyping (SKY) technique.
Results: All the patients had random numerical and structural aberrations were identified. Structural aberrations predominated and usually consisted of deletions, translocation, inversion and mosaicism of various chromosomes. Present study has detected 1, 7, 9, 11, 21, 22 and X, suggested that these chromosomal scratches are prevalent in schizophrenics. In comparison with experimental subjects, the control subjects exhibited very low levels of major CA ($P<0.05$).
Conclusions: In the present study, the high frequency of chromosomal rearrangements designates a potential role for mitotic indiscretion coupled with the centromere in schizophrenia mental disruption. The reason for this might be that these anomalies increase risk for schizophrenia in a relatively nonspecific way, such as contributing to disruption of normal embryogenesis of the nervous system. Identification of chromosome alterations may be helpful in understanding further molecular basis research of the disease in better way.

P-35-015
Cognitive antismoking and psychiatric effects of Varenicline in patients with schizophrenia or schizoaffective disorder

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Objectives: Varenicline has been shown to be an effective anti-smoking treatment in smokers without identified psychiatric illness, and the drug's pharmacology suggests possibilities of pro-cognitive effects. However, recent reports suggest varenicline may have the potential for important psychiatric side-effects in some people. We present the first prospective quantitative data on the effects of varenicline on cognitive function, cigarette smoking, and psychopathology in a small sample of schizophrenic patients.
Methods: 18 schizophrenic smokers were enrolled in an open-label study of varenicline with a pre-post design. Measures of cognitive function (RBANS, Virtual Water-Maze Task), cigarette smoking (cotinine levels, CO levels, self-reported smoking and smoking urges), and psychopathology (PANSS) were evaluated prior to and during treatment with varenicline. Data on psychopathology changes among schizophrenic smokers in another drug study, in which patients were not receiving varenicline, were used for comparison.
Results: 16 patients completed the study, and 2 patients terminated in the first two weeks of active varenicline because of complaints of nausea or shaking. Varenicline produced significant improvements in some cognitive test scores, primarily associated with verbal learning and memory, but not in scores on visual-spatial learning or memory or attention. Varenicline significantly decreased all indices of smoking, but did not produce complete smoking abstinence in most patients. During treatment with varenicline there were no significant increases in psychopathology scores and no patient developed signs of clinical depression or suicidal ideation.
Conclusions: Our small prospective study suggests that treatment with varenicline appears to have some beneficial cognitive effects. Varenicline appears to have some anti-smoking efficacy in schizophrenia. Treatment with varenicline may not increase psychopathology or depression in most patients with schizophrenia, but we cannot accurately estimate the absolute risk of a potentially rare side-effect from this small sample.

P-35-016
Schizophrenics show an upregulation of DNA-methyltransferase 1 (DNMT1)in blood lymphocytes: Implications for the epigenitic methylation hypothesis of schizophrenia

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Objectives: A leading hypothesis addressed by current schizophrenia research is that a downregulation of telencephalic GABAergic transmission is a key component in the pathogenesis of this disorder and increased levels of DNMT1 mRNA have been demonstrated in the prefrontal cortex of post-morten brains of schizophrenic patients (SZP). The primary goal of this study is to compare the levels of DNMT1 mRNA expression in blood lymphocytes of non-psychotic control subjects (NPS) and SZP. We have also investigated the relationship of DNMT1 Level to cigarette smoking and treatment with varenciline.
Methods: Subjects were patients with SZ in a tiertary care hosptial in the US or NPS. Lymphocytes were isolated by separation on Ficoll Plaque plus gradient and DNMT1 mRNA was assayed by RT-PCR procedures as previously described using G3PDH mRNA as the reference comparison. Continine and CO levels were measured in subjects. Some SZP who were cigarette smokers were studied. twice at baseline and after having been treated for 8 weeks with varenciline 2 mg/day.
Results: Results showed that schizophrenics approximately 2- fold, increase in DMNT1 mRNA level (P<.001). This difference was not significantly influenced by sex, antipsychotic drug, or cigarette smoking. However in the group of SZP in US sample, there was a trend for the few patients who smoked more (>15 cigarettes /day) to have lower DNMT1 mRNA compared to non-smoking schizophrenics. Correlations between DNMT1 mRNA and measures of smoking were different for schizophrenic smokers and control smokers. Preliminary data also suggested that treatment with varenciline over 9 weeks decreased DNMT1 levels in schizophrenic smokers.
Conclusions: Our findings suggest that DNMT1 mRNA in lymphocytes of schizophrenics may mirror changes found in autopsied brain, and may provide evidence for an epigenitic mechanism as an ethological factor in schizophrenic.

P-35-017
Treatment of schizophrenia with long-acting injectable risperidone

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Objectives: Rispolept Consta is long-acting injectable formulation of second generation antipsychotic risperidon, witch is incapsulated in microspheres with slow and steady release and provides therapeutic effect of one single dose for two weeks. It's indicated in treatment of broad range of schizophrenic patients. We have treated with Rispolept Consta ten patients and evaluated efficacy of treatment during period of one year.
Methods: Inclusion criteria was: young patients with schizophrenia according to Diagnostic and Statistical Manual of Mental Disorders-4th edition(DSM-IV) poor compliance, increased risk for relapse, low therapeutic efficacy of conventional antipsychotics(AP) or presence of significant side effect on conventional AP. We followed-up improvements in the Positive and Negative Symptoms Scale (PANSS), severity of disease in Clinical Global Impression Severity Scale (CGI-S), rate of clinical improvement in Clinical Global Impression Scale (CGI) and Global Assesment of Functioning Scale (GAF),health-related quality of life (QOL), praesens of side effects, number and lenght of hospitalization, discontinuation of therapy, patient's and therapist's satisfaction with therapy.
Results: Long-acting risperidone was associated with reduction of total PANSS score. All patients showed improvement on CGI-S, CGI, QOL and GAF skales.
Conclusions: Rispolept Consta is effective in treatment of positive and negative schizophrenic symptoms and it leads to significant clinical improvement with relatively good profile of side effects, better compliance, decreased number and lenght of hospitalization, improved global functioning, improved quality of life and increased patient's and therapist's satisfaction with therapy.

P-35-018
Glutamate and BDNF levels in psychosis

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Objectives: a) To determine glutamate levels and Brain Derived Neurotrofic Factor (BDNF) levels in a group of first psychotic episode patients and to compare them with a control group; and b) to study the changes in glutamate and BDNF along 1 year of follow up in the patients after psychopharmacological treatment.
Methods: The sample was composed by 108 people, 54 of them were first psychotic patients consecutively admitted in Santiago Apóstol Hospital, and 54 were normal volunteers matched by gender, age and socioeconomic status. All patients met DSM IV criteria for psychotic disorders. Mean age was 24.38 (±7.29). Glutamate and BDNF levels were analyzed four times: at index episode, at one month, at six months and at one year. Glutamate and BDNF levels were analyzed separately and together, creating a new neurobiological factor that included both data. Statistics were done using non parametric U de Mann-Whitney and Wilcoxon test (SPSS 15.0).

Results: Baseline patients` glutamate and BDNF levels were significantly lower than those found in the control group (z=-3.96; p≤0.001; z=-4.53; p≤0.001). In the first month we found reduced levels of glutamate and of BDNF in the patients group compared with the control group (z=-3.27; p≤0.001; z=-3.07; p≤0.01). In the sixth month and in the first year of follow up we didn't found any differences. In the follow up we found a significant increase in the glutamate levels between the first and sixth month (Z= -2.56; p≤0.05). The BDNF levels increased along the follow up until the sixth month (basal-1 month: Z= -2.88; p≤0.004 and 1-6 month: Z= -2.23; p≤0.05).
Conclusions: Glutamate and BDNF are related with the development of psychosis. With the pharmacological treatment the glutamate and BDNF levels increase significatively. These neurotransmitters could be relevant for the treatment of psychosis.

P-35-019
Association of Psychopathology and Deficits in Facial Affect Recognition in Bimodal Context in Greek patients with schizophrenia

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Objectives: Deficits in the recognition of facial expressions of emotion in patients with schizophrenia are well known from several studies. A study was performed in a Greek sample of patients with schizophrenia, to investigate deficits in the recognition of facial expressions, in bimodal context, and possible correlations with psychopathology.
Methods: Six males and three females, with schizophrenia (paranoid subtype), aged between 31-49 years, participated in the study. The visual stimuli consisted of eight photographs (male and female) for each of the emotions of happiness, sadness, fear and surprise. The auditory stimuli were twelve verbal statements with neutral intonation, for each of the four emotions, formulated and judged in a previous study with healthy participants to elicit these emotions3. "Bimodal scenes" were used, with congruent or incongruent emotional meaning of two variables. The two stimuli were presented simultaneously for 2 seconds. The participants were instructed to attend to the facial expression and name it choosing one out of four terms: happiness, sadness, fear, surprise. There was no time limit for the response. The whole procedure was computerized and the response was recorded. The patients' psychopathology was assessed with the Positive and Negative Symptoms Scale.
Results: Affect recognition negatively correlated with the positive subscale PANNS score in the incongruent context (r=-3.781, SE=0.147, p<0.05). This finding is in agreement with previous studies associating emotion recognition with core positive schizophrenic symptoms. The recognition of fear, in a congruent context, positively correlated with the general psychopathology score (r=4.806, SE=0.072, p=0.002) and negatively correlated (not statistically significant) with the negative subscale PANSS score, in agreement with a recent study suggesting an association of fear recognition and negative symptomatology.
Conclusions: In this study, deficits in facial emotion recognition in a bimodal context in patients with schizophrenia are associated with psychopathology. Further research is needed to elucidate this issue and its clinical implications.

P-35-020
Recurrence pattern of the patients who had been diagnosed with brief psychotic disorder: 2 years of follow up by retrospective chart review

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Objectives: The aim of current study was to evaluate the incidence and patterns of recurrence in patients with brief psychotic disorder for 2 years and find the predictor related to outcome.
Methods: We recruited the inpatients who were diagnosed with brief psychotic disorder from January 2001 to December 2005 and could be followed up for 2 years after discharge. During this period, recurrence of psychotic symptoms and other psychiatric disorders were assessed and relations between these recurrence and various clinical characteristics were evaluated.
Results: Twenty eight patients were included in this study with fulfillment of inclusion criteria. During 2 years of follow up periods, psychiatric disorders were recurred in 9 cases. 5 cases (17.8%) were re-diagnosed with schizophrenia, brief psychotic disorder recurred in 2 cases (7.1%), with full recovery of their functioning. 2 cases (7.1%) were re-diagnosed with bipolar I disorder with psychotic features.
Conclusions: During the 2 years of study periods, we detected recurrence of brief psychotic disorder in some cases, which means full recovery of functioning after psychotic breakdown. However, in more cases, their psychotic symptoms were re-diagnosed as schizophrenia and bipolar disorder. In the future, prospective studies which have large sample size would be needed.

P-45
Psychotic Disorders VII

P-45-001
Post-injection delirium/ sedation syndrome observed with olanzapine long-acting injection

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Objectives: A recognized potential risk of intramuscular products is accidental intravascular injection, the signs and symptoms of which are dependent on the formulation and safety profile of the injected medication.1 During clinical trials of olanzapine long-acting injection (LAI), cases were identified in which a cluster of adverse events characterized by post-injection delirium and/or excessive sedation were observed. This post-injection delirium/sedation syndrome (PDSS) appeared to be potentially related to inadvertent intravascular injection of a portion of the olanzapine LAI dose.
Methods: Safety data were pooled from all completed and ongoing olanzapine LAI clinical trials through the last database lock in 2007 (cutoff date: 30 Sep 2007), and adverse event data through 31 May 2008 were also reviewed for occurrence of potential PDSS cases. Incidence of post-injection delirium/sedation was estimated by dividing number of events by number of injections or number of patients.
Results: As of 31 May 2008, incidence of post-injection delirium/sedation syndrome following administration of olanzapine LAI was 0.07% per injection and 1.4% per patient. Affected patients presented with symptoms consistent with excessive systemic levels of olanzapine (e.g., sedation, dizziness, confusion, slurred speech, altered gait, weakness, muscle spasms, and/or unconsciousness). No clinically significant decreases in vital signs were observed. All patients recovered completely from signs and symptoms of post-injection delirium/sedation syndrome after 1.5 to 72 hours.
Conclusions: The incidence of PDSS with olanzapine LAI was similar to a reported rate of a similar syndrome observed with intramuscular procaine penicillin G.2 Special precautions when using olanzapine LAI include proper injection technique and implementation of a post-injection observation period. Post-injection delirium/sedation signs and symptoms should be managed as medically appropriate.

P-45-002
Visual scanning in schizophrenia: Effects of instructions on visual categorisation

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Objectives: Visual scanning of stimuli (e.g., faces, landscapes, fractals…) is known to be impaired in schizophrenia. Patients with schizophrenia usually make fewer fixations than healthy controls and their exploration duration is reduced. However, previous studies (e.g., Bestelmeyer et al., 2006) have examined visual scanning under passive viewing conditions. Our study was designed to examine whether individuals with schizophrenia are able to control the spatial orientation of their attention when they are guided by instructions.
Methods: Visual scan paths were measured in patients with schizophrenia (n=17) and control participants (n=21) by means of an eye tracker (Senso-Motoric Instruments, binocular, 350 Hz). Participants performed a "free viewing" task (baseline passive viewing) and several tasks in "active viewing" condition in which they were asked to categorize or identify pictures. Temporal and spatial characteristics of scan paths were compared for each group and task.
Results: In comparison with healthy controls, patients with schizophrenia exhibited reduced visual scan paths to stimuli in passive viewing condition, but did not differ from controls in the active viewing conditions.
Conclusions: This study shows an improvement of visual exploration in patients with schizophrenia when they are guided by instructions. The results are consistent with studies showing that patients are able to modulate their attention as a function of task demands and attentional load (e.g., Ducato et al., 2008).

P-45-003
Quantifying cortical thinning in first episode schizophrenia

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Objectives: There is growing evidence from automated MRI studies that cortical thickness is reduced in chronic schizophrenia. Mainly frontal-temporal regions are affected. Surprisingly, only a few studies investigated cortical thickness in first episode schizophrenia, although the examination of this disease state can be expected to provide further insight into onset and course of cortical thinning in this disorder.
Methods: 54 patients with first-episode schizophrenia according to DSM IV as well as 54 healty controls (matched for age and sex) were investigated with high resolution 1.5 T MRI. Cortical thickness was estimated as the distance between the gray-white matter border and the pial surface using the FreeSurfer software (http://surfer.nmr.mgh.harvard.edu). Statistical cortical maps were created to estimate differences of cortical thickness between the groups based on an entire cortex analysis.
Results: Findings revealed significant cortical thinning in prefronto-temporal, anterior cingulate and parietal cortex areas in patients with first episode schizophrenia. Cortical thinning ranged from 1.7 to 7.1 percent. Right dorsolateral prefrontal areas demonstrated the weakest (1.7 percent) and right ventrolateral-orbitofrontal regions the strongest cortical thinning (7.1 percent). The other brain regions appeared to be affected to a similar degree (4.4-5.7 percent), whereas inferior parietal regions were stronger affected than temporal and superiorfrontal areas.
Conclusions: Our findings of cortical thinning affected predominantly those cortical areas, which play a major role in the integration of heteromodal neuronal input. The heteromodal cortices constitute neuronal networks, which are responsible for the integration of multisensory input as well as for planning, conducting and evaluating behavior. Dysfunction of these brain areas leads to core symptoms of schizophrenia such as lack of attention, disorganisation and reality distortion. Hence, cortical thinning of the heteromodal association cortices might be one underlying neuroanatomical alteration leading to functional core deficits in schizophrenia. The different brain regions were differentially affected by cortical thinning. This might be related to different neuropathological alterations such as synaptic pruning or reduced neuropil.

P-45-004
Effect of agonists of metabotropic glutamate receptors on schizophrenia like behavior in rats

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Objectives: Major argument that the glutamatergic system may be disrupted in schizophrenia is the fact that antagonists of the NMDA receptors impair cognitive functioning in healthy volunteers. in a manner that is very similar to the cognitive deficits observed in schizophrenic patiens. There is evidence that the cognitive deficit in animals is inducible by application of NMDA antagonists, which suggests that dysfunction of NMDA receptors may be the primary cause of cognitive impairment. Hovewer the direct activation of NMDA receptors produces a global disruption in brain function. Hence indirect modulation of glutamatergic transmission by metabotropic glutamate receptors (mGluR) may represent promising approach for pharmacotherapy of schizophrenia. Preclinical studies suggest that two subtypes of mGluRs have the potential of ameliorating cognitive deficits in schizophrenia. These include mGluR5 (group I) receptors, which can directly modulate the function of NMDA channel, and the mGluR2/3 (group II) receptors, which presynapticaly regulate the release of glutamate.
Methods: We propose that agonists of mGluR II and mGluR5 could be effective in treatment of disturbances in animal model of schizophrenia based on inhibition of NMDA receptor by MK-801 90.1 mg/kg). Aim of this study was to compare effects of MAP4 (agonist of mGluR 2/3) and CHPG (agonist of mGluR5) on cognitive coordination, sensorimotor gating and locomotion in animal model of schizophrenia
Results: Aplication of CHPG did not leads to improvement of deficit of sensorimotor gating induced by MK-801. But it leads to improvement of deficit of cognitive coordination in model of schizophrenia. By contrast, aplication of MAP4 did not improve deficit of cognitive coordination and even worsened deficit of sensorimotor gating but decrease locomotion activity
Conclusions: Taken together activation of mGluR 2/3, but not activation of mGluR5 could improve the cognitive deficit in patients with schizophrenia
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P-45-005
Differential white matter alterations in schizophrenia: A study with DTI and tract-based spatial statistics

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Objectives: There is increasing evidence for white matter abnormalities in patients with schizophrenia. Most studies report decreased fractional anisotropy (FA) in interhemispheric commissural fibers as well as long-ranging fronto-parietal association fibers.
Methods: The present study used tract-based spatial statistics (TBSS) to investigate white matter integrity in 35 patients with schizophrenia and 35 healthy volunteers.
Results: Patients compared to healthy subjects exhibited significantly decreased FA in the corpus callosum, the cerebral peduncle, the left inferior fronto-occipital fasciculus, the anterior thalamic radiation, the right posterior corona radiata, the middle cerebellar peduncle, and the right superior longitudinal fasciculus. Increased FA was detectable in the inferior sections of the corticopontine-cerebellar circuitry.
Conclusions: Present data reveal extended cortical-subcortical alterations of white matter integrity in schizophrenia using advanced data analysis strategies. They corroborate preceding findings of white matter structural deficits in mainly long-ranging association fibers and provide first evidence for neuroplastic changes in terms of an increased directionality in more inferior fiber tracts.

P-45-006

The embryonic form of polysialyltransferase deficient mice demonstrate the working memory impairment: A core feature of schizophrenia–like phenotype

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Objectives: The function of neural cell adhesion molecule (NCAM) is regulated by posttranslational modifications. Among others the most important modification is the attachment of a polysialic acid by 2 polysialyltransferases – ST8SiaII and ST8SiaIV. The aim of this study was to find out whether the embryonic (ST8SiaII) or/and adulthood polysialyltransferase (ST8SiaIV) deficiency causes cognitive deficits and morphological alterations related to schizophrenia-like phenotype.
Methods: Male and female ST8SiaII-/-, ST8SiaIV-/- and their wild type littermates with an average age of 2-4 months were used in this study. For the quantification of the volume of the lateral ventricles and the dentate gyrus of hippocampus, and the cell density in the granular cell layer, hilus and regions CA1, CA2, CA3 of the hippocampus, haematoxylin-eosine staining was used. Cell numbers were quantified stereologically according to the optical fractionation method and the volume of the dentate gyrus and lateral ventricles was estimated according to the Cavaleri´s principle. To assess memory function mice were subjected to the object recognition test 2 and 24 hours after training (short- and long-term episodic memory) and spatial working memory task on T-maze.
Results: Morphological examination of the brain sections obtained from ST8SiaII knockout mice revealed an enlargement of lateral ventricles and increased cell density in the granular cell layer and regions CA2/CA3 of the hippocampus. Such alterations were not found in the brains of ST8SiaIV knockout mice. ST8SiaIV knockout mice demonstrated both impaired short- and long-term episodic memory. ST8SiaII knockout mice had deficits only in a short-term episodic memory. Furthermore, ST8SiaII knockout mice showed impairments in the working memory task.
Conclusions: Therefore, our preliminary data suggest that ST8SiaII deficiency in embryonic and early postnatal period causes schizophrenia-like alterations in the brain morphology and memory deficits. At the same time no such phenotype is observed when the polysialylation of NCAM is impaired in adulthood.

P-45-007

Familial and sporadic schizophrenia: A comparison of somatic diseases and abuse in patients and their relatives

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Objectives: Comparing patients with schizophrenia on the basis of familial and nonfamilial forms of the illness provides a promising approach to the identification of genes involved in schizophrenia [1]. The aim of this study was to search for somatic factors that discriminate between patients with and without heredity for schizophrenia and between their relatives.
Methods: 95 patients with the diagnosis of schizophrenia according to DSM-IV criteria were structurally interviewed about mental and physical health and alcohol- and substance use in themselves and their families. Besides this, complementary information was obtained from the patients´ case records. Patients with (41%) and without (59%) heredity for schizophrenia were then compared.
Results: The main difference found in this study was that significantly fewer patients with heredity, compared to patients without heredity, had relatives with cancer (P=0.005). This difference was still clearly significant (P=0.002) even after excluding one patient having a relative with both schizophrenia and cancer from the analysis.
Conclusions: This finding strongly supports the hypothesis [2] that a genetic predisposition to schizophrenia entails a protection against cancer.
References: [1] Malaspina D, Harlap S, Fennig S, et al. (2001) Advancing paternal age and the risk of schizophrenia. Archives of General Psychiatry 58:361-367. [2] Levav I, Lipshitz I, Novikov I, et al. (2007) Cancer risk among parents and siblings of patients with schizophrenia. British Journal of Psychiatry 190:156-161.

P-45-008

One year outcome of first psychotic episode: Tunisian inpatients population

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Objectives: The aim of this study was to describe the outcome of patients with first psychotic episode at one year.
Methods: it is a retrospective and descriptive study. It concerned patients hospitalized in psychiatry department of the university hospital of Monastir (Tunisia). Patients with diagnostic of organic psychosis and substance abuse were excluded. The inpatients sample was compound of 117 patients (84 Males and 33 females). The mean age was 27.8 ±11.3 years. We assessed outcome at one year follow up using the medical observation data.
Results: At one year, the rate of total recovery was 28.2%, relapse was 12.9% absence of recovery. The rate of lost patients was 56.3%. Final diagnostics of the first psychotic episode when using DSM-IV criteria were: brief psychotic disorder (33.5%), schizophrenia (32.6%), bipolar disorder (19.8%), schizophreniform disorder (7.8%) and schizo-affectif disorder (5.3%).
Conclusions: Those results suggest that a first psychotic episode is not systematically a first episode of schizophrenia. In fact, total recovery and the diagnostic of brief psychotic disorder and schizophrenia occur at the same rates. Identifying predictive factors at the first psychotic episode seems to be useful to adapt therapy in each case.

P-45-009

Impact of Schizophrenia Candidate Genes on Antisaccade Task performance in a population of young men

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Objectives: The antisaccade task dysfunction has been proposed to be a potential endophenotype for schizophrenia. It is unknown whether the expression of this endophenotype at the population level is modulated by the genetic variability of candidate susceptibility genes for schizophrenia.
Methods: We examined in a population of 2130 young military conscripts the impact of 26 single nucleotide polymorphisms (SNPs) within the RGS4, NRG1, DTNBP1, COMT, DAAO, BDNF, DAOA/G32, HT2A and DRD4 genes on the following antisaccade task indices of performance: error rate, mean antisaccade latency and antisaccade latency variability. Parametric regression analysis was used to assess the effects of each SNP on each of the parameters. In case of a significant effect ($P<0.05$) the effect was confirmed using non-parametric analysis namely bootstrap and permutation techniques.
Results: Significant associations of SNP 4 (rs 951436) and SNP18 (rs 2661319) of RGS4 gene were observed with the antisaccade error rate. Median antisaccade latency was significantly associated with the MDAAO-6 (rs3741775) SNP of DAAO gene and the NRG243177 SNP of NRG1 gene. Finally significant associations were observed between the COMTval/met polymorphism, the SNP 18 polymorphism of the RGS4 gene and the SNP MDAAO-6 of the DAAO gene with the variability of antisaccade latency.
Conclusions: Specific RGS4, COMT NRG1 and DAAO gene SNPs exerted modulating effects on indices of antisaccade task performance at the population level corroborating the view that this task is a potential schizophrenia endophenotype.

P-45-010
Larger time variability for basic decision processes in schizophrenia

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Objectives: Slower mean Reaction Time (RT), known as psychomotor slowing, is well documented in patients with schizophrenia. Several studies have demonstrated a slower RT as well as an increased error rate in patients performing the antisaccade task. Fewer studies have shown increased variability of RT in these patients suggesting a basic difference in the distribution of RT.
Methods: In this study, several saccade and antisaccade indices including median RT and its variability were measured for a visually triggered saccade task performed by 53 patients and 1089 control subjects and an antisaccade task performed by 45 patients and 2006 control subjects. Average cumulative RT distributions were derived for each group for correct saccades, correct antisaccades and error prosaccades and the RT distribution for each group was modeled using a decision signal rising linearly to a threshold signaling the beginning of the eye movement.
Results: There was a noticeable increase in the median RT for patients performing correct antisaccades while the median RT did not differ significantly between the two groups when performing error prosaccades or correct saccades. Moreover the patients RTs were much more variable from trial to trial leading to a difference in the average RT distribution of the patient group both for correct antisaccades and error prosaccades. The model application led to the conclusion that this difference in the distribution of RT for patients could be attributed to a basic difference in information processing leading to the decision to move the eyes.
Conclusions: These results may favor the hypothesis that a fundamental difference revealed in larger time variability in basic decision processes might be present in schizophrenia independent of the specific task used or the presence or not of psychomotor slowing.

P-45-011
Long-term treatment with Asenapine versus Olanzapine in subjects with persistent negative symptoms of Schizophrenia

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Objectives: The efficacy and safety of asenapine for persistent negative symptoms of schizophrenia were previously reported in a double-blind 26-week study using olanzapine as an active comparator. We now report a double-blind 26-week extension of that trial.
Methods: Subjects in the core study were randomized to flexible-dose asenapine 5 or 10 mg BID or olanzapine 5–20 mg QD for 26 weeks. Subjects who completed the core study and who would benefit from extended treatment could participate in this extension, on the same regimen. Results are reported for change in NSA-16 total score from baseline of the core study over a 1-year period. Data were analyzed using a mixed model for repeated measures.
Results: Of 349 subjects completing the core study, 306 entered the extension and received treatment; 279 comprised the ITT population; 266 completed 1 year of treatment. LS mean±SE changes in NSA-16 total score were –16.9±0.98 (baseline, 61.7±0.85) for asenapine vs –15.4±0.85 (baseline, 60.4±0.74) for olanzapine (P=0.2344). Little improvement was seen in positive or depressive symptoms, indicating improvement in negative symptoms was a primary effect. Changes on the Quality of Life Scale were 18.7±1.64 (baseline, 45.1±1.63) for asenapine and 16.4±1.4 (baseline, 47.7±1.42) for olanzapine (P=0.2838). For asenapine vs olanzapine at endpoint, the incidence of treatment-emergent AEs was 85.1% vs 74.4%; treatment-related AEs, 58.2% vs 58.1%; EPS reported as an AE, 9.7% vs 4.1%; and LS mean weight change, –1.4 kg vs 4.0 kg (P<0.0001).
Conclusions: Asenapine was comparable to olanzapine in subjects with persistent negative symptoms over 1 year of treatment. Asenapine was well tolerated, with a small weight decrease and low EPS incidence.

P-45-012
Dose selection of asenapine: Application of mathematical models based on D2 receptor occupancy

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Objectives: Asenapine is being developed for schizophrenia and bipolar disorder. We report on the development and application of mathematical models, based on dopamine D2 receptor occupancy, that were employed in dose selection for Phase III studies of asenapine in schizophrenia.
Methods: Clinical data for antipsychotic drugs were collected from public sources; in-house data were used for asenapine. D2 occupancy data originated from published positron emission tomography (PET) studies that included blood sampling for pharmacokinetics. Clinical efficacy data (group mean change in Positive and Negative Syndrome Scale [PANSS] total score) were taken from placebo-controlled trials (4–8 weeks); when evaluating extrapyramidal symptoms (EPS), measured using the Simpson-Angus Scale (SAS), additional non–placebo-controlled trials were included. A generally applicable model connecting antipsychotic dose, pharmacokinetics, D2 occupancy, PANSS response, and SAS response was developed and used to simulate the effects of asenapine at doses of 5–20 mg BID.
Results: Initial simulations indicated that clinically relevant decreases in PANSS total score (≥8 points vs placebo) occurred with asenapine dosages of 5 mg BID and higher. This prediction was confirmed in clinical trials, demonstrating significant efficacy vs placebo with 5 mg BID, but not at lower doses. The final model simulations, updated with the newly obtained data on asenapine, indicated that 5–10 mg BID would result in a mean PANSS decrease vs placebo of 8–10 points and a mean SAS response vs placebo of <0.2 points.
Conclusions: The results from simulations using this model framework based on D2 occupancy indicate that asenapine 5–10 mg BID provides antipsychotic efficacy with limited risk of EPS. This dose range has been tested in Phase III clinical trials in which the safety and efficacy of asenapine in schizophrenia was established. This research was supported by Schering-Plough.

P-45-013
Mentally Ill, Violence and Stigma

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Objectives: Widespread opinion is that psychiatric patients represent dangerous and criminogene population. Although researches find that they are not more aggressiv then the rest of "normal" population, stigma and fear in the society remain.
Methods: This study was conducted at Centre of Forensic Psychiatry in Specialized Psychiatric Hospital in Gornja Toponica, Nis in order to establish the connection between diagnostic entity and felony itself, as well as the type of felony. Center of Forensic Psychiatry conducts security measures towards the persons "not guilty by the reasons of mental disability". Patients were diagnosed according to Diagnostic and Statistical Manuel of Mental Disorders -4th edition (DSM-IV) criteria. Autors of the study postulate thet Personality Disorders do not represent esentially mentally ill persons, which is also sustained in Serbian criminal low (persons diagnosed as Personality disorders are responsible for their actions, as long as there are not comorbid circumstancial facts).
Results: Results of study showed that two-thirds of hospitalised patients are, or were, psychotic, with Schizophrenia paranoides as most represented diagnostic category. Their motivation for committing crimes was psychopathological and the risk of repeating the felonies was lower once we established remission. But, in group of Personality Disorders leading diagnostic category was Disocial Personality Disorders, and felonies were planned and with clear tendency towards material benefit. Also, there was no remorse.
Conclusions: In **Conclusions:** Should we fear of psychiatric illneses or psychopathy?

P-45-014
Implicit planning of simple motor sequences in schizophrenia as measured by the Line-Sequencing Task

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Objectives: Many studies of cognitive impairment in schizophrenia are directed at 'higher' dysfunctions, measured by executive neuropsychological tasks and explicit planning tests. We focused on implicit planning in a simple graphic motor task in which a sequence of single lines, gradually changing in direction, has to be drawn. We hypothesized that the schizophrenia patients would stick longer to a drawing direction that was progressively becoming more uncomfortable and that they would choose to switch to the reversed, more 'easy' drawing direction at a later stage than healthy controls.
Methods: The results from two studies are reported. The first study included 33 recent-onset schizophrenia patients and 33 matched healthy controls (Grootens et al, 2009); the second study included 85 stabilized schizophrenia patients and 30 matched healthy controls. For the Line-Sequencing Task, subjects are instructed to connect pairs of small open circles with straight lines in sequences of 10 pairs. The task contains three conditions: 1) line direction gradually shifting from horizontal to vertical, 2) line direction gradually shifting from vertical to horizontal, 3) line direction presented in a random way.
Results: Patients showed a significantly higher percentage of trials executed without directional switches. The percentages of 'awkward' upward strokes were much higher for the recent-onset and stabilized patients compared to their matched controls.
Conclusions: Patients more often opted for the uncomfortable bottom-up direction to draw the vertical lines and changed their orientation less often than the controls did. This seems to suggest a stronger tendency to perseverate. However, it seems more probable that patients adopt one single strategy to draw all lines from left to right and from bottom to top. By doing this, they avoid making a decision about drawing direction. The general conclusion is that schizophrenia patients show deficits in the implicit planning of simple motor sequences.

P-45-015
Psychobiology and prognosis of atypical psychosis

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Objectives: INTRODUCTION: The development of concepts of ‚atypical' psychoses in European countries and in the United States shows that there are various terminologies which are given to a group of psychoses unclassifiable within Kraepelinian dichotomy. Bouffee delirante (French school), cycloid psychoses (Leonhard, Perris), reactive psychoses (Scandinavian school) and acute schizoaffective psychoses (Kasanin) are the most common terms.
Methods: The subjects were 15 patients, 5 females and 10 males (the mean age at first hospitalization was 21.3 +/- 6.2 years), who were consecutively discharged from the Department of Psychiatry of Foligno and Aosta, between May 1996 and May 2004. The mean interval between first-admission and follow-up was 5 years. The social outcome was measured using Global Assessment of Functioning Scale (GAF) and Disability Assessment Schedule (WHO/DAS II).The subjects were divided into two groups according to Global Assessment of Functioning Scale (GAF) and Disability Assessment Schedule (WHO/DAS II): a favorable outcome group and an unfavorable outcome group. The following data were obtained from clinical records and analyzed: sex, family history of mental disorders, educational background, job experience, marital status, age at first contact to a psychiatrist, age at first hospitalization, type of onset, subtype of atypical psychosis (Bouffee delirante, cycloid psychosis, reactive psychosis) and symptoms at the time of first hospitalization. Symptoms at the time of first hospitalization included delusions, hallucinations, disorders of ego consciousness, thought disorders, emotional disturbances, lack of spontaneity, catatonic symptoms, hypochondriac-cenestopathic symptoms, disorganized behavior, and suicide attempts.
Results: A comparison of psychopathological symptoms at the time of first hospitalization between the favorable and unfavorable outcome groups revealed significant differences in patients with diagnosis of cycloid psychosis.
Conclusions: The diagnosis of cycloid psychosis present at the time of first hospitalization were observed more frequently in the unfavorable outcome group than in the favorable outcome group.

P-45-016
Possible new treatment strategy for schizophrenia: A neural network regeneration therapy

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Objectives: Currently hypothesis focused on the progressive morphological changes of the brain in schizophrenia, and thus the maintenance and the repair of damaged neural network is a key strategy for schizophrenia treatment. In the previous study, we investigated the effects of atypical antipsychotics on the neuronal differentiation of neural stem cells (NSCs) and the survival of mature neurons prepared from rat embryos. The atypical antipsychotics have shown the promotive effects on the neuronal differentiation of NSCs and the survival of neurons, indicating that atypical antipsychotics-induced alteration of neurogenesis and/or survival could contribute to the neural network repair impaired in the schizophrenic brain.
Methods: In the present work, we demonstrated the usefulness of intravenous transplantation of NSCs to the neurodevelopmental model rat of schizophrenia against its behavioral abnormalities, and suggested the possibility of regenerative therapy for schizophrenia. Maternal infection during pregnancy has been associated with increased risk for schizophrenia in offspring.
Results: We have shown the potential of migration of transplanted NSCs into the brain by visualizing fluorescent cell marker and RI, and the recovery of behavioral abnormality of schizophrenic model rat which was caused by the maternal injection of synthetic double strand RNA polyriboinosinic-polyribocytidilic acid (poly (I:C)) in the memory, cognition, and social interaction tasks. We further assessed the characteristics of transplanted cells, especially in the field of amygdala, DG, and cingulate cortex, those are the areas NSCs concentrated much when transplanted in the shchizophrenic model rat.
Conclusions: The results suggested that the intravenous NSC transplantation may be an advanced approach to recover the neural network damage and CNS dysfunctions in schizophrenia.

P-45-017
Subnanosecond fluorescence spectroscopy in the study of albumin binding sites in first - episode drug-naive patients with paranoid schizophrenia

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Objectives: Albumin (SA) is the main extracellular transport protein of human body. Conformational properties of SA binding sites are changed in chronic mental disorders [Smolina 2007, Uzbekov 2008]. The detection of those changes is potentially useful for evaluation of patients' state. Nevertheless, in the first-episode drug –naive patients (FES) minimal or no changes of SA sites were detected by conventional techniques. Subnanosecond fluorescence spectroscopy is a technique in which single photons after excitation of protein-bound fluorophore with pulse of 0.1 nanosecond are detected. The aim of the study was to evaluate this technique as a molecular tool to detect conformational changes of the protein of FES.
Methods: Serum from 13 FES (12 men, 1 woman, 23-46 years) with paranoid schizophrenia (F20.0) and 7 healthy volunteers (controls, 5 men, 2 women, 27-46 years) were studied. The properties of albumin sites were examined with albumin-specific probe CAPIDAN (naphthalimide derivative) [Gryzunov 2006] at different ionic composition of the medium. Fluorescence decay technique with resolution of 0.6 nanosecond and a special method of decay amplitude analysis were used.

Results: The set of used techniques made it possible to obtain information about the state of four different binding sites in SA globule. The sites of SA of the FES differed significantly from ones of the controls ($p<0.05$). The revealed differences are related to particularities of electrostatic-and-hydrophobic interaction in the SA globule of FES as compared with volunteers.
Conclusions: Subnanosecond fluorescence technique in combination with albumin-specific fluorescent probe and variation of ionic composition of the medium is a perspective molecular tool to study molecular mechanisms of mental disorders and for evaluation of the patients' state.

P-45-018
Probabilistic classification and gambling in medicated schizophrenic patients: Comparison of olanzapine, risperidone, clozapine and typical antipsychotics

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Objectives: People with schizophrenia are treated with antipsychotic medications that block dopamine D2 receptors. These medications produce cognitive deficits in normals raising the possibility that similar deficits observed in schizophrenic patients result from the medication. We evaluated cognitive function in schizophrenic patients treated with different antipsychotics known to differentially affect the striatum and medial prefrontal cortex (mpfc). We tested the hypothesis that patients treated with olanzapine or clozapine that affect mpfc more than striatum will show greater impairments on a task that relies on mpfc than on one that relies on striatum and that patients treated with respiridone or typicals that affect striatum more than mpfc will show greater impairment on a task that relies on striatum than on a task that relies on mpfc.
Methods: Tasks included a probabilistic classification learning (PCL) task sensitive to striatal damage and Iowa Gambling Task (IGT) sensitive to mpfc damage. Patients had a DSM-IV diagnosis of schizophrenia or schizoaffective disorder and were treated with the olanzapine (n=21), risperidone (n=16), clozapine (n=16) or typical antipsychotics (n=19); a normal control group numbered 26.
Results: On PCL the Control ($p<.01$) and Clozapine ($p<.05$) but not the Olanzapine or Risperidone groups improved from block to block. On the IGT the Control ($p<.05$) and Risperidone ($p<.03$) but not the Olanzapine or Clozapine groups improved over blocks. Patient groups did not differ significantly in declarative memory or on the Mini Mental State Exam.
Conclusions: Results showed that typicals and the atypical risperidone had a greater effect on the PCL task that is sensitive to striatal damage and that clozapine (and to a lesser extent olanzapine) had a greater effect on the IGT task that is sensitive to mpfc damage. These data suggest that antipsychotic medications affect cognition in schizophrenic patients and that the nature of the deficit interacts with the regional effect profile of the medication.

P-46
Psychotic Disorders VIII

P-46-001
Serum nitric oxide levels and schizophrenia: A pilot study

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Objectives: An abnormality in neurodevelopment is one of leading hypothesis in possible ethiology of schizophrenia (SCH), where higher concentrations of nitric oxide (NO) found to be neurotoxic. We aimed to investigate whether the serum levels of nitric oxide differ between patients suffering from schizophrenia and healthy controls.
Methods: The study population were consisted of inpatients (n=20) who met DSM-IV diagnostic criteria for SCH confirmed by Structured Clinical Interview (SCID 1) and healthy controls (n=20). In order to exclude psychiatric morbidity in control subjects the same diagnostic procedure was applied. NO concentration in serum was determined by classic colorimetric Griess reaction. Conversion of nitrate into nitrite was done with elementary zinc.
Results: Serum NO level was significantly higher in patients with SCH (23, 26 ± 1, 76 μmol/L; X±SEM) than in control subjects (14, 36±1, 42 μmol/L; X±SEM, $p=0.001$).
Conclusions: Our preliminary findings of increased serum NO in patients with SCH indicate its potential role in pathophysiology of this severe psychiatric disorder. However, those results are preliminary and have to be confirmed in sample of larger size. Bearing in mind heterogeneity in symptom expression, course and treatment our future survey has to be focused on research of this particular characteristics and NO role in ethiopathology of SCH

P-46-002
Oxidative stress – linked changes in patients with schizophrenia and metabolic syndrome

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Objectives: Our aim was to assess the levels of some markers of oxidative stress - total plasma homocysteine (tHcy), superoxide dismutase (SOD), glutathione peroxidase (GPx), and human serum paraoxonase (PON1) arylesterase and paraoxonase activities - in schizophrenia patients with and without metabolic syndrome.
Methods: 70 patients who met the DSM-IV-TR criteria for the diagnosis of schizophrenia and treated for at least 1 year in the Outpatient setting of the Psychiatric Clinic No III Cluj-Napoca, Romania – either with mono-therapy, or with a combination of 2 or 3 antipsychotic drugs – were included in the study. Patients who met the criteria for metabolic syndrome (N=14) were compared with a group of patients with schizophrenia without metabolic syndrome (N=19), and also with a group of healthy volunteers (N=39). tHcy concentrations were assessed by RP-HPLC, red blood cell vitamin B12 and serum folate levels were assessed by electrochemiluminiscence, and SOD, GPx and PON1 activities were determined spectrophotometrically.
Results: No significant differences between the study groups were observed regarding tHcy, folate or vitamin B12 concentrations, nor GPx or PON1 paraoxonase activities. Higher activities of SOD were observed in schizophrenic patients when compared to controls ($p = 0,001$). Schizophrenic patients who did not develop metabolic syndrome presented significantly higher SOD activities as compared both to controls ($p = 0,001$) and patients with MS ($p = 0,042$). Schizophrenic patients who presented metabolic syndrome also had higher levels of SOD activities, as compared to controls, but this increase in activity did not reach statistical significance ($p = 0,118$). Schizophrenic patients also presented significantly lower PON1 arylesterase activities as compared with controls ($p = 0,016$).
Conclusions: Our study did not find any significant differences in the oxidative markers assessed, in the two schizophrenic patient subgroups, apart from higher SOD activities in patients without MS.

P-46-003
Schizophrenia deficits of interference-control processes in perception and memory

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Objectives: Deficits of cognitive control (CC), including inhibition over interference in working memory (WM), have been repeatedly reported in schizophrenia. A single cause, either a generalized cognitive deficit that manifests when the task is difficult, or a specific deficit leading to widespread consequences, has been assumed to underlie these effects. Contrary to this view, we hypothesized that specific aspects of CC are selectively impaired in schizophrenia.

Methods: A group of schizophrenics and a group of age-matched controls performed item-recognition WM tasks that measured the ability to ignore distracting perceptual information and the ability to suppress intruding information in WM. In each task, a word-set containing four words (2 red, 2 blue) was presented, followed by a delay, then a memory probe. In the "Ignore" task, instructions to attend to words of one color appeared before the word-set. In the "Suppress" task, instructions to remember words of one color appeared after the word-set. Forty percent of the probes were words subjects were to attend to (positives), 30% were words subjects were not to attend to (dropped-negatives, DN), and 30% were words that had not appeared in the word-set (non-familiar negatives, NFN).
Results: Difference scores (DS) for DN minus NFN were computed for reaction time (RT) and error rate (ER) for the two types of tasks. These comparisons revealed similar DS in patients and controls for both RT and ER in "Ignore". However, in "Suppress", patients showed significantly greater DS than controls in RT and reliably increased DS for error rate. In contrast, ER in NFN trials did not differ between groups in either task, suggesting that the deficit was not due to an overall effect of task difficulty.
Conclusions: These results indicate that schizophrenics are impaired in suppressing information that is already in WM, but relatively intact in inhibiting information prior to entry into WM.

P-46-004
The ketamine model of schizophrenia and semantic memory

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Objectives: To determine whether ketamine is a viable drug model for schizophrenia.
Methods: In a placebo controlled, double blind study, 22 healthy participants with no history of psychotic illness were given a continuous low dose of either saline or ketamine while they performed a number of semantic memory tasks. The results of the ketamine condition were compared to a matched schizophrenia group to determine whether patterns of performance were similar.
Results: Results demonstrate that the control participants were indeed impaired in performing semantic tasks whilst under the influence of ketamine. Schizophrenia data is currently being collected.
Conclusions: Ketamine does indeed impair semantic memory function. This impairment is similar to the impairment noted amongst schizophrenia groups in the literature. This suggests that ketamine may be a useful drug model for schizophrenia.

P-46-005
Episodic memory in schizophrenic patients, their biological relatives and normal people

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Objectives: In order to better understanding of the schizophrenia, the present study examines one of the most problem, memory impairments, specially episodic memory in schizophrenic patients, their biological relatives and comparison with normal people.
Methods: 20 schizophrenic patients, 20 their biological relatives and 20 normal people were randomly selected and William's individual episodic memory test (WIEMT) was administered on them. In the research to the participants were presented 15 target words (5 pleasant, 5 unpleasant ,5 neutral words).The participants were asked to recall a past memory associated with target words. ANOVA test was used to analyze the data.
Results: Finding showed significant differences among groups. Majority of schizophrenics oriented to choose neutral and somewhat unpleasant stimuli (words) and recall their past memory with depressive and unpleasant theme and their relatives too. But majority of normal people choose the better and pleasant words with good and pleasant their past memory.
Conclusions: Our results reveal that deficits in episodic memory can be regarded one of the most prominent cognitive deficits in schizophrenia and should thus be taken seriously in both its diagnosis and treatment. So it stresses the importance of assessing memory function impairments in clinical settings. Also choosing the neutral (and not pleasant) stimuli (words) may cause tendency to depressed mood and it can impair social cognition in schizophrenia that may be an important predictor of social dysfunction.

P-46-006
Neural correlates of the recognition processing of emotional words in patients with schizophrenia

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Objectives: The aim of this study was to investigate the recognition processing of words which associated with emotional picture in patients with schizophrenia using fMRI.
Methods: Fifteen normal volunteers and fifteen patients with schizophrenia were participated. All participants performed the finding-main-theme task while watching pictures containing emotional events in which they had to select a main theme among three words on the pictures. The words consisted of a main theme word, a main theme-related word and a main theme-unrelated word. Following task during fMRI was to recognize the words which consisted of main theme words, related words, unrelated words, and new words. A 3T MR scanner was used for fMRI (28 contiguous slices; TR=2500 ms; and TE=50 ms). Using SPM2, the main theme words condition was compared with the other words conditions in each group.
Results: In the main versus new comparison, the normal participants showed activations in the right lingual gyrus, the bilateral anterior cerebellum and the middle frontal gyrus, whereas the patients with schizophrenia did not show any significant activation. In the main versus related condition, the normal participants showed activations in the right insula and the bilateral middle frontal gyrus, whereas the patients with schizophrenia showed activations in the thalamus. In the main versus unrelated comparison, the normal participants revealed activations in the right superior colliculus, the left parahippocampal gyrus, the lingual gyrus, and the cingulate gyrus, whereas the patients with schizophrenia showed activations in the right superior temporal gyrus, the precentral gyrus, the medial frontal gyrus and the left insula.
Conclusions: These findings revealed the differences in recognition processing between the normal participants and the patients with schizophrenia. The characteristic of a brain activity during recognition processing for main theme words in schizophrenia was to be related to emotional processing rather than memory retrieval

P-46-007
Differential impairment of mesolimbic reward prediction and prediction error processing in unmedicated schizophrenics

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Objectives: Dysfunction of cortical and subcortical dopaminergic neurotransmission has for long been implicated in the pathogenesis of schizophrenia. Several studies (e. g. Juckel et al., 2005) have demonstrated that schizophrenic patients show an impaired ventral striatal response to reward-predicting stimuli. Recent data show that healthy elderly and patients with Parkinson's disease show a diminished mesolimbic reward prediction response, but a strong ventral striatal response to reward feedback.
Methods: We used a delayed monetary incentive task (Knutson et al., 2001) in an fMRI experiment of 25 unmedicated schizophrenics and 29 matched healthy controls.

Results: Young healthy adults showed a robust ventral striatal response to both the anticipation of a monetary gain and to the anticipation of an avoidable monetary loss. No such responses were observed in the patients. Schizophrenics instead showed a strong ventral striatal response to positive feedback (i. e. monetary gain). Notably, no ventral striatal response to a successfully avoided monetary loss was observed in the patients.
Conclusions: Our results demonstrate that schizophrenic patients, albeit being impaired in ventral striatal reward prediction, can generate mesolimbic prediction errors to gains. On the other hand, a successfully avoided loss might be insufficient to elicit a mesolimbic response in the patients, possibly due to the low signal-to-noise ratio in the mesolimbic dopamine system in schizophrenia.

P-46-008
Perinatal immune activation impairs emotional and cognitive functions with altered hippocampal glutamatergic neurotransmission in adult mice

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Objectives: Epidemiological studies have suggested that maternal infection during pregnancy is an environmental risk factor for the offspring to develop psychiatric disorders, including schizophrenia. However, little is known about the neurodevelopmental mechanisms by which perinatal infection induces brain and behavioral dysfunctions in later life. To develop a mouse model of the epidemiologic findings in schizophrenia, neonatal mice were treated with polyriboinosinic-polyribocytidilic acid (polyI:C) that induces strong innate immune responses. The emotional and cognitive functions were analyzed by various behavioral batteries in adult.
Methods: Neonatal ICR mice were repeatedly injected polyI:C for 5 days (postnatal day 2 to 6). They were subjected to behavioral analysis at the age of 8-10 weeks old. Cognitive and emotional functions were analyzed by using open field test, novel object recognition test, social interaction test, and prepulse inhibition test. To measure extracellular glutamate release in the hippocampus, in vivo microdialysis was carried out.
Results: The polyI:C-treated mice showed impairments of emotional behaviors, object recognition memory, social behaviors, and sensorimotor gating in prepulse inhibition test, compared to saline-treated control group. In vivo microdialysis revealed that depolarization-evoked glutamate release in the hippocampus was impaired in polyI:C-treated mice compared to vehicle-treated control mice.
Conclusions: These results suggest that polyI:C treatment during the perinatal stage in mice results in an impaired emotional and cognitive function with altered hippocampal glutamatergic neurotransmission in adult.

P-46-009
Improvement in cognitive functioning in schizophrenia after 6-month treatment with olanzapine

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Objectives: Positive effect of olanzapine on cognitive functions in schizophrenia was confirmed in many papers accessible in the literature. The objective of our study is to evaluate the effect of olanzapine treatment on cognitive functions in patients suffering from schizophrenia during a six-month observation.
Methods: Twenty patients with a diagnosis of schizophrenia according to ICD-10 diagnostic criteria for research were examined. 1 day before initiation of olanzapine a baseline assessment was performed. The neuropsychological examination was repeated 28 days, 60 days, 3 months, and 6 months after the beginning of treatment. The use of benzodiazepines was interrupted 48 hours before each assessment, and a continuous comedication with benzodiazepines never lasted longer than 48 hours. No other additional medication was administered. Cognitrone (COG) and Vienna Reaction Test (RT), both tests being a part of Vienna TEST System, were used.
The Positive and Negative Symptom Scale (PANSS) was also used to evaluate general nonpsychotic psychiatric symptoms, positive psychotic symptoms, and negative symptoms. The assessment with the use of PANSS took place on the same days as the neuropsychological examination.
Results: We have shown with the use of neurocognitive battery, that patients treated with olanzapine improved during the treatment. It is notable that this improvement was observed already on the 28th day of the treatment.
Conclusions: The above data here may be useful in encouraging clinicians to use olanzapine across the broad range of schizophrenic patients.

P-46-010
Impact of cognitive functions and anxiety on the quality of life in schizophrenia

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Objectives: The purpose of the research was to find a relationship between selected cognitive functions and anxiety in relation to the quality of life in subjective assessment in schizophrenic patients.
Methods: The study encompassed a group of patients hospitalized and continuing the treatment after the hospitalization in an outpatient setting. The battery of cognitive neuropsychological tests used to assess cognitive functions included: trail making test, and Stroop test. The intensity of anxiety as state and trait was assessed with the Spielberger State-Trait Anxiety Inventory (STAI).The patients were also requested to fill in the Life Quality Scale questionnaire and the questionnaire of the Frankfort Scale of mental and physical state. The results were analyzed statistically.
Results: In the examined group statistically significant relation was found between the results of measuring psychomotor speed, visual-spatial working memory, as well as intensity of anxiety as trait in a group of patients who have a negative opinion about the quality of their life. The correlation between negative opinion only about contacts with friends or eating meals was found in the group with anxiety as trait-was not found among the patients with psychomotor disruption.
Conclusions: The above correlations between cognitive and executive tests results show how important are that interactions in the process of constructing a good rehabilitation program for patients with schizophrenia.

P-46-011
Improvement of immediate and delayed recall in schizophrenia after a 6-month rehabilitation program

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Objectives: Patients with schizophrenia suffer from cognitive impairment which lead to problems in self-care, independent living, social and occupational functioning. It has been reported that psychosocial intervention may help these patients demonstrate improvement in areas of impaired functioning. Within this context, a comprehensive system of psychiatric rehabilitation interventions has been developed by our group. The first stage of this program includes therapeutic activities-psychoeducation, rehabilitation training activities, physical and cultural activities. We tried to assess the potential improvement in the patients' cognitive profile after the completion of this 6-month stage compared to baseline state at entry in the program.
Methods: Thirty-one patients with schizophrenia according to DSM-IV-TR criteria -20 men and 11 women, aged 22 - 53 years- gave informed consent before entering the study. All the patients chosen were in a stable condition. The patients were assessed both at the beginning and at the end of the 6-month stage with the following tests: Trail Making A and Trail Making B for visuospatial attention and executive functions, Stroop Neuropsychological Screening Test for selective attention, Rey Auditory Verbal Learning test (RAVLT) for verbal memory span and efficiency of learning, Wechsler Adult Intelligent Scale and Raven's Progressive Matrices for IQ, and the Brief Psychiatric Rating Scale for current psychopathology.

Results: Six subjects did not complete the six-month stage: 4 presented with recurrent psychotic symptoms and 2 chose not to continue. In the remaining 25 patients (completers), a significant improvement (u=224.5, p<0.05 Mann Whitney non-parametric test) was demonstrated in the scores of RAVLT at the end of the 6-month stage compared to baseline scores.
Conclusions: It has been shown that this six-month stage might be successful in improving immediate memory, efficiency of learning and delayed recall. On the other hand, significant improvement was not demonstrated in visuospatial and selective attention and executive functions.

P-46-012
Influence of psychopharmacotherapy on the aspects of secual self-perception in patients suffering from schizophrenia or depression

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Objectives: It is a well established fact that psychopharmacs influence sexual functioning in patients suffering from schizophrenia or depression. The aim of this research was to establish if psychopharmacs have an influence on the aspects of sexual self-perception in patients suffering from schizophrenia or depression, compared to healthy individuals.
Methods: 100 patients suffering from schizophrenia and 100 patients suffering from depression have been included in the research, as well as 100 healthy individuals. DSM-IV (TR) classification was used in order to diagnose those two disorders and Bezinovic's questionnaire in order to asses the aspects of sexual self-perception. Patients suffering from schizophrenia were divided into two groups: a) those treated with typical antipsychotics and b) those treated with atypical antipsychotics. Patients suffering from depression were also divided into two groups: a) those treated with SSRI's and b) those treated with various other antidepressants.
Results: Results show that healthy individuals score higher on all of the aspects of sexual self-perception compared to patients suffering from schizophrenia or depression. Furthermore, there is an evident difference regarding the aspect of sexual consciousness where patients suffering from depression treated with SSRI's score higher than patients suffering from schizophrenia treated with typical antipsychotics, while there are no statistically significant differences among other subgroups of patients.
Conclusions: We can conclude that psychopharmacs influence all of the aspects of sexual self-perception in patients suffering from schizophrenia or depression, but also that there are certain differences between patients suffering from schizophrenia and depression treated with different psychopharmacs.

P-46-013
Efficacy of modafinil in treating clozapine-associated sedation in patients with schizophrenia

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Objectives: Aim of the study is to provide evidence of efficacy of Modafinil (MOD) in treating Clozapine (CLZ)-associated sedation in patients with Schizophrenia.
Methods: In this prospective study, 10 patients with schizophrenia resistant to 1st line antipsychotic medication hospitalized in our department were selected. CLZ was administered (mean dose of CLZ: 370mg/d) and patients were responding well concerning psychosis. However, after CLZ reaching or exceeding daily dose of 100mg, patients complained of somnolence and sedation, confirmed by medical and paramedical staff of our department. Tolerance to the sedative effects of CLZ did not develop after a month of stabilizing its effective dose. MOD was then added to all 10 patients (mean dose: 110 mg/d). Epworth Sleepiness Scale (ESS) was used to measure sleepiness before and after MOD addition and t-test was used for comparison.
Results: A week after MOD initiation patients started improving in the sense that sedation was no longer a subjective complaint and sleep hours per day decreased from mean 11 to mean 8, before and after MOD addition respectively. A decrease in ESS score was observed. Dose of CLZ did not decrease. The effect of MOD was maintained at follow-up examinations conducted weekly for 3 months following patients' discharge. Side effects were not noted after MOD addition.
Conclusions: MOD seemed effective in treating CLZ-associated sedation and sleepiness in all 9 cases, maintaining its effect for at least 3 months. Psychosis was not exacerbated after MOD addition in any of our cases in contrast to one citation traced mentioning one case report. Possibly further studies with larger patient samples are needed to confirm our findings.

P-46-015
Cognitive measures in healthy controls and schizophrenic probands

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Objectives: Cognitive deficits are clinically relevant because they interfere in schizophrenic patients' daily lives, impairing relationships and working abilities.This study aims to evaluate cognitive abnormalities in healthy individuals and schizophrenic patients, in order to direct the practice of rehabilitation to the most deficient areas.
Methods: A cross-sectional study was design. Participants were 16 schizophrenic patients (followed in a rehabilitation unit) and 16 controls (no Axis I or II disorders), aged 22-65 (mean 44 and 46, respectively). All participants underwent assessment of a questionnaire with sociodemographic and clinical data and neuropsychological tests. Data were analysed with SPSS, version 15.0.
Results: Schizophrenic patients underperformed compared to healthy individuals in attention-concentration, calculation, language, drawing, copying and frontal function (p<0.05) and learning, recall and semantic memory (p<0.01). All cases were under antipsychotics. No significant statistical difference was found between those taking typical or atypical antipsychotics (p>0.05).
Conclusions: Cognitive deficits in schizophrenia affect the majority of patients. Deficits were severe and generalized. Their identification is relevant in order to direct rehabilitation to the most impaired areas.

P-46-016
Reducing stigma and discrimination against people with mental disorders

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Objectives: Stigma results from a process whereby certain individuals and groups are unjustifiably rendered shameful, excluded and discriminated against. Stigmatizing is a common human characteristic, it is pervasive and subtle in its effects, and it is difficult to counteract without clear and conscious strategies. Also, we can't exclude problem of self stigmatization, which means that mentally ill person have own shame and feeling of worthless, because of being ill.
Methods: In this study we presented 60 patients with main diagnosis of schizophrenia and schizophrenia similar disorders according to DSM IV whose had high scores at scale of Self – Stigmatization Questionnaire and bad outcome of Questionnaire of Quality of Life designed by WHO. All members of sample population were treated by medicaments, and to half of them were applied CBT based interventions for reduction symptoms of self – stigmatization.
Results: In 24 patients from first group we had significant reduction score at scale of self stigmatization and in 18 of them we had growth of score at scale of quality of life. Second group didn't show this changes (only 7 patient had reduction on stigmatization scale and 5 of them had bigger score of quality of life) after we finished research.
Conclusions: In the subgroup mentally ill patients suffering of self stigmatization CBT interventions applied in group setting and focused on facing and overcoming felling of shame and worthless, are highly effective. This kind of psychotherapy may improve quality of life mentally ill people and help them to restitute a part of their dignity and assumption.

P-46-017

Synergistic impacts of DISC1 mutation and neonatal polyI: C treatment on adult phenotypes in mice: A novel mouse model of schizophrenia with gene – environment interactions

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Objectives: Schizophrenia is a devastating psychiatric disorder that impairs mental and social functioning. Several genetic and environmental factors have been found to be associated with an increased risk to develop schizophrenia. Disrupted-in-schizophrenia 1 (DISC1) is one of the susceptibility genes for schizophrenia, and transgenic mice with the dominant-negative form of DISC1 (DN-DISC1) exhibit mild behavioral and histological abnormalities related to schizophrenia. In addition, an environmental factor such as viral infection during neurodevelopment has been attributed to a higher risk of schizophrenia. Here we study a possible interaction of genetic and environmental factors on neurodevelopment in mouse model by using a DISC1 genetically-engineered mice under exposure to the synthetic double strand RNA polyriboinosinic-polyribocytidilic acid (polyI:C).
Methods: Neonatal wild-type (WT) and DN-DISC1 mice (Hikida et al., 2007) were repeatedly injected polyI:C for 5 days. Behavioral analyses such as Y-maze test, novel object recognition test, fear conditioning test, social interaction test, and MK-801-induced hyperactiviy, were conducted at the age of 8 weeks old. Parvalbumin-positive GABAergic interneurons and adult neurogenesis were analyzed immunohistochemically.
Results: The polyI:C-treated DN-DISC1 (polyI:C/DN-DISC1) mice showed severe deficits in hippocampus-dependent memory and social behaviors in adolescence as compared with vehicle-treated WT (vehicle/WT) mice, while DN-DISC1 or polyI:C treatment alone had little effects. MK-801-induced hyperactivity was also significantly potentiated in the polyI:C/DN-DISC1 mice. The number of parvalbumin-positive interneurons in the medial prefrontal cortex was decreased while the survival of newborn cells in the hippocampus was increased in the polyI:C/DN-DISC1 mice as compared with vehicle/WT mice.
Conclusions: Our findings indicate synergistic impacts of DISC1 mutation and polyI:C administration on adult phenotypes in mice at both behavioral and anatomical levels. Neonatal polyI:C treatment in DN-DISC1 mice provides a valuable animal model for schizophrenia with gene-environment interactions.

P-46-018

Psychopathologic changes after anticholinergic challenge in drug-free patients with schizophrenia and healthy volunteers

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Objectives: The variety of different symptoms in schizophrenia can not be explained by the dopamine-hypothesis alone. In particular the neurobiological substrate of negative and cognitive symptoms is still not sufficiently explored. This study is based on a model, which explains the heterogeneity of the clinical symptoms in patients with schizophrenia by an imbalance in dopaminergic and cholinergic transmission. The purpose of this open, ongoing study is to investigate the dynamics of cholinergic/dopaminergic interactions in unmedicated patients with schizophrenia and healthy controls.
Methods: Ten medication-free (> six months) patients with schizophrenia and seven healthy controls were included, yet. They took part in two measurements: first a baseline examination without medication, then a second measurement preceded by administration of a single dose of the subtype-nonselective acetylcholine receptor antagonist biperiden (5 mg intravenously). In both conditions psychopathology was measured using the standardized PANSS interview. The acquired data were analyzed using t-tests.
Results: In both groups biperiden caused a significant increase of PANSS total score (patient group: 70 ± 20 without biperiden, 96 ± 21 with biperiden; healthy controls: 30 ± 0.4 without biperiden, 43 ± 11 with biperiden). This increase was significantly more pronounced in patients than in healthy controls (p=0.043). When the five-factor model of the PANSS was applied, highly significant increases in scores for negative symptoms (average increase: patients 33%, p=0,007; controls: 30%, p=0,02) and excitation (average increase: patients 92%, p=0,004; controls: 71%, p=0,005) were documented. In the patients group positive symptoms also increased significantly (+45%; p=0,001).
Conclusions: This systematic examination shows that an anticholinergic stimulation causes an exacerbation of psychotic symptoms in unmedicated patients with schizophrenia and healthy controls. Our results support the theory that stimulation of muscarinic acetylcholine receptors might mediate antipsychotic effects and that these receptors are hyperactive in schizophrenia.

P-46-019

Relationship between thyroid hormone concentrations and severity of mental symptoms in acute psychoses

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Objectives: The aim was to evaluate relationship between thyroid axis hormone concentrations and severity of mental symptoms in patients with acute psychosis.
Methods: Blood samples where drawn for the assessment of free thyroxine (FT4), free triiodothyronine (FT3), thyroid stimulating hormone (TSH), and thyroid peroxidase antibodies (TPOAb) concentrations in 104 consecutive patients with acute psychotic disorders such as schizophrenia, shizoaffective, delusional disorder and affective psychosis at the time of admission to the mental hospital. Thirteen patients with high TPOAb concentrations, indicating autoimmune thyroiditis and patients with high TSH concentrations, indicating hypothyroidism, were excluded from the study. Severity of mental symptoms was assessed using Brief Psychiatric Rating Scale (BPRS). Pearson's coefficients of correlations between thyroid axis hormone concentrations and severity of mental symptoms were calculated for 91 patients
Results: Total score of the BPRS did not correlate with any thyroid axis hormone concentration. However, severity of affective symptoms assessed by the BPRS showed significant relationships with thyroid axis hormone concentrations. FT4 concentrations showed negative correlations with scores of depressive mood (-0.303, p=0.004), feeling of guilt (-0.284, p=0.006), and blunted or inappropriate affect (-0.227, p=0.031). FT3 concentrations showed positive correlations with scores of grandiosity (0.210, p=0.045) and euphoria (0.237, p=0.024), and negative correlations with scores of motor retardation (-0.297, p=0.004) and emotional withdrawal (-0.218, p=0.038). TSH did show significant correlation with score of any psychiatric symptom.
Conclusions: Thyroid axis hormone concentrations are not related with general severity of mental symptoms in patients with acute psychoses. However, thyroid hormone concentrations correlate with affective symptoms of psychosis.

P-08
Brain Function I

P-08-001
Pharmacological characterization of the rhesus macaque Nociceptin receptor

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Objectives: The Nociceptin Orphanin FQ peptide (NOP) receptor (also known as ORL1 or N/OFQR) is a Gi-coupled GPCR belonging to the opioid receptor family and is widely distributed in the human brain. Based on rodent models, NOP receptor agonists may be useful for the treatment of pain, anxiety, cough, drug dependence, while antagonists might be of interest for dementia and Parkinson's disease. Unfortunately, rodent models have sometimes produced contradictory data regarding the direction of pharmacological modulation required for therapeutic use. Therefore, the use of an animal model closer to humans might help to clarify such issues. In this study we characterize the rhesus monkey (Macaca mulatta) NOP receptor in order to evaluate its response to NOP agonists and antagonists as a first step to translational pharmacology.
Results: The rhesus monkey NOP receptor was cloned by PCR from monkey brain. Sequencing identified 3 amino acid changes, versus the human receptor, located mainly in and around TM5. After expression in CHO cells, saturation binding of 3H-NOP showed a 2 site binding with a high affinity binding of Kd= 0.028nM and low affinity binding of 3nM. Binding of reference agonists and antagonists showed similar affinity to the human receptor. Also agonistic functional activity of reference compounds in a cAMP assay was similar to human data. A stable cell line expressing rhesus NOP was analyzed in high content screening and showed ~40% of constitutive receptor internalization. Nevertheless the labeled receptor is almost exclusively found in spot like structures after treatment with Nociceptin.
Conclusions: We conclude that the pharmacology of the rhesus monkey NOP receptor is very similar to the human receptor and that compounds active on the rhesus monkey NOP receptor should also be active on the human receptor. Using an animal model closer to human may allow clarifying the role of NOP in diseased states.

P-08-002
Possible role of FK-506 against 3-nitropropionic acid induced behavioral, biochemical, mitochondrial and neurochemical changes in striatum, cortex and hippocampus of rat brain

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Objectives: FK506 is well known immunosuppressant, currently being used for prevention of allograft rejection. Recently, neuroprotective effect of FK-506 has been reported through invitro models. Present study has been designed to investigate the possible role FK506, against 3-nitropropionic acid induced behavioural, biochemical, mitochondrial and neurochemical alterations in the striatum, cortex and hippocampus of rats.
Methods: Systemic 3-nitropropionic acid (3-NPA) administration for 14 days impaired locomotor activity, grip strength, body weight, oxidative damage [raised malondialdehyde, nitrite concentration, depleted antioxidant enzymes (SOD and catalase)], alteration in mitochondria enzyme complex (I, II, III and IV) and levels of bioamines (dopamine and norepinephrine) in striatum, cortex and hippocampus areas of rat brain.
Results: Further, FK-506 (0.5, 1 and 2 mg/kg) treatment significantly reversed these behavioral, biochemical, cellular and neurochemical changes in striatum, cortex and hippocampus areas of rat brain. However, effect was not dose dependent.
Conclusions: Study suggests that protective effect of FK506 could be due to its neuromodulatory action against 3-NP induced behavioural, cellular, neurochemical and oxidative damage in rat.

P-08-003
The role of nitric oxide system in the anticonvulsant effect of the cannabinoid CB1 agonist ACEA in the pentylenetetrazole-induced seizure in mice

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Objectives: Cannabinoid system plays a central role in the seizure threshold modulation which is mainly mediated through activation of the cannabinoid CB1 receptor. There is also several evidence of interaction between cannabinoid system and other neurotransmitters including nitric oxide. Using model of clonic seizure induced by pentylenetetrazole (PTZ) in male NMRI mice, we investigated whether NO is involved in the effects of cannabinoids on the seizure threshold.
Methods: Male NMRI mice 23-30 gr were used. In order to measure the seizure threshold PTZ (0.5 %) was infused in to the tail vain of freely moving animal by 30-gauge needle with constant rate of 1 mi/min.
Results: Injection of the selective cannabinoid CB1 agonist ACEA (2 mg/kg, i.p.) significantly increased the seizure threshold which was prevented by pretreatment with the selective CB1 antagonist AM251 (1 mg/kg, i.p.). The NO precursor L-arginine (50 and 100 mg/kg, i.p.) potentiated the anticonvulsant effects of the sub-effective dose of ACEA (1 mg/kg, i.p.). Pre-treatment with non-effective doses of the non-specific NOS inhibitor L-NAME (15 and 30 mg/kg, i.p.) and the specific neuronal NOS inhibitor 7-NI (40 and 80 mg/kg, i.p.) but not the inducible NOS inhibitor aminoguanidine (10, 50 and 100 mg/kg, i.p.) prevented the anticonvulsant effect of ACEA (2 mg/kg, i.p.). Co-administration of non-effective dose of AM251 (0.5 mg/kg) with both low and per se non-effective doses of L-NAME (1 mg/kg, i.p.) and 7-NI (10 mg/kg, i.p.) had significant ($P<0.01$) effect in preventing the anticonvulsant effect of ACEA (2 mg/kg, i.p.).
Conclusions: Our findings demonstrated that central NO system could be involved in the anticonvulsant properties of the specific cannabinoid CB1 agonist ACEA, emphasizing on the interaction between two systems in the seizure modulation.

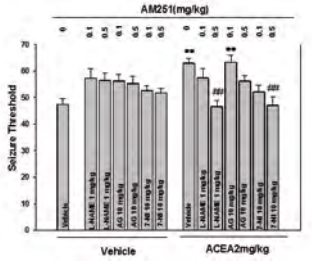

Figure 7. Effects of co-administration of a low doses of specific cannabinoid CB1 receptor antagonist, AM251 (0.1, 0.5 mg/kg) with different and per se non-effective doses of L-NAME (1 mg/kg), 7-NI (10 mg/kg) and AG (10 mg/kg) on the potent anticonvulsant effects of effective dose (2 mg/kg) of ACEA, a specific cannabinoid CB1 receptor agonist. AM251 and non effective doses of different NOS inhibitors or Vehicle were administered simoultaneusly15 min before i.p. injection of ACEA and 75 min before determination of PTZ seizure threshold. Each group consisted of at least 8 mice. Data are expressed as mean + S.E.M. of seizure threshold in each group. ** $P < 0.01$ compared with saline/vehicle control group; ## $P < 0.01$ compared with ACEA/vehicle control group.

P-08-005
[3H]-YM-09151-2 binding sites in human brain postmortem

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Objectives: The controversial and limited data on the distribution of dopamine (DA) receptors of type 4 (D4) in the human brain, prompted us to explore their density and pharmacology in the prefrontal cortex, striatum and hippocampus, by comparing and substracting the bindings obtained with different ligands.
Methods: Brain samples were taken during autopsy of 5 subjects. Tissue homogenates were incubated with increasing concentration of [3H]-YM-09151-2 and L-745,870 and/or sulpiride to define the non-specific binding. 1-Phenyl-2-propylaminopentane was used to block sigma receptors in some assays. The different potency of the [3H]-YM-09151-2 binding to D2/D3 and D4 receptors was also explored.
Results: D4 receptors, defined as described above, were found only in the hippocampus at low density, while in the prefrontal cortex and striatum our methodologies revealed a preponderance of D2/D3 and sigma receptors.
Conclusions: In conclusion, our findings underline that is still problematic to explore D4 receptors in the human brain with the available binding techniques.

P-08-006

A relationship between Brain-Derived Neurotrophic Factor and romantic attachment

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Objectives: Social attachment is a dimension which includes emotional, cognitive and behavioral features and develops from the first relationships between the infant and the caregivers. Oxytocin, vasopressin and, recently, neurotrophins (NTs) have been suggested to be involved in its neurobiology; however, no study has addressed the possible relationship between Brain-Derived Neurotrophin Factor (BDNF) and romantic attachment, a social behavior typical of human adulthood. Consequently, we aimed to investigate the possible involvement of BDNF plasma levels and romantic attachment.
Methods: Twenty-four healthy subjects (12 men, 12 women, mean age 30.8 ± 4.9 years) were included in this study. Romantic attachment was assessed by the Italian version (of the so-called "Experiences in Close Relationships" (ECR) questionnaire (Brennan et al., 1998), a self-report instrument developed specifically for its evaluation. BDNF levels were measured by an enzyme-linked immunosorbent assay.
Results: Women did not differ from men in terms of the demographic characteristics, distribution of attachment styles and mean BDNF levels but they showed a significantly higher score at the ECR anxiety scale than men ($p= 0.010$) and significant and negative correlation between the ECR avoidance scale and BDNF levels ($r = -0.87$, $p = 0.0001$. In women, BDNF levels were significantly and negatively correlated with the following ECR items: the #1 and the #13, while positive correlations were measured with the #20, #31 and #33. On the contrary, men showed only one negative correlation with the ECR item #6.
Conclusions: These results represent the first observations of links between BDNF and romantic attachment features in a sample of healthy subjects. BDNF may play a role in promoting social relationships through a specific effect to diminish avoidance and fear of the other, while reducing social stress responses. The involvement of BDNF in stress responses might be gender-related and, perhaps, based on hormonal and genotype interactions.

P-08-007

Men axillary extracts modify the affinity of the platelet serotonin transporter and impulsiveness in women

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Objectives: The pheromones are volatile compounds secreted into the environment by one individual and perceived by another of the same species, in which they trigger a physiological response or behavioral change. In consideration of the possible relationships between pheromones, serotonin (5-HT) and mood, the aim of this study was to assess the possible changes of a peripheral marker of the serotonergic system, i. e., the platelet 5HT transporter and of some psychological tests, in a group of twelve women after one-hour long application of men axillary extracts.
Methods: The 5-HT transporter was evaluated by means of the specific binding of 3H-paroxetine (3H-Par) to platelet membranes, as well as by means of 3H-5-HT reuptake in whole platelets, at baseline (T0) and after one-hour long stimulation (T1) with men axillary extracts. The following tests were used: the "Experiences in Close Relationships" Questionnaire (ECR), the latest version of the Barratt Impulsiveness Scale (BIS-11), and the Structured Clinical Interview for Mood Spectrum, self-reported version (SCI-MOOD last month).
Results: The dissociation constant (Kd) values of 3H-Par binding showed a significant decrease after the exposure to men axillary extracts, as compared with baseline values, while the the Bmax values and 3H-5-HT reuptake parameters did not show any change. Two factors of the BIS showed statistically significant differences, in particular, the attentional and the motor impulsiveness which both decreased at T1. Furthermore, at T0, the Kd values correlated significantly and positively with the factor of motor impulsiveness. At T1, a significant and positive correlation was measured between the Kd values and two ECR attachment styles, the secure and preoccupied, as well as with the ECR anxiety scale.
Conclusions: These findings suggest that axillary extracts, and perhaps pheromones carried by them, may provoke a rapid enhancement of the affinity state of the 5-HT transporter.

P-08-008

Study of influence Agonists and Antagonists of Dopaminergic Receptors on morphine-induced analgesia and tolerance

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Objectives: The effect of influence agonists and antagonists of dopaminergic receptors on morphine-induced analgesia and tolerance was investigated.
Methods: Experiments were carried out in albino rats (200-250 g). As a model of pain we used tail stimulation with focused infrared light. An opioid analgesic (morphine) and an agonist (parlodel, 0.05-0.1 mg/kg) and antagonist (alkopride,.1-4 mg/kg) of dopaminergic receptors were used for neuropharmacologicalanalysis
Results: Parlodel at dose of 0.05 and 0.1 mg/Kg did not affect the base line of tail flick latency of rat but dose-dependently potentiated the morphine analgesia. Pretreatment of rats with 5 mg/kg of alkoprid, a D-2 antagonist, not only blocked the effect of 0.1 mg/kg of parlodel but also antagonized the morphine analgesia. Daily injections of 10 mg/kg of morphine rapidly developed tolerance to the analgesic effect in control animals. Daily combined treatment of parlodel with morphine suppressed the development of tolerance to morphine suppressed the development of tolerance to morphine analgesia in a dose-dependent manner. However, in the animals daily treated with parlodel (0.1 mg/kg) plus alkoprid (4 mg/kg), the development of tolerance to the morphine analgesia was not significantly modified
Conclusions: Modification of morfine-induced analgesia and tolerance must be accomplished through an interaction of the opioid and dopaminergic systems

P-08-009

Uncoupling the D1-NMDA receptor complex Promotes NMDA-dependent LTP and working memory

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Objectives: Although dopamine D1 receptors are involved in working memory, how D1 receptors contribute to this process remains unclear. Numerous studies have shown that D1 receptors have extensive functional interaction with NMDA receptor. Our group has previously demonstrated that D1 receptors were able to regulate NMDA receptor functions through direct protein-protein interactions involving the carboxyl terminals of D1 receptors and NMDA receptor NR1a and NR2A subunits respectively. In the current study we explored the effects of the D1-NR1 interaction on NMDA receptor-dependent LTP and working memory by using the TAT–conjugated interfering peptide (TAT-t2).
Methods: mEPSCs are recorded in rat hippocampal primary cultures. Co-immunoprecipitation and CaMKII activity are measured in hippocampal slices and hippocampal neurons under the specified experimental conditions respectively. Working memory was assessed using a delayed match to place protocol in the Morris Water Maze following administration of the TAT- t2 peptide.

Results: Electrophysiology experiments showed that activation of D1 receptor upregulates NMDA receptor-mediated LTP in a CaMKII-dependent manner. Furthermore, D1 receptor agonist stimulation promotes the NR1-CaMKII coupling and enhances the CaMKII activity; and the D1 receptor-mediated effects can be blocked by the application of the TAT-t2 peptide. Interestingly, animals injected with TAT-t2 peptide exhibited significant impaired working memory.
Conclusions: Our study showed a critical role of NMDA-D1 direct protein-protein interaction in NMDA receptor-mediated LTP and working memory and implicated the involvement of CAMKII in this process.

P-08-010
Phospholipids in dynamics of free radical oxidation of lipids in biological membranes brain under conditions of Parkinson's disease

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Objectives: Oxsdative stress resulting from the imbalance between reactive oxygen species formation and antioxidant defenses plays a major role in the pathogenesis of Parkinson's disease. Quantitative and qualitative compositions of phospholipids as well as lipid peroxidation were studied in outer and inner mitochondrial membranes and microsomal fraction from rat brain in under the experimental Parkinson's disease.
Methods: The Parkinson's disease model was obtained by N-methyl-4phenyl,1,2,3,6-tetrahydropyridine injection in rats. According to the resuls of our investigation, in the experimental Parkimson's disease amount of phospholipids mainly cardiolipids and phosphatidyletanolamines, was increased in the inner and decreased in outer mitochondrial membranes. Phosphatidylcholines and phosphatidylserines were increased in microsomal fraction (using the method of thin-layer chromatography on silicagel). At the same time, lipid peroxidation was activated both in ascorbate- and NADPH-dependent systems of oxidation (determined malonic dialdehyde and hydroxides).
Results: These data suggest, that lipid peroxidation affects the composition of mitochondrial membranes either by means of removing of the substances from membranes or via their redistribution between the subcellular fractions.
Conclusions: It must be note that the high concentrations of lipid peroxides which have a membranotoxic, membranolytic properties play an impotant role as a main compounds in the formation of phatogenetic mechanisms of Parkinson's disease.

P-08-011
Sarcosine reversed the MK-801-induced disruption of spontaneous alternation behavior in mice

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Objectives: Since the N-methyl-D-aspartate (NMDA) receptor is thought to be involved in cognition, activation of NMDA receptors might enhance cognitive performance. Glycine is a positive modulator of NMDA receptors, and an increase in endogenous glycine in the synaptic clefts through inhibition of glycine transporters may therefore lead to the improvement of cognitive impairments. Spontaneous alternation behavior has been recognized as one of the models for the measurement of working memory performance. Working memory is thought to be one of the most important domains of cognitive impairments in schizophrenia. The aim of this study is to assess the effect of a glycine transporter-1 (GlyT1) inhibitor on this behavior.
Methods: In this study, we examined the effect of N-methyl glycine (sarcosine), one of the most commonly used GlyT1 inhibitors, on working memory deficit in mice by observing spontaneous alternation behavior in the Y-maze after treatment with MK-801. In addition, we examined the effects of some other antipsychotics, such as haloperidol, risperidone, and clozapine to compare with sarcosine.
Results: After treatment with MK-801, the alternation rate decreased to the chance level (about 50%). Sarcosine significantly attenuated the decrease in alternation rate induced by MK-801 at doses of 5-20 mg/kg, whereas haloperidol (0.025-0.2 mg/kg po), risperidone (0.0125-0.1 mg/kg po), and clozapine (0.1-3 mg/kg po) had no significant effect.
Conclusions: These results suggest that sarcosine could improve cognitive impairments in the hypoglutamatergic state mimicked by treatment with MK-801, while the currently available antipsychotics could not. Since the hypoglutamatergic state is thought to be one of the candidates of the pathogenesis of schizophrenia, GlyT1 inhibitors may be a useful for treatment for the cognitive impairments associated with schizophrenia that cannot be improved by currently available antipsychotics.

P-08-012
Effect of sytemic administration of CH 113 on cognitive functions after excitotoxic hippocampus lesions in spatial learning task

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Objectives: It has been repeatedly demonstrated across species that the hippocampus is critical for spatial learning and memory. An excitotoxic action of glutamate contributes to the pathological outcome of certain neuropsychiatric disorders. In the present study, the cognitive performance of rats with NMDA-induced excitotoxic lesions of dorsal hippocampus has been compared to the neuroprotective drug - CH113-treated rats.
Methods: The rats treated with CH113 were divided into 12 subgroups, 4 administration schedule subgroups (30 minutes after, 30 minutes before and after, 3 hours and 24 hours after NMDA lesion) at 3 doses (0.01; 0.1 and 10 mg/kg i.p.). Cognitive functions after lesion were tested in aktive allothetic place avoidance task (AAPA). The principle of this task is that rats are moving over a uniform circular arena, on which an arbitrarily located unmarked sector is defined, entering which is punished by a mild footshock. Successful performance of the task requires that the snímal identifies its position and the position of the shock sector in the room frame. The AAPA task is highly dependent upon hippocampus and requires more complex cognitive abilities (including cognitive coordination) than classical behavioral tests.
Results: Systemic administration of CH113 at all doses, applied 30 minutes after lesion improved performance of AAPA tasks compared to non-treated lesioned rats. Administration of CH113 alone revealed no serious side effects (hyperlocomotion and motor disturbances), which are typical for experimental drugs protecting against neuronal loss caused by NMDA excitotoxicity (especialy non-competitive antagonists of NMDAR).
Conclusions: We conclude that blockade of excitatory transmission at the NMDA receptor without side effects by CH113 may represent a potential therapeutic approach to the acute treatment of neuropsychiatric disorders linked with this excitotoxic effect of glutamate. This project was supported by grants IGA MZd NR/9180-3, GACR 309/07/0341 and MSMT 1M0517.

P-08-013
Limbic system surgery for the treatment of obsessive compulsive disorders

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Objectives: The use of stereotatic approaches to various regions within the limbic system was gradualy expanded over the next 20 years - to treat mental disorders considered untractable by conventional psychiatric methods. Obsessional compulsive disorder can be extremely distressing and treatment resistant. When all others methods of treatment including beharvior - cognitive therapy have failed and disability and distrass are unbearable, limbic system surgery can be considered.

Methods: Fourteen patients were underwent to psychosurgery with chronic, severe obsessive compulsive disorders. Their mean duration of illness was 10,5 years and all of them was considered untractable by two psychiatrists. The patients were cassified according to DSM IV diagnosis. The severity of the illness were rated by the scale Obsessive compulsive of Yale- Brown; and CGI (Clinical global impression). Neuropsychological evaluation were aplicated before and after the treatment during two years. All the operations are carried in the clinical Hospital from São Paulo by the same neurosurgeon using a stereotatic approach. The mains targets were anterior bilateral cingulotomy and inominatotomy (imbic lencotomy).
Results: After 24 months 6 of the 14 patients were rated as much improved. Two were symptoms free. Four were improved and other two patients did not improve but not worse. Adverse events will be discussed.
Conclusions: Stereotatic technic has dramatically reduced the danger of side-effects in functional neurosurgery. All cases presented modifications and a better response to pharmacological treatment with low doses of psychotropic drugs. This surgical procedure which should not be neglected by psychiatrists means are able to relieve human to a greater degree.

P-08-014
Involvement of 5-HT2B receptors in the regulation of energy homeostasis

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Objectives: Eating disorders are an important healthy problem. Dexfenfluramine (DF) was prescribed as an anorexic molecule for the treatment of obesity. DF promotes 5-HT release and inhibits its recapture, with little selectivity for 5-HT receptors. Many studies identified 5-HT2C receptors in DF-induced hypophagia; however DF still leads to hypophagia in 5-HT2C-/- mice. Norfenfluramine, the main DF metabolite, is a selective to 5-HT2B/2C receptor agonist. Therefore, we investigated a putative role of 5-HT2B receptors in feeding behaviour.
Methods: Mice were fasted 24hours. They received an acute injection of anorexic drugs 20 minutes before the onset of the dark phase. Food was returned at the onset of the dark cycle, and cumulative food intake was recorded during 4hours. Different 5-HT receptors antagonists used were injected one hour before the dark phase.
Results: In 5-HT2B-/- mice, no modification in 5-HT2A/2C receptors expression was observed. These mutant mice have no modification in body weight and meal size at 10 weeks, but plasmatic level of leptin is decreased. Strikingly, 5-HT2B-/- mice present no hypophagic response to DF. These findings are further validated by the lack of hypophagic response to DF of wild type mice treated with RS124445, a selective antagonist of 5-HT2B receptors. Furthermore, hypophagia induced by 5-HT2C agonists is similar in 5-HT2B-/- mice and control. These observations are similar in SERT-/-mice, DF has no effect on food intake, but 5-HT2C agonists induced a hypophagia.
Conclusions: These findings indicate that activation of 5-HT2B receptors is a linking step in anorexic effect of DF. Also it seems that the 5-HT2B receptors modulate the DF effect in the same way that SERT, so we hypothese that the role of these receptor is presynatic. In order to test this hypothesis we performed bain microdialysis experiment on awake mice.

P-08-015
First characterization of tryptophan hydroxylase 2 knockout mice

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Objectives: Serotonin (5-HT) has long been implicated in the etiopathogenesis of a wide spectrum of psychiatric disorders and as trophic factor in various processes of early development and brain plasticity. Key enzymes in 5-HT synthesis are the two isoforms of tryptophan hydroxylase (TPH), TPH1 and TPH2, whose differential role in 5-HT synthesis is still discussed controversially. This study tries to clarify the origin of central 5-HT and its impact on murine brain development using the newly generated Tph2 knockout (-/-) mice.
Methods: Initial histological phenotyping of Tph2 -/- mice targeting serotonergic markers (e.g. Tph2, Tph1, 5-HT, SERT, Pet-1 and Vmat2) as well as the dopaminergic and GABAergic systems were carried out in single and double labeling experiments using immunohistochemistry and in situ hybridization. In addition, HPLC measurements of 5-HT and its metabolites are currently conducted in different brain regions.
Results: Lack of Tph2 results in complete deficiency of 5-HT synthesis within the brain indicated by the absence of 5-HT immunoreactive cells in the raphe nuclei. Nevertheless, Tph2 -/- mice survive without obvious developmental brain defects. Formation of serotonergic neurons, although unable to produce 5-HT, seems to be unaffected, as revealed by Pet-1 and SERT expression pattern.
Conclusions: These results confirm Tph2 as the exclusive neuronal isoform responsible for 5-HT synthesis within the brain. Interestingly, central synthesis and neurotransmission of 5-HT seems neither necessary for survival and development of Tph2 -/- mice, nor for differentiation of the serotonergic system itself.

P-08-016
Possible Roles of BDNF – induced Microglial Intracellular Ca 2+ Elevation in the pathophysiology of psychiatric disorders

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Objectives: Microglia are the intrinsic immune cells and release many factors including proinflammatory cytokines, nitric oxide (NO) and neurotrophins after the disturbance in the brain. In addition, elevation of intracellular Ca2+ concentrations ([Ca2+]i) is required for the release of cytokines and NO from activated microglia. There is increasing evidence that suggests that pathophysiology of psychiatric disorders is related to the activation of inflammatory responses in the brain. We have recently reported that antipsychotics suppressed the release of NO and cytokines from activated microglia[1]. Brain-derived neurotrophic factor (BDNF) is a neurotrophin well known for its roles in the pathophysiology of psychiatric disorders. On the other hand, alteration of intracellular Ca2+ signaling also underlies the pathophysiology of psychiatric illness. BDNF increases [Ca2+]i in neurons and astrocytes. However, there have been no prior reports on how BDNF affects intracellular Ca2+ mobilization in microglia.
Methods: We tested the effects of BDNF on [Ca2+]i in both murine microglial cell line, 6-3 and primary rat microglial cells, using the fura-2 imaging. We also measured the amount of NO released from activated microglia using Griess reaction assays.
Results: BDNF induced sustained increase in [Ca2+]i through the truncated neurotrophin TrkB receptors, activation of PLC pathway and store-operated calcium entry in murine microglial cells. We also observed that pretreatment of BDNF suppressed both the generation of NO and the IFN-γ-induced increase in [Ca2+]i, along with a rise in basal [Ca2+]i in microglial cells. In addition, pretreatment of selective serotonin reuptake inhibitor (SSRI) potentiated the BDNF-induced elevation of [Ca2+]i in microglial cells.
Conclusions: Our results suggest that BDNF could regulate the inflammatory responses via the modulation of microglial Ca^{2+} signaling in the brain. Moreover, BDNF-induced microglial Ca^{2+} elevation might have important roles in both pathophysiology and treatment of psychiatric disorders. 1.Kato T et al.,J Neurochem 2008:106(2):815-25

P-08-017

Central effects of antidiuretic peptide desmopressin after its peripheral application on spontaneous behavior of rats

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Sixtus Hynie

Objectives: Vasopressin (AVP) and oxytocin have not only typical peripheral effects but in the brain they also have significant central regulatory actions as neurotransmitters and neuromodulators. AVP participates on the ACTH release during stress and plays a significant role in cognitive functions and emotionality. Its analog desmopressin (DDAVP) devoid of pressoric actions is routinely used as antidiuretic drug. In spite of that there is not enough data concerning its central effects. Thus, the aim of this work was to determine changes in spontaneous behavior of rats in the open-field after peripheral application of DDAVP.

Methods: We used male Wistar rats. DDAVP (1-desamino-8-D-arginin vasopressin) (PolyPeptide Laboraries, Czech Republic) was administered i.p. in doses from 0.03 to 3.0 mg/kg b.w. Exploratory activity was studied in an open-field apparatus with circular arena (diameter 150 cm). Behavioral parameters were videorecorded with the software AnyMaze (Stoelting Co., IL, USA). ANOVA was used for statistical analysis.

Results: DDAVP given peripherally substantially changed behavior of rats in the open-field device. After all used doses we observed inhibition of horizontal as well vertical exploratory activities. Significant sedative action was found already from doses starting from 0.1 mg/kg b.w. These effects disappeared after 24 hours. In spite of the fact that DDAVP is peptide drug with limited passage through blood brain barrier, we observed very substantial inhibition already after very small doses. Unlike oxytocin that has two-phase action (stimulatory effect of low doses and inhibitory effect of high doses), DDAVP had only sedative effects.

Conclusions: Peptide DDAVP, given peripherally, reveals remarkable inhibitory effects on spontaneous behavior of rats in the open-field. Our findings support the notion that this drug may have some therapeutic indications in the treatment of several psychiatric disturbances. Supported by MSM 0021620806.

P-08-018

Renalase, a novel monoamine oxidase, is synthesised in the central nervous system

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Objectives: In the central nervous system (CNS), the oxidative deamination of monoamine neurotransmitters is accomplished by two membrane-bound enzymes: monoamine oxidase and vascular adhesion protein-1. The combined activities of these proteins are crucial for the regulation of neurotransmitter disposition and consequently normal brain function. Recently, the discovery of a novel soluble monoamine oxidase, renalase, was reported. Given the functional similarities between renalase and MAO, we investigated if the tissue expression pattern of these proteins overlapped.

Methods: Human tissue samples were obtained from the Victorian Institute of Forensic Medicine Tissue Donor Bank at autopsy. Tissues were obtained from donors who died from a variety of causes, including suicide. Total RNA and soluble protein were obtained from various tissues. Reverse-transcription PCR and Western blotting were used to identify renalase gene expression in these tissues.

Results: Analysis of samples obtained from tissue donors revealed that renalase has a far larger representation in human tissues than previously reported. Using western blotting techniques, we observed renalase in the hypothalamus, pons, medulla oblongata, cerebellum, pituitary gland, cortex and spinal cord. We used RT-PCR to validate these observations. Furthermore, we identified several splice variants of the renalase transcript. These splice variants appear to be tissue-specific and point to a "fine-tuning" of renalase function.

Conclusions: Here, we report for the first time, the identification of a novel soluble monoamine oxidase, renalase in the human CNS. We reveal the existence of several splice variants of the renalase gene. Our findings provide further insight into the pathways regulating monoamine neurotransmitter disposition in the brain. Future investigations into the structural and functional characteristics of renalase may help to facilitate our ability to diagnose and treat disorders involving an imbalance in the levels of monoamine neurotransmitters.

P-08-019

Is tyramine hydroxylation to dopamine operative in the brain?

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Objectives: In vitro studies demonstrated that dopamine can be formed in brain microsomes via tyramine hydroxylation, catalyzed by the cytochrome P450 2D isoforms (CYP2Ds) - human CYP2D6 and rat CYP2D2, CYP2D4 and CYP2D18. The aim of the present work was to find out whether that alternative pathway of dopamine synthesis occurred in the brain in vivo.

Methods: The first experiment was carried out on male Wistar rats which had the classic pathway of dopamine synthesis (from tyrosine) inhibited by prior administration of reserpine (10 mg/kg sc) and α-methyl-p-tyrosine (α-MT; 300 mg/kg ip). Some rats were then treated with pargyline (150 mg/kg ip) to prevent the degradation of tyramine and tyramine-derived dopamine. Some rats of the latter group (reserpine + α-MT + pargyline) also received the specific CYP2D inhibitor quinine (50 mg/kg ip.) to inhibit the alternative pathway of dopamine synthesis. Dopamine levels were measured in brain structures (the nucleus accumbens, substancia nigra, striatum, prefrontal cortex, truncus cerebri, cerebellum, olfactory bulbs and the remainder of the brain). The second experiment was conducted on reserpinized rats injected with α-MT, which were then given tyramine (100-500 µM) by local infusion to the striatum (a microdialysis method). The levels of tissue dopamine in brain structures and of extracellular striatal dopamine were measured using the HPLC method with electrochemical detection.

Results: Quinine, a specific CYP2D inhibitor, significantly decreased dopamine level in the striatum and nucleus accumbens of reserpinized rats after inhibition of the classic pathway of dopamine synthesis. Local infusion of tyramine to the striatum by a microdialysis method evoked an increase in extracellular dopamine level in vivo.

Conclusions: The results of our study indicate that hydroxylation of tyramine to dopamine, catalyzed by CYP2D, is operative in rat brain in vivo. This alternative pathway of dopamine formation in the brain may have some implications for Parkinson's disease and drug addiction.

P-18
Brain Function II

P-18-001

Analysis of a novel, stress-inducible transcript in the mouse brain

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Abstract: Aiming at identifying potential novel stress regulated genes we studied the effects of 24 hours maternal deprivation on gene expression in the paraventricular nucleus (PVN) of 9 day-old mice using a microarray approach. Among the strongest regulated genes we discovered a novel transcript of so far unknown function (working name MPIP-101), which showed a pronounced upregulation after maternal deprivation. This gene codes for a short hypothetical protein that is conserved throughout many species. The aim of the current study is the functional analysis of the expression and regulation of this gene in neonatal and adult mouse brain. In neonate mice, glucocorticoid receptor (GR)-antagonist treatment prevented the maternal deprivation induced upregulation of MPIP-101 mRNA in the PVN, indicating a GR dependant gene regulation.

This finding is in line with a promoter analysis of this gene, which revealed several functional GRE sites. In adult mice MPIP-101 is strongly expressed in the CA3 region of the hippocampus, in the cortex and the cerebellum, with very low expression in the PVN under basal conditions. Dexamethasone treatment and food deprivation resulted in a profound induction of gene expression in the PVN, confirming the data of the experiments in neonatal mice. Hippocampal over expression in vivo using an adeno-associated viral vector revealed improved cognitive flexibility in the reversal learning task of the morris water maze, as well as a more active stress coping behavior in the forced swim test. Further MPIP-101 over expression was found to modulate the electrophysiological properties of the hippocampus. In ongoing studies we will analyze the cellular localization of this interesting candidate, its interaction with other proteins and assess a possible co-localization with central stress markers.

P-18-002
Two types of personality changes due to brain damage: A case-control study

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Objectives: To find out the peculiarities of formation of personality changes due to brain damage of traumatic, infectious, toxic genesis, and how different factors conduce to their development.
Methods: It was carried out a case-control study at a specialized clinic during 10 years. The study groups were formed from all inpatients with non-psychotic disturbances due brain damage of traumatic, infectious, toxic genesis (F06-07), diagnosed according to ICD-10 and clinical-psychopathological analysis. Using specially designed questionnaires the psychiatric and somatic-neurological states of the mentioned patients have assessed. They also completed Hopkins Symptom Inventory (SCL-90). There were identified 36 patients who developed personality changes of hypochondriacal type (Hypochondriacal group - HGr). 57 patients with personality changes of explosive type selected by chance formed the Explosive group (EGr). 31 patients with neurotic disorders due to brain damage and without personality changes selected by chance included in the Control group (CGr).
Results: There were not found significant differences between 3 groups by the sex, age of the onset and duration of the disorder. Statistically significant differences were found by familial occurrence of mental disorders and preinjury accentuations of character between the HGr and CGr ($p<0.05$). 89.5% patients of the EGr were affected by severe psychogenic factors before the brain damage and/or after it, but only 32.2% of the HGr and 22.2% of the CGr had the same influences. So the number of distressed patients in EGr was significantly higher than in HGr ($p<0.001$) and CGr ($p<0.001$). There were significant differences on some subscales of SCL-90 between the 3 groups.
Conclusions: There is certainly interplay of factors in the genesis of personality changes due to brain damage, with an intertwining of neurological and non-neurological contributions. The hereditary, constitutional and psychogenic factors are of great importance in the typological formation of the personality changes due to organic brain damage.

P-18-003
Novel cognitive enhancing dipeptide Noopept modulats inhibitory synaptic transmission in hippocampus

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Objectives: The aim of this study was to investigate whether novel prolin- containing dipeptide Noopept (NP) influences synaptic transmission in central neurons. NP was synthesized as peptide analog of pirazetam which is known as one of the most efficient memory- enhancing drugs Besides of nootropic activity NP displays also anxiolitic effects. Our previous experiments performed on isolated molluscan neurons revealed that NP efficiently suppress different types of potassium currents (Bukanova et al., 2002) Proceeding from this observation we hypothesized that NP can influence synaptic transmission in central neurons by the regulation of transmitter release from synaptic terminals.
Methods: To test this hypothesis we measured the effect of NP on spontaneous IPSCs in CA1 pyramidal cells in rat hippocampal slices using patch- clamp technique in hole- cell configuration.
Results: It was found that NP(1μM) increases spike- dependant release of GABA from ter.minals of inhibitory interneurons on CA1 pyramidal cells. It manifests itself in the increase of amplitude and frequency of spontaneous TTX- sensitive sIPSCs whereas TTX- non sensitive mIPSCs remain unchanged. TEA (10 mM) evoked similar but stronger effect than NP producing in some cells rhythmical bursts of IPSCs.
Conclusions: At least two mechanisms can be considered to explain the effect of NP: 1 Block of potassium channels in the terminals of inhibitory interneurons 2. Excitation of inhibitory interneurons which terminate on CA1 pyramidal cells through the suppression of a resting K+ conductance as it has been earlier demonstrated for CCK- 85 (Miller et al, 1997) and TRH (Deng et al.,2006). Increase of tonic inhibition mediated by NP can be interpreted in the framework of its anxiolitic or anticonvulsant activity whereas an explanation of its memory- enhancing effect remains to be elucidated. Supported by: Russian Foundation for Basic Research (Grants 08-04-00978 and 07-04-12122)

P-18-004
Oxidative and antioxidative capacity in LPS treated mice

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Objectives: Ischemic/reperfusion injury, inflammatory processes and other oxidative stress enhances the formation of reactive oxygen species (ROS) and cytokine (IL-6) - production, which in turn interferes with vascular tone resulting in cellular damage and organ dysfunction. Important is the state of oxidative and antioxidative capacity, which is predicted by cellular concentrations of SH-groups, ATP, glucose, lactate) and enzyme activities (glutathione reductase;GR; glutathione-S.Transferase, GST; myeloperidase, MPO; NADPHoxidase, NADPHox). Aim of our investigation were the changes in the antioxidant capacity peripheral as well as in the CNS after peripher induced inflammation.
Methods: Microdialyse probes were stereotactically implanted in the striatum of balb/c mice to measure ROS and IL-6. Brain, aorta and blood ROS were detected by electron spin resonance spectroscopy using CMH as spin label. IL,-6 (blood and brain) and 8-OHdG (urine) were measured using commercial kits form MD and Centaur. Experiments were started with a 2h control period following a 3h LPS (100μg/kg, i.p.) period terminated by euthanizing the animals and freezing tissue (brain, liver, lung, heart, pancreas, kidney and duodenum). Blood born ROS and aorta ROS were analyzed immediatally.
Results: LPS increased significantly ROS release in the striatum, blood born ROS and the formation of ROS in aorta. Il-6 is 2fold enhanced in the striatum and increased from 7 up to 1850 pg/ml in plasma. 8-OHdG is doubled in urine. Antioxidative SH-group capacity is significant diminished in all tissues and blood. GR activity in some tissue was significantly increased. LPS enhanced MPO activity up to 8-10 fold, while NADPHox activity were slightly enhanced. LPS diminished extracellular glucose in brain and plasma significantly.
Conclusions: We here present an in vivo method for the measurement of radical formation in the brain. LPS-induced oxidative stress affects mainly SH-groups (glutathione) and neuronal damage is measurable. Glutathione reduction is probably due to glucose reduction.

P-18-005
To the role of hydrogensulfide in psychiatric disorders: A preliminary study in mice

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Objectives: Nitric oxid (NO), carbon monoxide (CO) and hydrogensulfide (H2S) are endogenously formed vascular gases active in the multilevel regulation of pathophysiological functions in mammalian tissues. H2S produced by cystathionine-ß-synthase (brain) or cystathionine-gamma-lyase (systemic) cle K+ATP channels and H2S is involved in corticotropin-releasing-hormone formation in the hypothalamus. H2S levels are decreased in the brains of Alzheimer´s patients and promotes central long-term potentiation by enhancing sensitivity to NMDA receptors. H2S is systemically enhanced in septic shock, pancreatitis and other diseases with a systemic inflammatory reaction. Up to now there are no data available about the role of hydrogensulphide in psychiatric disorders. Aim of the investigation was to analyse in a first step mouse striatal glutamate and reactive oxygen species after local and systemic sulphide application.
Methods: Microdialysis probes were stereotactically implanted into the striatum of balb/c mice. NaHS was co-infused in ringer solution (1.5µl/min) via microdialysis probe together with the spin label CMH to measure ROS. ROS were detected by electron spin resonance spectroscopy. Central nervous glutamate formation was analyzed by Tandem MR Spectroscopy. For analyzing the systemic inflammatory reactions plasma sulphide content, ROS content in blood, myeloperoxidase activity in lung and duodenum, as well as NADPHox-activity in liver were investigated.
Results: Local striatal application of NaHS results in a diminished ROS formation combined with an increase in extracellular glutamate. Systemic application of NaHS induced a significant decrease in blood born ROS and an increase in plasma H2S of mice. The application of NaHS in liver homogenat showed a biphasic and concentration dependent formation of ROS. The i.p. injection of NaHS results in a highly significant increase in lung MPO.
Conclusions: H2S is a new neuromediator such as NO and CO. Our data indicate that H2S is able to interact with the formation of glutamate and reactive oxygen species, important for the pathophysiology of schizophrenia or major depression.

P-18-006
Cannabinoid receptor activation in the basolateral amygdala blocks the effects of stress on the acquisition and extinction of inhibitory avoidance

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Objectives: Despite the efficacy of behavior therapy for human anxiety disorders, extinction-like treatments require repeated cue exposures and are vulnerable to reversal by a number of environmental factors, particularly stress. The endocannabinoid system has recently emerged as important in the regulation of extinction learning and in the regulation of the hypothalamic-pituitary-adrenal axis. Here, we aimed to examine the involvement of the cannabinoid CB1 receptor in the basolateral amygdala (BLA) in inhibitory avoidance (IA) conditioning and extinction and to test whether cannabinoid activation would reverse the effects of stress on these memory processes.
Methods: To that end, the CB1/2-receptor synthetic full agonist WIN55,212-2 (5 µg/0.5µl) was microinjected into the BLA either before conditioning, or before the first extinction trial or after the first extinction trial with or without exposure to environmental stress.
Results: WIN55,212-2 microinjected into the BLA had no effect on IA conditioning or extinction by itself. However, microinjecting WIN55,212-2 into the BLA prior to exposing the rats to the elevated platform stress reversed the stressor's enhancing effects on IA conditioning, and its impairing effects on IA extinction. Importantly, WIN55,212-2 microinjected into the BLA reduced stress-induced elevations in corticosterone levels. Control experiments demonstrated that: (i) the effects of WIN55,212-2 could not be attributed to sensory-motor deficits as these parameters seemed unchanged by WIN55,212-2 microinjected into the BLA, and that (ii) the CB1 receptor in the BLA is crucially involved in the extinction of IA, as the CB1 receptor antagonist AM251 (6 ng/0.5µl) microinjected into the BLA significantly blocked extinction.
Conclusions: These results may support a wide therapeutic application for cannabinoids in the treatment of diseases associated with inappropriate retention of aversive memories and stress-related disorders.

P-18-008
Neurotoxic trace elements in bipolar disorder

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Objectives: Determinate the involvement of certain trace elements, which are potentially neurotoxic, in the development of neurodegenerative processes. Lead, copper, thallium and zinc are well known neurotoxics, and for them it´s not safe threshold.
Methods: Lead and cadmium concentrations have been measured by electrothermal atomic absorption spectrometry, in a sample of 25 patients diagnosed of bipolar disorder.
Results: We have observed superior lead concentrations in blood and urine, cadmium in blood and urine, zinc in blood and thallium in urine, in the group of bipolar patients.
Conclusions: More research is required to clarify the role of these neurotoxics in the ethiopatogenia or aggravation of cognitive dysfunctions in bipolar disorder.

P-18-009
Matrix Metalloproteinases in the Cerebrospinal fluid of suicide attempters

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Objectives: Matrix metalloproteinases (MMPs) are involved in the regulation of inflammatory reactions and immunity. Several lines of evidence suggest a possible association between inflammation and suicidal behavior. The objective of the present study was to assess the levels of matrix metalloproteinases (MMPs) in the cerebrospinal fluid (CSF) of suicide attempters. In addition, the hypothesis that MMP levels may correlate with different aspects of suicidal behavior was tested.
Methods: MMP1, MMP3 and MMP9 were measured in the CSF of suicide attempters (n=111) and healthy controls (n=44) using Mesoscale Discovery multiplex MMP immunoassay. Patients were classified according to diagnosis and violent or non-violent suicide attempt. Suicidal ideation and depressive symptoms were evaluated using the Suicide Assessment Scale and the Montgomery – Åsberg Depression Rating Scale (MADRS). Non-normally distributed variables were transformed into natural logarithms (ln) before analysis. Student's T-test, Spearman rank correlation coefficient (rho) test and linear regression were used for statistical analysis (using SPSS 16 software).
Results: No differences in MMP1, MMP3 and MMP9 levels were observed when all suicide attempters were compared to healthy controls. However, adjustment disorder and substance abuse were significant independent predictors of MMP1 levels in the CSF of suicide attempters, in models correcting for comorbid psychiatric diagnoses (beta = 0.202, p = 0.031 and beta = 0.226, p = 0.012, respectively).
Conclusions: Our results indicate that alteration in MMP1 expression occurs in subsets of suicide attempters. This finding could have important implications for the discovery of suicide-associated biomarkers and for the elucidation of pathophysiological mechanisms in suicidal behavior.

P-18-010

The role of Urocortin peptides in regulating the central stress response: Evidence from a novel Urocortin triple knockout mouse model

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Objectives: The corticotropin releasing factor (CRF) -peptide family includes, in addition to CRF, the three Urocortin (Ucn) peptides (Ucn1, 2 and 3). These peptides are involved in integrating the neuroendocrine, autonomic and behavioral responses to stressors through selective activation of the two CRF receptors, CRFR1 and CRFR2, both widely expressed in stress-related brain nuclei. CRF has relatively lower affinity for CRFR2 than for CRFR1, Ucn1 has equal affinities for both receptors, and Ucn2 and Ucn3 appear to be selective for CRFR2. Opposing roles in regulating the central stress response were suggested for the two receptors systems; the CRF-R1 system was found critical for initiating stress responses while the CRF-R2 system appears principal for reestablishing homeostasis.
Methods: This study evaluated the role of Ucn1, 2 and 3 in regulating the central stress response by utilizing a novel knockout mice model we generated, lacking all three known Urocortins (tripleUcnKO). We compared anxiety indices of tripleUcnKO mice with those of wild-type mice (WT), under basal conditions and both immediately and 24 hours following exposure to an acute stressor.
Results: Under basal conditions and immediately following exposure to acute stress, tripleUcnKO mice did not differ from WT mice in most anxiety indices of the Open- Field and Dark- Light transfer tests. However, 24 hrs following the exposure to stress tripleUcnKO mice exhibited increased anxiety compared to WT mice. Furthermore, tripleUcnKO mice continued to appear anxious even 10 days following the stress exposure as indicated by increased freezing in the fear conditioning context test. In addition, tripleUcnKO mice exhibited an altered corticosterone response profile following restraint stress.
Conclusions: The results suggest a key role for endogenous CRFR2 ligands in the coping mechanisms following stressful experience and support the tripleUcnKO mouse line as a useful stress sensitive mouse model. Further elucidating the role of central Urocortins in the central stress response may provide new insights for the development of novel therapeutics for stress-related psychopathologies.

P-18-011

GABAergic neurons in the lateral habenula regulate anxiety-related behabior via the serotonergic raphe neurons

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Objectives: The lateral habenula (LHb) receives afferents primarily from limbic brain regions that are directly or indirectly innervated by the cortex. The LHb efferents mainly target the serotonergic dorsal and median raphe. Some serotonergic neurons in the raphe nuclei project back to the LHb. Therefore, the LHb forms a node of connection between the cortex and brainstem serotonergic neurons. However, it is little known what kind of neuron in the LHb adjusts the serotonergic neurons in the raphe nuclei. The goal of the present study was to determine functional role of the unilateral LHb on behavioral indices of anxiety, and to characterize the neurons in the LHb projected to the raphe nuclei.
Methods: Male Wistar rats were used. For electrolytic lesion of the unilateral LHb, a bipolar electrode was inserted stereotaxically into the LHb, and applied a direct current of 300 μA for 20 seconds. Behavioral analyses by open field and elevated plus-maze were tested. Rats were injected iontophoretically a retrograde tracer, fluoro-gold, into the median raphe nucleus using intact rats. Subsequently, these retrogradely labeling neurons in the LHb were combined with anti GAD 65/67 antibody, and additionally we conducted fluorescent in situ hybridization to detect GAD67 mRNA in these labeling neurons.
Results: Rats receiving LHb lesion exhibited increased locomotion activity in the open field, and showed decreasing percentage of time spent on open arms in the plus-maze test when compared to sham operation. In immunohistochemical study, the population of GAD65/67 positive neurons in the LHb was about 81% among neurons which target the median raphe. In fluorescent in situ hybridization study, however, retrogradely labeling neurons by fluoro-gold did not express GAD67 mRNA.
Conclusions: These data suggest that the GABAergic neurons expressing GAD65 in the LHb might control the serotonergic activity in the raphe underlying regulation of locomotor activity and unconditioned fear.

P-18-012

Abnormal cortical morphology in offenders with psychopathy

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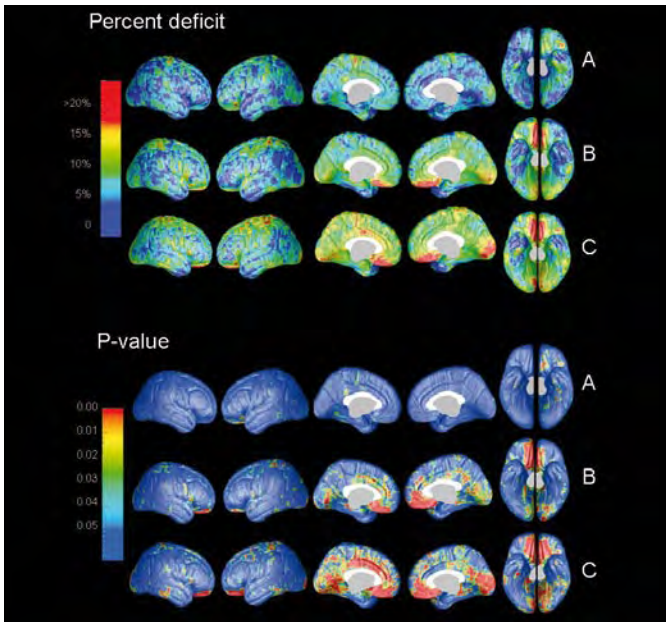
Objectives: Recent findings suggest that psychopathy may be associated with cerebral anomalies, particularly in limbic subcortical and cortical regions. Aim of this study was to examine the cerebral cortex in subjects with different degrees of psychopathy but no evidence of major mental disorders, with an advanced mapping procedure.
Methods: Twelve offenders with high psychopathy (PCL-R score ≥ 30), 14 offenders with medium psychopathy (PCL-R score < 30), and 25 age-matched healthy subjects underwent high resolution 3D magnetic resonance imaging. A cortical pattern matching pipeline was used to assess local gray matter density. Statistical maps of the mean percent difference between groups were computed at a threshold of p=0.05. Permutation tests were used to produce an overall p-value for the uncorrected statistical maps. Statistical tests for effects of substance abuse were also performed.
Results: Gray matter deficits up to 20% in the medial orbitofrontal, cingulate and parahippocampal regions characterized the offenders with psychopathy, and were proportional to the severity of psychopathy. Differences relative to healthy subjects were also significant after controlling for multiple comparisons. Correlation analyses revealed that the most significant volume loss, observed in the left orbitofrontal cortex in the high versus medium psychopathy comparison, was explained by Cooke's F1 subscores. Comparisons of polysubstance and amphetamine users versus non-users showed that the findings were attributable to psychopathy and not to substance abuse.
Conclusions: The findings support the view that psychopathy is associated with cortical abnormalities in structures closely connected to the limbic system.



P-18-013
Abnormal hippocampal shape in offenders with psychopathy

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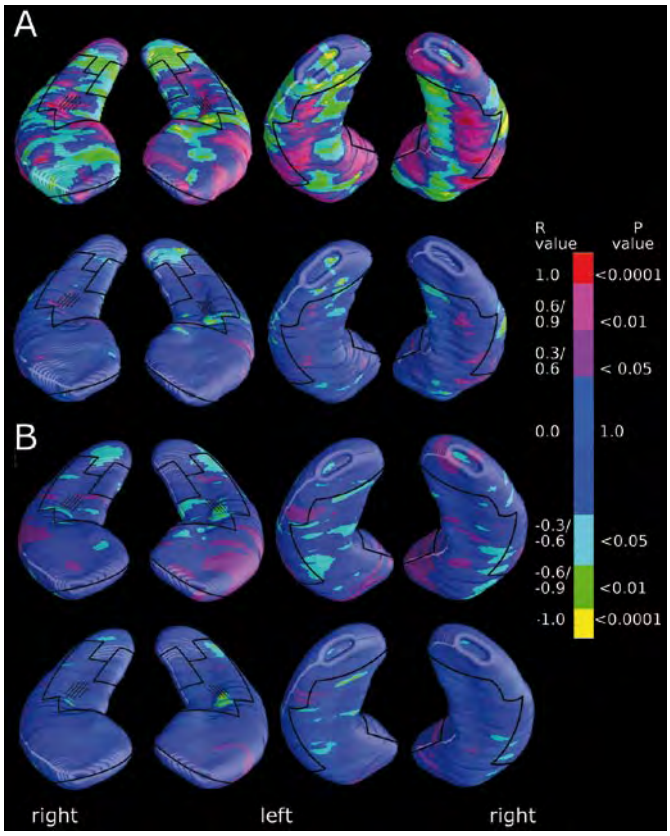
Objectives: Posterior hippocampal volumes correlate negatively with severity of psychopathy, but local morphological differences from controls and confounding effects of substance abuse are unknown. Aim of this study was to investigate hippocampal morphology in offenders with psychopathy.
Methods: Manual tracings from magnetic resonance images of 26 offenders (age: 32.5±8.4) with different degree of psychopathy (12 high, 14 medium psychopathy, based on the Psychopathy Checklist-Revised) and 25 healthy controls (34.6±10.8) were used for statistical modeling of local changes with a surface-based radial distance mapping method. ($p<0.05$; correction for multiple comparisons with permutation tests).
Results: Offenders and controls had similar hippocampal volume. Local analysis showed that the high psychopathy group had significantly smaller volumes along a ribbon on the longitudinal axis, on both the dorsal and ventral aspects, when compared with healthy controls and medium psychopathy group. The opposite comparison revealed abnormal enlargement of the lateral borders, in both the right and left hippocampi of both high and medium psychopathy groups versus controls, covering CA1, CA2-3 and subicular regions. A permutation test revealed a group difference ($p<0.002$) for both hippocampi, indicating that the results survived correction for multiple comparisons. Extensive check for confounders denoted that the findings could not be attributable to other variables than the degree of psychopathy.
Conclusions: Habitually violent offenders exhibit a specific abnormal hippocampal morphology, but similar total amount of hippocampal gray matter. The peculiar 8-shaped morphology, in coronal sections, may reflect abnormal development of inner structures such as the dentate gyrus, known to be crucial for fear-conditioning.



P-18-014
Pattern of cerebral anomalies in older persons with schizophrenia and Alzheimer's disease

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Objectives: Different cognitive impairment is described for elderly people with Alzheimer's disease (AD) and with schizophrenia, but the patterns of cerebral anomalies at direct comparison are unknown. Objective of this study was to identify the differences in the grey (GM) and white matter (WM) of people with geriatric schizophrenia and AD with Voxel-based Morphometry (VBM).
Methods: Twenty elderly subjects with schizophrenia from a psychogeriatric ward, 19 consecutive outpatients with AD and 19 controls underwent high resolution 3D magnetic resonance imaging. VBM was performed with SPM2. P was set at 0.05-FDR corrected for the comparisons with controls and 0.005 uncorrected for direct comparisons of patient groups.
Results: Subjects with schizophrenia compared to controls had smaller GM in the thalamus (cluster size (mm3), z, peak coordinates: 73;5.83;14,-10,8), parahippocampal gyrus, putamen (6000;3.91;26,10,0), cingulate, insular, frontal and occipital gyri. AD patients versus controls had atrophy in the thalamus (315;5.93;14,-14,10), medial frontal gyrus, and parietal lobe, extending to the cuneus and precuneus. On the direct comparison of schizophrenia versus AD, a cluster of atrophy could be observed in the precuneus of AD patients (20424;4.08;-14,-62,32). The WM experiment showed atrophy along the whole corpus callosum in schizophrenics versus controls (349;5.69;-10,30,14) and, to a lesser extent, in the AD sample versus controls (126;5.35;-4,12,22). On the direct comparison the schizophrenia sample exhibited smaller WM volume in the right cerebellum (2576;3.97;8,-46,-42).
Conclusions: The patterns of GM and WM anomalies overlapped in schizophrenia and AD, but the two samples showed an opposite trend, with greater GM involvement in the AD sample, and more WM anomalies in the schizophrenia sample. This may reflect the different pathogeneses, degenerative in AD and developmental in schizophrenia.

P-18-015
Structural brain pathology and violent crime: Revisiting a possibly underestimated factor

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Objectives: We aimed at exploring whether structural brain pathology might be a factor that considerably contributes to the disposition to commit violent crimes. Furthermore, we wanted to assess whether brain pathology is a predictor of violence that is independent of other factors such as childhood trauma, ADHD and personality traits.
Methods: Cranial CT and MRT scans of about 300 violent and non-violent perpetrators were blindedly screened for structural damage and compared to non-criminal controls. Additionally in a subset childhood trauma, ADHD, personality traits and general psychopathology were assessed and data was submitted to a factor analysis.
Results: Violent perpetrators had significantly more severe signs of structural brain pathology as compared to non-violent perpetrators and controls. Non-violent perpetrators did not significantly differ from controls. Factor analysis revealed that brain pathology, childhood trauma and ADHD constituted independent factors contributing to the disposition to commit violent crimes.
Conclusions: The results suggest that structural brain pathology has to be regarded as an uttermost important factor in the etiology of violent crime that is independent of other known predictors usually surveyed using psychometric and anamnestic instruments. These findings lay a cornerstone for a careful neuropsychiatric assessment of violent perpetrators.

P-18-016

Mediation of anticonvulsant effect of Locus Coeruleus via noradrenergic and galaninergic transmissions

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Objectives: Epilepsy is a chronic neurological disorder, with a prevalence of about 1-2% in general population. Current antiepileptic drugs regulate excitability of structures either responsible for epileptogenesis or involved in seizure control, or modulate the action of biologically active endogenous substances participating in either generation or inhibition of epileptic activity. Investigation of neuromediator systems involved in modulation of seizures is an important approach for development of effective strategies for epilepsy treatment. Self-sustained status epilepticus (SSSE) is considered animal models of temporal lobe epilepsy (TLE), the most common refractory adult focal epilepsy. Locus coeruleus (LC) is a noradrenergic structure and endogenous modulator of epilepsy. The data obtained from lesion/depletion and stimulation studies indicate anticonvulsant role of LC and endogenous NE. Majority of LC terminals contains galanin (GAL), which is the predominant neuropeptide in LC neurons.
Methods: The main objective of the current experiments was to determine the possible contribution of galanin to adrenergic modulation of limbic seizures. We were studying influences of galanin on initiation of low-Mg2+ epileptiform activity and on maintenance of already developed epileptiform activity in response to Mg2+ free ACSF. We had two different designs of experiments: (1) Galanine agonist or antagonist was applied simultaneously with Mg2+ free ACSF for one hour. (2)After one hour of Mg2+ free ACSF application, galanin introduction of agonist or antagonist was introduced in zero Mg2+ ACSF, then after one hour treatment the drug was washed out from Mg2+ free ACSF and than the recording continued for one more hour.
Results: The results demonstrate that galanin agonist-galnon significantlydelayed the initiation of epileptiform activity in response to zero-Mg2+ACSF.
Conclusions: However it did not change the maintenance of already developed epileptiform activity, as the treatment with galnon did not much influence the spiking frequency in a case of fully developed Low-Mg2+ epileptiform activity. The study was supported by a grant CRDF/GNSF/GRDF.

P-18-017

The reoencephalophy characteristic of the vascular channel at patients discirculatory Encephalopathy

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Objectives: 200 persons at the age from 20 till 55 years with a various condition of vessels of a brain which have been divided into three groups are surveyed. I (control) group included 50 persons at the age of 28-52 years at which the condition of vascular system was within norm. In II group - 72 persons at the age of 31-53 years with a hypertensive DE, and in III - 78 persons at the age of 30-55 years which have suffered owing to failure on Chernobyl Atomic Power Station (CAPS) with signs DE.
Methods: registration reoentephalography (REG) at the surveyed spent by means of the diagnostic automated complex «Kardia+» (made by «Metecol» Chernigov Ukraine). The received results were analyzed in statistical packages Statistica Neural Networks 4.0C (StatSoft. Inc., 1999) and MedStat (2004).
Results: received results REG testify that at persons with DE and at the persons who have suffered owing to failure on CAPS with DE in comparison with control group, are defined authentic (the dispersive analysis, criterion Kruskala-Uollisa) changes of some indicators, p <0,05. Are defined REG indicators of a condition of a vascular channel at an early stage at persons of control group, with disease a hypertensive DE and at the persons who have suffered owing to failure on CAPS, with DE. At the persons who have suffered owing to failure on CAPS, with disease a hypertensive DE, authentic decrease in amplitude of waves, change of a vascular tone, decrease puls bloodfiller, difficulty of venous outflow in comparison with control group (p <0,05) was observed.
Conclusions: informative indicators (amplitude of software reogram for right hemyspher and amplitudes of software for left hemyspher) which allow to diagnose pathological deviations of a vascular channel are established.

P-18-018

Patterns of cognitive dysfunction in first psychosis episode and borderline personality disorder: A comparative neuropsychological study

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Objectives: The recent peak in Neuropsychology has made the number of studies supporting the evidence of cognitive deficits in first psychosis episode grow. Regarding borderline personality disorder, several of the few studies done by now demonstrate a cognitive dysfunction as well. These cognitive alterations in both cases seem to be a prefrontal predominance pattern. Assessing the existence of specific patterns of neuropsychological dysfunction in first psychosis episode patients and in borderline personality disorder patients and comparing the differences between both groups if exist.
Methods: It is a comparative cross sectional study, with a sample of 15 borderline personality disorder patients, 15 first psychosis episode patients and 15 healthy controls without any previous or current psychiatric, neurological or systemic illness. The three groups are made up of people with similar characteristics with regard to age, sex, education level and hand dominance. A neuropsychological evaluation protocol of prefrontal functions is applied, consisting of: Buschke Test (FCRST, the Free and Cued Selective Recall Test, FAS Test (a verbal fluency test classified as an executive function test); Trail Making Test A ; STROOP Test ; WAIS III ; and Wisconsin Card Sorting Test
Results: -Both, FIRST PSYCHOSIS EPISODES and BPD, have a significative alteration (p<0,05) as compared to controls in: FAS, NOE, Trail Making Test A and B, Symbol Digit Modalities Test, Letters and Numbers, Wisconsin Card Sorting Test and STROOP test. -Comparing FIRST PSYCHOSIS EPISODES to BPD, a significative greater alteration (p<0,05) is demonstrated in BPD group in: Letters and Numbers and STROOP test (percentage of mistakes). -Moreover, considering BPD group, a greater alteration is clearly shown in: Trail Making Test A, Trail Making Test B, Simbol Digit Modalities Test and Wisconsin Card Sorting Test.
Conclusions: EXPLORATION between both disorders. And higher intensity of congnitive dysfunction in BPD. -Each specific pattern could be the following: - First Psychosis Episodes: Dorsolateral Frontal Cortex - Borderline Personality Disorder: Dorsolateral Frontal Cortex, Orbitofrontal Cortex and Anterior Cingular Cortex.

P-18-019

Theta-burst repetitive transcranial magnetic stimulation of the motor cortex improves obsessive compulsive disorder: Preliminary findings of an open-label study

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Abstract: The rTMS is a non-invasive stimulation of the brain and most studies have proven its efficacy in treating of depression. There is a less experience for rTMS in the treatment of obsessive-compulsive disorder (OCD). Fast-frequency or low-frequency (1Hz) rTMS over the left DLPFC, low-frequency rTMS over the right DLPFC failed to produce significant improvement. We know only one positive study using left DLPFC rapid (10 Hz) or right DLPFC low-frequency (1 Hz) rTMS for patients with resistant OCD. Greenberg observed that a single session of 20 Hz right prefrontal cortex stimulation produced a significant decrease in compulsive urges in OCD patients lasting over eight hours, comparing to the 20 Hz left prefrontal rTMS. Slow rTMS to the supplementary motor area resulted in a significant improvement of OCD symptoms. The deep brain stimulation (DBS) and rTMS of the motor cortex improves some advanced forms of Parkinson's disease. DBS seems to bee also a promising method to improve the treatment-refractory obsessive-compulsive disorder. We hypotheses, that rTMS over the motor cortex would be able to improve the OCD symptoms.

Recently Huang et al. proposed the rTMS version of the classic theta burst stimulation (TBS) protocol, used to induce LTP/LTD in brain slices. Comparing to the "classic" slow (0.5- 2 Hz) or rapid (5 - 20 Hz) rTMS, the TBS produces a controllable, consistent, long-lasting and powerful effect on motor cortex physiology and we proposed to apply the TBS, over the bilateral motor cortex. We report here 9 patients treated between September 2007 and January 2009 with OCD symptoms improved with TBS treatment. The TBS protocol consisted at 15 sessions of iTBS over the right and left motor cortex (hand area), 100% of active motor threshold, 10 busts of 3 stimuli at 50 Hz, repeated at intervals of 200 ms (5 Hz), over the right (cTBS) and left (followed by 8 second pause, iTBS). The total number of 3-busts was 350 over each M1 cortex (1050 pulses/ each motor cortex/day). The medications were not changed during the TBS treatment. All OCD evaluations were made blindly by the same experienced psychologist formed for the Y-BOCS quotation. This primary clinical result seems to bee very interesting for some individuals suffering from chronic treatment-resistant OCD. The TBS appears as a new, effective, safe and well tolerated method to treat resistant OCD, inducing a rapid clinical response with the decrease of the Y-BOCS, at least comparable with deep brain stimulation results.

P-18-020
Types of immune imbalance in patients with neurotic disorders

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Objectives: The analysis of immune status of patients with neurotic disorders has allowed allocating 3 types of immune imbalance: a immunocompensation type - without clinical disorders and disturbances in immunograms; immunodecompensation syndrome - without clinical disorders with minimal changes in one of the parts of immunity; syndrome of secondary immune insufficiency – disturbance in several parts of immunity in combination with infectious, allergic, infectious-allergic and autoimmune disorders. Immunocompensation type was found in 15% of patients with neurotic disorders (in healthy persons in 44%). We in 48% of patients and 42% of healthy persons observed immunodecompensation syndrome. Syndrome of secondary immune deficiency in patients with neurotic disorders was found in 37% of patients, whereas in healthy persons - in 14%.
Methods: We have examined clinical-dynamic parameters in 741 patients with neurotic disorders, under treatment at Polyclinic Department of Mental Health Research Institute. Questioning 126 patients with card of preclinical immunological examination was carried out, as well as in 64 patients investigation of comprehensive immunological status was carried out. Control was immunological data of 67 healthy persons.
Results: Neurotic disorders were subdivided as follows: anxiety–phobic disorders (F40) - 16,8 %; other phobic disorders (F41) - 7,5 %; obsessive-compulsive disorders (F42) - 2,5 %; reaction to heavy stress (F43) - 15,7 %; dissociative disorders (F44) - 8,9 %; somatoform disorders (F45) - 7,6 %; other neurotic disorders, including a neurasthenia (F 48) - 41 %.
Conclusions: Thus, neurotic conditions are multifactor disorders where mental and corporal spheres of a patient are closely interconnected. Medical and rehabilitation tactics for this group of patients should be complex and comprehensive: with sedative influence on mental condition of the patient, therapy of comorbid somatic disorders and activation of the immune status.

P-18-021
A single session of temporo-parietal transcranial magnetic stimulation – may improve dyslexia

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TABLE 1: **Performance of the subjects in the time of completion of RAN Test, before and after rTMS**

Scores/ Subjects	*Colors*		*Letters*		*Digits*		*Objects*	
	B	A	B	A	B	A	B	A
S1	50	50	58	46	39	40	85	82
S2	42	37	25	22	31	24	60	60
S3	71	71	65	58	55	47	91	75
S4	35	39	31	28	28	31	54	53
Mean	49,50	49,25	44,75	38,50	38,25	35,50	72,50	67,50
DP	15,59	15,59	19,70	16,52	12,09	10,08	18,23	13,33

Legends: B = Before; A = After; SD = Standart Deviation.

P-26
Brain Function III

P-26-001
Emotional processing within the Subthalamic nucleus in human

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Objectives: Basal ganglia receive projections from the cortex that are thought to be segregated into three circuits: motor, associative and limbic. In recent animal and human studies, the STN has been implicated in emotional processing. Recent data obtained in parkinsonian (PD) patients treated by STN stimulation suggest that this nucleus operates some kind of motor, cognitive and emotional integration (Mallet, 2007). The objective of this study is to determine the implication of the subthalamic nucleus (STN) in emotional processing and to study the integration of emotional and motor information in this basal ganglia structure.
Methods: Subthalamic local field potentials (STN-LFP) were recorded in 10 PD patients that underwent surgery for bilateral STN electrodes implantation. Recordings were performed while the subjects executed an emotional and decisional task. The task was based on a "Go"/"No Go" paradigm, with emotional (positive and negative) and neutral pictures as stimuli. Subjects had to indicate the emotional picture ("Go" condition) or the neutral picture ("NoGo" condition) by a motor response. The STN-LFP location was assessed with a 3D deformable atlas of human basal ganglia.
Results: The presentation of the picture evoked a potential (EP) within the STN, starting 150 ms after the picture presentation and reaching its maximum at 350 ms. For contacts located into the ventro-medial part of the STN, the EP amplitude was significantly higher for negative pictures than for neutral pictures ($p<0.01$). This difference was not related to ocular movement or to the motor response.
Conclusions: This study confirms that some STN neuronal assemblies are implicated in emotional processing in human, in particular the ventro-medial part (associative-limbic), in line with the Parent's model (Parent 1990). Stimulation of this part of the nucleus could be responsible for the behavioral modifications observed in some PD patients following deep brain stimulation.

P-26-002
A novelty / familiarity signal in the human dorsal thalamus

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Objectives: The hippocampal formation and adjacent medial temporal lobe (MTL) structures play a critical role in declarative memory processes, and converging evidence suggests that an important function of the hippocampus is the detection of novel events. The mediodorsal and midline nuclei of the thalamus are highly interconnected with the MTL memory system and are involved in the communication between the hippocampus and neocortical structures.
Methods: Here we investigated thalamic neural oscillations in four patients undergoing deep brain stimulation (DBS) of the Vim nucleus of the thalamus for essential tremor (three cases) or Parkinson's disease (one case). Patients performed a visual oddball task with complex scene stimuli and were instructed to respond to a specific target picture only. In addition to the baseline picture and the target picture, novel and familiar oddballs were presented. Thalamic local field potentials (LFPs) were recorded bipolarly from adjacent contact pairs of the DBS electrode (three contact pairs per site). Event-related LFP activity was analyzed using continuous wavelet transformation.
Results: During the presentation of novel, but not familiar non-target oddballs, we observed a sustained increase in thalamic high theta / low alpha oscillatory activity (7 – 9 Hz), which started at approximately 500 ms after stimulus presentation and lasted for about 300 ms. This novelty-specific theta/alpha increase was most pronounced at the proximal contact pair, which was located most dorsally. Importantly, since no motor response was required to non-target oddballs, the observed novelty-related amplitude increases could not be explained by movement-related thalamic activity.
Conclusions: Our results suggest that novelty detection might involve the relaying of novel information between the neocortex and MTL via dorsal or midline thalamic nuclei, and that this information appears to be coded in the high theta range. High-resolution fMRI might help to further characterize the precise contribution of different thalamic nuclei to MTL-dependent novelty processing.

P-26-003
No differences in the prevalence of cavum septum pellucidum and adhesio interthalamica between first-episode psychotic patients and healthy controls: A population-based study

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Abstract: Early neurodevelopmental alterations are considered one of the possible etiologic hypotheses for psychosis. Two of these abnormalities are the cavum septum pellucidum (CSP) and the absence of adhesio interthalamica (AI). Several magnetic resonance imaging (MRI) studies have investigated CSP and AI in psychosis, with conflicting findings. Differences in the prevalence of large CSP were seen in six of 13 researches; and five of ten studies related higher incidence of non-AI in patients. Such discrepancies could be fairly explained by differences in imaging techniques, CSP/AI definition criteria among the reports, and heterogeneity in the selection of the sample. For minimizing these contradictory results, recent works have employed more quantitative methods to analyze CSP e AI. However, there is no study that has carefully selected the subjects, particularly using a population-based sample. The objective of the present research was to evaluate, by using MRI, the CSP and the non-AI in first-episode psychotic patients, including a population-based sample in order to examine these alterations. The sample was composed by 122 first-episode psychotic subjects, who established contact with mental health services in the city of São Paulo between 2002 and 2005. For obtaining a population-based sample of controls, 94 next-door neighbors of each patient were invited to participate, matched on socio-demographic characteristics of cases. We investigated prevalence of small and large CSP (i.e., > 6 mm in length) and the volume of the cavity, as well as the incidence of non-AI.

No significant differences were found between patients and controls in any of the measures of CSP and AI. Likewise, there was no association between these structures and neuropsychological tests. However, the absence of AI was higher among men when all the subjects were pooled together. This increased prevalence of non-AI in men is in agreement with the literature, given that sexual dimorphism seems to be related to abnormalities in this structure. On the other hand, the lack of differences between patients and controls in both CSP and AI data suggests that these abnormalities may not be neurodevelopmental markers of psychosis and cast doubt over the notion that they play a major role in the neurobiology of such disorders. Further, it emphasizes the importance of the strict selection of the sample, since bias in subject's recruitment could interfere in the results of case-control studies.

P-26-004
Reduced left hippocampal N-Acetylaspartate (NAA) in panic disorder patients detected by (1)H magnetic resonance spectroscopy imaging

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Abstract: Panic disorder (PD) is an anxiety disorder that affects close to 3% of the general population. Recent neuroanatomical theories of PD propose an extensive involvement of limbic system in the pathophysiology of this condition. In fact, several structural and functional neuroimaging studies have shown changes in limbic structures, such as the hippocampus, in PD patients. Despite this, no prior study has examined exclusively the hippocampal neurochemistry in this disorder. Therefore, the current study used proton magnetic resonance spectroscopy imaging (1H-MRSI) to examine possible abnormalities in the hippocampus in PD patients. Twenty-five patients meeting the DSM-IV criteria for PD and eighteen psychiatrically healthy controls were investigated. The subjects were matched based on gender, age, handedness, years of education, and socioeconomic level. N-acetylaspartate (NAA, a putative marker of neuronal viability) and choline (Cho, involved in the synthesis and degradation of cell membranes) levels were quantified relative to creatine (Cr, which is thought to be relatively stable among individuals and in different metabolic condition) in both right and left hippocampi. Compared to controls, panic patients demonstrated significantly lower NAA/Cr in the left hippocampus. No other difference was detected. This result is consistent with previous neuroimaging findings of hippocampal alterations in PD and provides the first neurochemical evidence suggestive of involvement of this structure in the disorder. Moreover, the decrease in the left hippocampal NAA/Cr in PD may possible reflect neuronal loss and/or neuronal metabolic dysfunction, and could be related to a deficit in evaluating ambiguous cues.

P-26-007
Basal hypothalamic pituitary adrenal axis activity and hippocampal volumes: The SMART-MR study

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Objectives: Smaller hippocampal volumes have been associated with neuropsychiatric disorders and it has frequently been hypothesized that high levels of glucocorticoids explain this association. However, few studies examined the direct relation between hypothalamic-pituitary-adrenal (HPA) axis activity and hippocampal volumes. We examined the association between different aspects of HPA-axis activity and hippocampal volumes in a large sample of middle aged persons.

Methods: Within the SMART-MR study, a cohort study on early brain changes on MRI among patients with a history of arterial disease, diurnal cortisol rhythm was assessed with 6 saliva samples, collected at awakening and 30, 45 and 60 minutes thereafter, and at 10PM and 11PM in 383 participants (mean age 62±9 years). Dexamethasone (0.5 mg) was administered at 11PM and saliva was sampled the next morning at awakening. Diurnal cortisol profile was defined as the cortisol awakening response; mean evening values; and the suppressibility of the HPA-axis after dexamethasone. Volumes of the hippocampus were manually traced on a 3-dimensional FFE T1-weighted MRI scan with isotropic voxels and were expressed relative to intracranial volume.
Results: Mean total relative hippocampal volume was 6.2 ± 0.7 ml. Linear regression analyses, adjusted for age, sex, vascular risk factors and global brain atrophy showed that participants with higher evening levels had smaller hippocampal volumes (B per SD increase= -0.08 ml; 95%CI -0.15 to -0.01 ml). The awakening response and cortisol levels after dexamethasone were not significantly associated with hippocampal volume.
Conclusions: In this population, higher evening cortisol levels were associated with smaller hippocampal volumes, independent of total brain volume. The cortisol response after awakening and cortisol after dexamethasone suppression were not associated with hippocampal volume. Future studies should examine whether elevated evening cortisol is a cause or a consequence of smaller hippocampal volume and whether it increases risk for neuropsychiatric disorders.

P-26-008
Early and late life events and salivary cortisol in older persons

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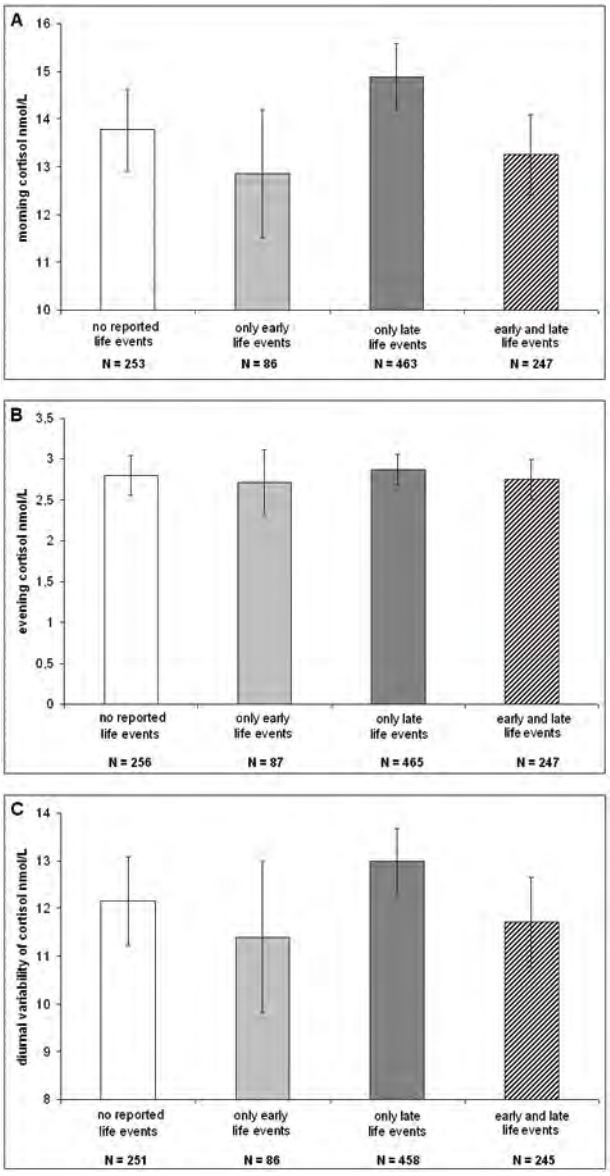
Objectives: It has been hypothesized that stressful life events are associated with changes in hypothalamic pituitary adrenal (HPA) axis regulation, which may increase the susceptibility to psychiatric disorders. It has also been suggested that HPA-axis regulation is affected by aging. However the association between life events and HPA-axis regulation has not been studied in older persons before. Therefore we investigated the association of early and late life events with salivary cortisol levels in older persons.
Methods: Within the Longitudinal Aging Study Amsterdam(LASA) 1,055 participants (47% male), aged 63-93 years, collected saliva within 30 minutes after waking and late in the evening. Early (before age 18 years) and late life events (within 3 years prior to interview) were assessed during a home interview. The associations between life events and cortisol levels were adjusted for demographics, cardiovascular risk factors and depressive symptoms.
Results: Within our study sample, the median morning and evening cortisol levels were 15.0 nmol/L (10-90% 7.4–27.0 nmol/L) and 2.8 nmol/L (10-90% 1.5–6.3 nmol/L), respectively. Persons who reported early life events showed lower levels of log-transformed morning cortisol (B=-0.10;95%CI -0.17 to 0.04) and flattened diurnal variability of cortisol (B=-1.06;95%CI -2.05 to-0.08). Persons who reported two or more late life events showed higher levels of log-transformed morning cortisol (B=0.10;95%CI 0.02 to 0.18) and higher diurnal variability (B=1.19;95%CI 0.05 to 2.33). No associations were found with evening cortisol.

Conclusions: The results of this large population-based study of older persons suggest a differential association of early and late life events with HPA-axis regulation; early life events were associated with hypo-secretion of morning cortisol and flattened diurnal variability, while late life events were associated with elevated secretion of morning cortisol and high diurnal variability of cortisol.



P-26-009
Spatial memory following neurotoxin lesion of the basal cholinergic system

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Objectives: In this experiment the ability of medial septal (MS) and Nucleus basalis magnocellularis (NBM) excitotoxic (ibotenic acid) lesioned and sham-operated rats to learn the location of a visible, as well as submerged platform in a water maze has been investigated.
Methods: A total of 36 male outbred albino rats were used in the present study. The animals were randomly assigned to sham-lesioned (n = 12) and MS (n = 12) and NBM (n = 12) ibotenic acid lesioned groups. Animals were tested in a standard Morris water-maze. The rats' responses on the competition test were classified as either cue or place, based on the swim path for those trials.

Results: Sham-operated rats acquired both the visible and hidden platform versions of the task, but when required to choose between the spatial location they had learned and the visible platform in a new location majority of them swam first to the old spatial location.An overview of the data from both competition trials for each group show that the sham-operated rats in 21 trials out of 24 competition test trials used place strategy, while MS-lesioned ones used this strategy in 14 trials and NBM-lesioned rats used this strategy in 6 trials only. Decreased place-bias in NBM and MS-lesioned rats compared to the sham-operated rats was significant.
Conclusions: These findings suggest that in MS and NBM-lesioned rats behavior was not affected by spatial information and responding to local reinforced cues was enhanced. These data add to a growing literature demonstrating that these structures are essential for accurate spatial learning and suggest their role in processing information about the spatial environment.

P-26-010
Correlation and predictor characteristics of the interhemispheric balance and Romberg's coefficient after electroconvulsive therapy

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Objectives: To assess and compare the correlation and predictor characteristics of the interhemispheric balance and Romberg's coefficient after electroconvulsive therapy (ECT) in mental patients.
Methods: A series of 84 mental patients following ECT were examined with special regard to responses to Romberg's and bilateral sensorimotor coordinometric tests. There were 73 females and 11 males with a mean age of 34.6 years. The ECT was carried out by prof. Ch. Merjanov at the former Medical academy of Sofia. New quantitative evaluations of the restorative dynamics of changes of interhemispheric balance and Romberg's coefficient in mental patients before and after ECT were given. We applied ANOVA-test, correlation and simple as well multiple regression analyses testing the correlation between each of psychomotor and cognitive parameters. A correlation coefficient (r) with $p<0.05$ was considered significant.
Results: Our study demonstrated ($p<0.05$) the well-known fact of phasic character of postural, movement and cognitive mobilization and restitution processes in the human brain under extreme conditions. It was established a significant biphasic dynamics of the Romberg's coefficient ($p<0.001$) and the interhemispheric balance ($p<0.002$).
Conclusions: The results we obtained showed that the psychomotor and cognitive tests we used serve for monitoring ($p<0.05$) the ECT in mental patients.

P-26-011
Potentiation of Gamma Oscillatory Activity through Repetitive Transcranial Magnetic Stimulation (rTMS) of the Dorsolateral Prefrontal Cortex in Healthy Subjects

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Objectives: Neural oscillations in the gamma (γ) frequency range (30-50 Hz) have been associated with higher order cognitive processes. Working memory (WM), a cognitive task that involves the on-line maintenance and manipulation of information, has been shown to elicit increases in γ oscillations with greater cognitive demand, particularly in frontal brain regions such as the dorsal lateral prefrontal cortex (DLPFC). The generation and modulation of γ oscillations have been attributed to inhibitory interneuron networks that use γ –aminobutyric acid (GABA) as their principle neurotransmitter. Repetitive transcranial magnetic stimulation (rTMS) represents a non-invasive method to stimulate the cortex that has been shown to modify cognition and GABA inhibitory mechanisms, particularly with higher frequencies (i.e., 10-20 Hz). The aim of this study, therefore, was to measure the effect of high-frequency 20 Hz rTMS over the DLPFC on γ oscillations elicited during the N-back WM task in healthy subjects.
Methods: Twenty-two healthy subjects were randomized to receive either active or placebo-controlled sham stimulation and were blind to their group assignment. Subjects completed the N-back task while their EEG was recorded pre- and post- 20 Hz rTMS applied to both to the right and left DLPFC.
Results: Active rTMS increased γ oscillations generated during the N-back compared to sham stimulation and baseline (i.e., pre-rTMS) with the greatest enhancement in the N-back condition with the highest cognitive demand. Evaluation of other frequency bands revealed no significant change suggesting that rTMS selectively modulates activity within the γ frequency range in frontal brain regions.
Conclusions: These findings provide important insights into the neurophysiological mechanisms that underlie higher order cognitive processes. Also, these findings may help guide future studies evaluating rTMS as a cognitive enhancing strategy in neuropsychiatric disorders that present cognitive deficits as part of their symptom profiles.

P-26-012
Manic episode associated with temporal lobe epilepsy and sclerosis of amygdala and left hippocampal: A case report

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Objectives: The hippocampal formation has been a centrepiece of neuropathology investigations of psychiatric disorder. Depression is reported most frequently (60%) in patients with Temporal Lobe Epilepsy (TLE) left, and possibly hippocampal sclerosis (HS) (Quiske et al., 2000). However there are very few studies on the association of TLE with HS and manic episode. This is the objective of describing a clinical observation.
Methods: We report a case of a 23 year-old right handed woman with no personal or family history of psychiatric disorders, who was addressed by, neurologist for an acute manic episode with ideas of grandiosity, decreased need for sleep, disinhibition, irritable mood, flight of ideas. During the initial interview, she appeared to be over friendly, but with grandiose thoughts. Her speech was spontaneous and rapid. In the past year, she had consulted a neurologist for complex partial seizures. The magnetic resonance imaging showed a clear atrophy of the amygdala and the hippocampus left. Interictal EEG revealed discharges paroxysmal predominantly to on the left temporal lobe.
Results: The diagnosis of manic episode was according to the Diagnostic and Statistical Manual fourth edition (DSM IV) criteria of Mental Disorders (APA, 94). After two months of treatment with olanzapine 10 mg/day and carbamazepine 600 mg/day, the patient has improved significantly. The symptoms of acute manic episode are resolved, seizures are completely disappeared. The observed symptoms seemed to differ from those of the typical manic episode because of the patient's rapid response to treatment.
Conclusions: To our knowledge, there is not enough data currently exists on the prevalence of manic episode in epileptic seizures. Previous reports of hippocampal volume in patients with bipolar disorder have been inconsistent in their findings. This clinical case is interesting because of its association with recent seizures, and the dominant position in the left temporal lobe and HS.

P-26-013
Ultrastructural alterations of astrocytes in the hippocampus in schizophrenia

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Objectives: Astrocytes affect regulation of energy and glutamate metabolism. Altered expression of astroglial enzymes and transporters, participating glutamate neurotransmission, have been detected in the hippocampus of schizophrenics. Previously we found the ultrastructural alterations of glutamatergic mossy fiber synapses in the CA3 hippocampal region in schizophrenia. To verify whether there are the ultrastructural abnormalities of astrocytes, we performed electron microscopic morphometric study of astrocytes in the CA3 hippocampal region from schizophrenia and control brains.

Methods: Samples of the hippocampus from the brains of 19 schizophrenic patients and 16 normal control subjects, matched by age, gender and postmortem interval were studied. ICD-10 diagnostic criteria for schizophrenia were used. The following parameters were estimated in stratum pyramidale of CA3 region: areas of cell somata, cytoplasm and nucleus; volume fraction (Vv) and area density (Na) of mitochondria; Vv of lipofuscin granules in astrocytic cytoplasm.
Results: There were no significant differences between control and schizophrenia groups. Young control subjects (<50 y.o., n=6) had significantly lower area of astrocytic cell, nucleus and cytoplasm and significantly higher Vv ($p<0.05$) and Na of mitochondria ($p<0.01$) than old controls (>50 y.o., n=10). These interactions are disturbed in schizophrenia: for all parameters there were no significant differences between young (n=7) and old (n=12) schizophrenic subjects. Astrocytic size (but not Vv and Na of mitochondria or Vv lipofuscin granules) correlated significantly and positively with age in control and schizophrenic cases. Both Vv and Na of mitochondria correlated negatively and significantly with duration of illness (respectively: $R = -0.66$, $p = 0.002$; $R = -0.72$, $p = 0.001$). Vv of lipofuscin granules correlated positively and significantly with duration of disease ($R = 0.072$, $p = 0.001$).
Conclusions: These data suggest progressive disturbances of astrocytic function due to deficit of mitochondria in schizophrenia. Supported by the Stanley Medical Research Institute.

P-26-014
The role of electroencephalography in diagnostic process in psychiatry – case report

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Objectives: We want to emphasize the role of electroencephalography (EEG) in the diagnostic process in psychiatry.
Methods: This is a case report of a 57-year-old man with delusional psychotic state with impulsive aggressive and autoagressive behaviour several days before admission to psychiatric hospital. From the patient history: headache 10 days before. CT of the brain did not reveal any malformations. Neurological state at admission: hemi paresis latens lateris sinistri Psychic state: euphoria, incoherent though, reduction of drive and instincts, visual hallucinations. EEG: frequency and amplitude instability, with alfa activity of 9 Hz, irresponsible on open and close eyes at the right side and intervals of sharp waves on right temporo-parietal derivations. This is why we performed MRI of the brain with contrast, which revealed disturbances in the frontal-temporo-parietal girusis on the right hemisphere, with affection of the leptomeninges. Lumbar punction and Fundus oculi were with out significance for the case.
Results: The EEG was followed-up for tree times in the period of tree weeks, and the asymmetry persists.
Conclusions: Without the performance of EEG witch pointed out that there is brain affection with morphological changes we would not perform further investigations that revealed the etiology of the disorder - astrocytoma (low grade) that needs a neuro-radiological follow-up.

P-26-015
Metabolic syndrome in brain injury patients in a rehabilitation hospital

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Objectives: Context: Acquired brain injury can lead to a variety of psychiatric presentations, and also disturbance of neuro-endocrine function. The treatment of the neurobehavioural consequences of brain injury involves the judicious use of psychotropic medication which can produce varying side-effects. Metabolic Syndrome is one of the most serious and disabling side-effects representing a co-occurrence of a number of conditions which predict heart disease and diabetes. **Objectives:** The aim of the study was to determine the prevalence of, and screening for Metabolic Syndrome in an All-male Forensic Brain Injury Rehabilitation setting in contrast with non-brain injured male patients in a generic forensic psychiatric setting.
Methods: The study comprises a Cross sectional Survey in which we collected retrospective data for 37 inpatients resident at St. Mary's Hospital, a national secure brain injury rehabilitation service. The data collected included demographic details, diagnosis and medication, smoking behaviour, BMI, Waist Circumference, Blood Pressure and Lipid Profile.
Results: 38% of patients sampled met diagnostic criteria for Metabolic Syndrome according to the NCEP-ATP III Criteria, demonstrating an over-representation of Metabolic Syndrome in the client group sampled when compared with the prevalence in community and generic forensic samples. Almost all of the patients (93%) were prescribed anti-psychotics and half of these patients were also on mood stabilizers.
Conclusions: Patients with acquired brain injury in a secure rehabilitation service appear to be at increased risk of developing metabolic syndrome. Caution should therefore be exercised in relation to the choice and use of antipsychotic medication prescribed, and the health risks addressed by means of robust screening and monitoring mechanisms and an emphasis on supporting smoking cessation, healthy diet and increased exercise.

P-26-016
Peripheral nerve injury alters dopamine receptor numbers in the nucleus accumbens in a subpopulation of rats, which display sensory and affective disabilities

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Kevin Keay

P-26-017
Integrative function of single neurons in the human subthalamic nucleus during checking behavior

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Objectives: Human behavior depends on complex interactions between cognition and emotion. How does the brain combine these two dimensions to make a decision and elaborate a goal-directed action remains unclear. One hypothesis is that such an integrative process might occur owing to the convergence of information through the basal ganglia. Recently, the associative and limbic STN have been proposed as potential targets for deep brain stimulation in patients with medically-resistant form of obsessive compulsive disorders (OCD).
Methods: We took the opportunity of the last study to investigate the role of STN neurons in the processing of cognitive information. We used an instrumental task (CT), adapted from a sample-to-matching task, that specifically offered the opportunity to verify once one subject has made a choice. Single unit neuronal recordings were made in the STN whereas patients with obsessive compulsive disorders (OCD) performed the CT.
Results: Among 125 single neurons recorded during task performance, 45 (36%) were task-related. Modifications of activity (either excitation or inhibition) were observed in relation with: visual information during the study phase (28%), the choice phase (22%), or the checking phase (20%), movement execution during the choice phase (37%), or the checking phase (35%) and during the evaluation phase at the end of the task (i.e. yes or no, 56%). We found that STN neurons frequently responded in a polymodal manner to cognitive, premotor and emotional events. Moreover, discharge frequency was influenced by checking behavior.
Conclusions: These results suggest that STN neurons process multiple sources of information in accordance with the model of information convergence within the basal ganglia. They also demonstrate that the STN plays a part in the physiology of doubt, a critical feature of OCD pathophysiology.

P-26-018
Age-related increase of the number of oligodendrocytes is dysregulated in the prefrontal cortex in schizophrenia and mood disorders

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Objectives: The postnatal maturation of the human prefrontal cortex is associated with substantial increase of number of oligodendrocytes. Morphometric studies provide evidence of decreased numerical density (Nv) of oligodendrocytes in the prefrontal cortex in schizophrenia and mood disorders. To gain further understanding the role of oligodendrocytes in the pathogenesis of schizophrenia and mood disorders we studied the effect of age on Nv of oligodendrocytes in the prefrontal cortex in schizophrenia and mood disorders.
Methods: Brain collections from Mental Health Research Center and Stanley Medical Research Institute were used. Age-related changes in Nv of oligodendrocytes in layer VI and in adjacent white matter were examined in BA10 of subjects with schizophrenia and matched controls (32 subjects per group), and in BA9 of subjects with schizophrenia, bipolar disorder, major depression and controls (15 subjects per group).
Results: Regression analysis of BA10 revealed significant Nv of oligodendrocytes by age interaction in layer VI ($F = 6.55$, $p = 0.015$), and white matter ($F = 20.44$, $p < 0.001$) in control group, but not in schizophrenic group ($F = 0.02$, $p = 0.9$, $F = 0.90$, $p = 0.34$ respectively). Similar interactions were found in BA9 in layer VI ($F = 10.05$, $p = 0.007$) and white matter ($F = 5.48$, $p = 0.03$) in control group, but not in psychiatric groups (all $p > 0.05$).
Conclusions: The absence of normal increase in the number of oligodendrocytes in gray and white matter with age in schizophrenia and mood disorders suggests that age-related process of oligodendrocyte maturation is dysregulated in schizophrenia and mood disorders. Supported by the Stanley Medical Research Institute.

P-26-019
Involvement of the brain in the regulation of liver cytochrome P450 expression

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Objectives: Cytochrome P450 (CYP) contributes to the metabolism of neuro- and sex steroids, neurotransmitters (dopamine, serotonin) and drugs such as, e.g., psychotropics. The CYP genes are activated transcriptionally by endogenous hormones remaining under control of the central nervous system (CNS). Our recent studies demonstrated the role of dopamine in the regulation of liver CYP via D2 receptors and pituitary hormones. Since hypothalamic neurons that control pituitary function receive noradrenergic and serotonergic inputs, it seemed of interest to determine whether these systems affected the expression of liver CYP.
Methods: Methods: Rats were injected intraperitoneally with one of the following neurotoxins: N-(2-chloroethyl)-N-ethyl-2-bromobenzylamine (DSP-4; 1 x 50 mg/kg), p-chlorophenylalanine (PCPA, 2 x 150 mg/kg), or p-chloroamphetamine (PCA; 2 x 10 mg/kg). One week after neurotoxin injection, the activity and protein levels of CYP isoforms were measured in rat liver microsomes. The levels of noradrenaline, serotonin, dopamine and their metabolites were assessed in selected brain structures.
Results: The neurotoxins potently and selectively diminished the level of the targeted neurotransmitter in the respective brain structures. DSP-4 (a selective neurotoxin to noradrenergic terminals) decreased the activity of CYP2C11, CYP2B and CYP3A. PCPA (an inhibitor of serotonin synthesis) reduced the activity of CYP2C11 and CYP3A. By destroying serotonin terminals, PCA diminished the activity of CYP2C11 and CYP3A. At the same time, PCPA and PCA increased the activity of CYP1A2. Similar changes were observed in the case of CYP protein levels.
Conclusions: The applied neurotoxins affect the activity and protein levels of liver CYPs which are regulated by pituitary hormones. Since these hormones remain under control of the CNS, it is suggested that brain noradrenergic and serotonergic systems are important to the physiological regulation of CYP. These findings imply that neuroactive drugs acting via these systems may thus change the expression of CYP which may have an impact on their pharmacological effect and drug interactions.

P-26-021
Effects of pre-sleep negative mood induction on subsequent sleep

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P-47
Brain Function IV

P-47-001
Efficiency and security with TMS in depressive episodes

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Objectives: To demonstrate the effectiveness and safety of repetitive Transcranial Magnetic Stimulation (rTMS) treatment in patients with affective disorders. Two groups with depressive episodes, according to DSM-IV, were compared. Bilateral or unilateral stimulation of the frontal lobes was applied.
Methods: The first group (35 patients) received unilateral stimulation, and the second (37 patients) received bilateral stimulation. Exclusion criteria were epilepsy, cardiac pacemaker.alcoholism, drug abuse, brain trauma, neurologic diseases, patients aged over 75. Both groups included patients with and without antidepressive medication; fixed doses were maintained. A Magstim Rapid repetitive Transcranial Magnetic Stimulator was used. Effectiveness was assesed on the basis of pre and post treatment Beck and Hamilton scales, and 50% decrease with respect to baseline was considered as improvement criterion. Patients signed written consent.
Results: 67% (CI: 48-82) (Beck) and 61% (CI:47-77) (Hamilton) of the patients improved their respective scores in the first group.The results of the second group were 75.7% (CI:62-89) (Beck) and 85% (68-85) (Hamilton), respectively.
Conclusions: The treatment was well tolerated, even with daily application of 4200 stimuli. No seizures were induced. A greater number of patients responded to bilateral compared to unilateral stimulation.

P-47-002
Change in heart rate variability after electroconvulsive therapy in patients with major depressive disorders

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Objectives: Heart rate variability (HRV), the amount of fluctuations around the mean heart rate, can be used to assess the cardiac autonomic nervous system (1,2). Because electroconvulsive therapy (ECT) is a strong stimulus to the autonomic nervous system (ANS), especially to the cardiac ANS, it's aimed to evaluate the effects of ECT on cardiac autonomic functions (CAF) in patients with major depressive disorder (MDD) using HRV analysis in this study.
Methods: 24 hour Holter monitoring was performed before and after third and last ECT sessions and three weeks after the treatment period in 14 patients with MDD to evaluate acute and sub acute effects of ECT on CAF. Measures of HRV were obtained from these recordings. Changes in HRV values before and after ECT treatment and its relationship with treatment outcome were analyzed. Treatment response was determined by the 17-item Hamilton Rating Scale for Depression (HRSD).
Results: No significant differences were found in HRV values of pre and post treatment recordings. HRV values did not correlate with HRSD scores and no relation was found between treatment response and HRV analysis.
Conclusions: A change in HRV related to ECT treatment of MDD could not be revealed in the present study. As HRV is a promising quantitative marker of autonomic activity, unaffected cardiac autonomic activity is likely associated with the safety of ECT. However, sample size in this study is too small to make a definite conclusion and further research with larger sample sizes is necessary to clarify the relationship between ECT and HRV.

P-47-003
Reduced cortical inhibition in Japanese patients with schizophrenia under medication

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Objectives: Reduced cortical inhibition has been suggested as a neurophysiological measures of pathophysiological mechanism in schizophrenia. However, previous studies using paired-pulse transcranial magnetic stimulation (ppTMS) to investigate resting motor threshold (RMT), short-interval cortical inhibition (SICI) and intracortical facilitation (ICF), have been inconsistent in regarding effect of medication and there has been little information in Asian-patients.We examined short-interval cortical inhibition in Japanese schizophrenia patients under antipsychotic medication by paired-pulse TMS.
Methods: Ten right-handed patients are compared with ten right-handed, age- and gender-matched normal control subjects. We stimulated left motor cortex with conditioning stimulus at 80% of RMT followed by test stimulus at 130% of RMT. Interstimulus interval was set at 2 and 3msec for SICI, and at 10 and 15msec for ICF.
Results: The patient group demonstrated a reduction in SICI as compared with healthy controls (schizophrenia 0.85, control 0.35, P<0.01). RMT and ICF showed no group difference. Significant relationship was not found on MT, SICI, ICF with medication dosages, use of benzodiazepines, or symptom scores with the Positive and Negative Syndrome Scale (PANSS), the Brief Psychiatric Rating Scale (BPRS).
Conclusions: These results demonstrate that short-interval cortical inhibition is reduced in Japanese medicated patients with schizophrenia and suggest that a GABAegic deficit might be involved in schizophrenic pathophysiology.

P-47-004
Repetitive transcranial magnetic stimulation: Elderly depressed-neuronavegated study

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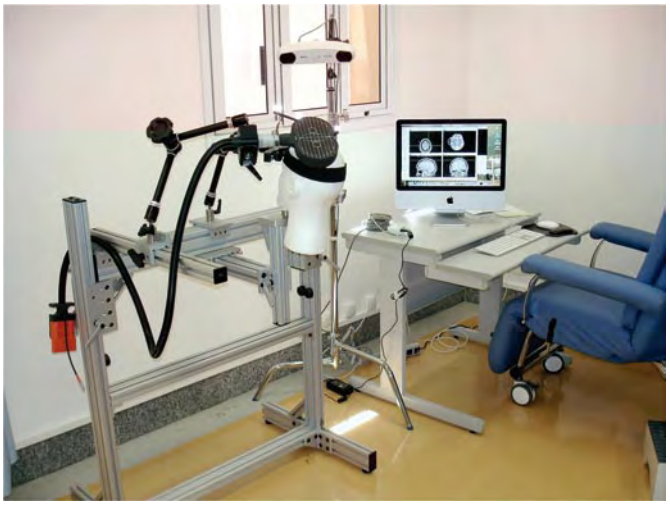
Objectives: Double-blind, controlled and randomized study to investigate antidepressive efficacy of Repetitive Transcranial Magnetic Stimulation (rTMS) in elderly.
Methods:
- 40 patients (SCID/DSM-IV)
- Male/Female
- 60 - 75 years
- Absence of psychiatric comorbidity
- Randomly assigned to 4 weeks of daily treatment:active rTMS + placebo or SHAM TMS + citalopram, follow-up of 4 weeks
- Neuronavegated
- Pulse intensity corrected based on atrophy degree by the formule: Intensity = MT x [EXP(-0.36 x MC)] / EXP(-0.36 x PC) MT: Motor Threshold MC: distance between scalp/Motor Cortex PC: distance between scalp/Prefrontal Cortex
- Parameters
- Left Dorsolateral Prefrontal Cortex
- 5 Hz
- 10 seconds on
- 20 seconds off
- intensity corrected
- 25 trains/day
- 20 days - figure-8 coil
- Scales: before and after rTMS, after follow-up 1) Hamilton Depression Rating Scale-17 2) Visual Analogue Scale 3) Clinical Global Impression 4) Mini-Mental State Examination 5) Neuropsychlogical tests

Results: on data collection (results to be presented at the WFSBP/2009)

Conclusions: To our knowledge, this is the first neuronavegated pulse intensity corrected study of rTMS in elderly depressed patients. The prefrontal cortex atrophy appears to happen faster with age when compared with the motor cortex. These factors could be related to a lower rTMS antidepressive reponse in older subjects. The correction formule for atrophy intent to minimaze this effect by adaptating correctly the intensity. Besides this, the local of stimulation will be identified by neuronavegation which improves the precision target point, as well as the distance between prefrontal and motor cortices.



P-47-005
The influence of HF-rTMS treatment on 5-HT 2A receptor binding in medication-resistant unipolar depressed patients

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Objectives: As repetitive transcranial magnetic stimulation (rTMS) seems to be a promising new strategy to treat depression, the underlying neurobiological mechanism as to how this non-invasive technique can alter depressive states remains unclear. We wanted to examine the neurobiological impact of high frequency (HF)-rTMS treatment, applied to the left dorsolateral prefrontal cortex (DLPFC), on postsynaptic 5-HT2A receptor binding in a sample of severely depressed patients, as measured with 123I-5-I-R91150 single photon emission computed tomography (SPECT) before and after treatment.
Methods: Twenty-one antidepressant-free unipolar melancholic depressed patients, all at least stage III treatment resistant, were studied. As age-dependent reductions in 5-HT2A receptor binding indices (BI) in the cortex consistently has been reported, to control for baseline differences, patients were matched with 21 healthy controls for age and gender. Patients received 10 sessions of suprathreshold (110 %) HF-rTMS (10 Hz), delivered with a figure-of-eight-shaped coil (1560 pulses per session). In order to accurately target the left DLPFC, the precise stimulation site was determined using MRI non-stereotactic guidance.
Results: Compared to the control group, patients displayed significantly less baseline 5-HT2A receptor binding in the DLPFC and significantly higher baseline 5-HT2A receptor binding in the hippocampus. Nine of the twenty-one patients (43%) were responders, as defined by a 50% reduction of the baseline 17-item Hamilton Depression Rating Scale (HDRS) score. Successful HF-rTMS treatment correlated positively with 5-HT2A receptor binding in the DLPFC and correlated negatively with hippocampal 5-HT2A receptor uptake values.
Conclusions: Our results suggest that 5-HT2A receptors might execute different functions, depending as to where they are located in the brain. Our results might imply that a successful HF-rTMS intervention affects the same neurocircuitries 'dysregulated' in major depression. The observed up-regulation of dorsolateral and down-regulation in the hippocampal 5-HT2A uptake values compares to (non)pharmacological interventions in major depression.

P-47-006
Monitoring of ECT Service in a Mental Health Trust in the UK: An audit-based report

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Objectives: Electroconvulsive therapy (ECT) is an effective yet controversial biological treatment entity. The major threat to its continued use stems from concerns about how it is administered. To help overcome this, ECT Accreditation Service (ECTAS) was launched in 2003 by The Royal College of Psychiatrists (RCPsych); our Trust being one of the participating clinics. We proposed to assess, through an audit process, whether our ECT clinic met the ECTAS standards.
Methods: The audit was carried out in a Mental Health NHS Trust in UK and comprised internal and external validation processes. Internal Audit: 10 patients suffering with mental illness were randomly selected from the sample available who had received bilateral ECT in the years 2007-2008. The data and records of these patients were studied, using a retrospective chart review design, against the ECTAS standards for ECT administration. A 5-patient re-audit was carried out after the external audit. External Audit: An external ECTAS on-site peer-review was conducted by RCPsych on five parameters (documentation, treatment run through, environment and facilities, staff interview, patient questionnaire) in the same timeframe with subsequent review of the 5 re-audit patients. The data was analysed in terms of frequency tabulation and percentages.
Results: Initial internal audit results provided overall scores (i.e. 70% compliance) indicative of 'inconsistent practice'; mainly in documentation, recording of consent and side-effect monitoring. The external audit highlighted poor compliance with parameters of 'documentation' & 'environment and facilities' which was addressed satisfactorily (as confirmed in the re-audit). This led to a Category 2 'approved' accreditation by the ECTAS team.
Conclusions: The internal audit demonstrated inconsistency in some areas of practice, which was highlighted through monitoring by an external review process. ECTAS can enable consistent monitoring of standards of administration of ECT and adhering to principles of clinical governance across UK.

P-47-007
Optimise ECT techniques: The effects of pulse width manipulation on the efficacy of ECT treatment in depression

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Objectives: Although electroconvulsive therapy (ECT) techniques have progressed in the past decades, retrograde amnesia remains an important adverse effect of ECT (Lisanby et al 2000), which prevents the more widespread use of this most efficacious treatment of depression. Studies suggest that clinicians can to a certain degree manipulate the efficacy and amnesic effects of ECT. Unfortunately more efficacious forms of ECT seem to induce more amnesia. ECT with bilateral electrode placement has been shown to be more efficacious than unilateral electrode placement but also carries an increased risk of memory problems (Sackeim et al., 1993). These authors showed that the relative strength of electrical stimulation above the seizure threshold was a major determinant for the efficacy of ECT. Unilateral ECT was more efficacious if the seizure was generated by an electrical stimulus with charges (mC) of at least two and a half times above the seizure threshold compared to an electrical stimulus just above seizure threshold. Higher electrical stimulations resulted in significantly more adverse cognitive effects. ECT studies have used electrical stimulation with brief pulse devices delivering pulse widths of 1 msec. Newer ECT devices can deliver pulse widths of 0.3 msec. or less, the so called ultrabrief pulse stimulation. Few studies are available thus far on the use of ultrabrief pulse devices, but the results are promising (Pisvejc et al., 1998; Lisanby & Sackeim 2001). In this study we aim to compare treatment with brief-pulse (1 msec.) versus ultrabrief pulse (0.3 msec.) stimulation. The amnesic effects and the antidepressive efficacy of both treatments are compared. We hypothesize that treatment with ultrabrief pulse stimulation and briefpulse stimulation have an equal antidepressive action.
This poster or free communication presents the background of this methodology and preliminary results of this prospective single blind controlled study in a clinical setting.

P-47-008
ECT efficacy: Correlations between clinical improvement, memory performance and memory complaints

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Objectives: In this study we aim to evaluate the clinical efficacy of ECT use in severe psychiatric disorders and also the relationship between subjective memory complaints and objective memory performance.
Methods: 26 patients were evaluated with clinical assessment tools as BPRS, YMRS, HRSD, BFCRS. From this sample, 12 patients completed the neurocognitive assessment with California Verbal Learning Test (CVLT) and Subjective Memory Complain Scale (SMCS). Inclusion criteria were: 1) fulfillment of the DSM-IV criteria for catatonia and major depressive episode, bipolar disorder, paranoid schizophrenia who do not respond or respond incompletely to pharmacotherapy; 2) ECT was considered optimal treatment. The patients received a mean number of 8 sessions of ECT (± 1,8 sd). Mean age was 39,4 years (± 13,65 sd). Patients were submitted to bitemporal ECT. All patients gave informed consent. Regarding inferential statistical procedures, we used Wilcoxon test and Spearman's rho ($p<0,05$).
Results: Non-parametric correlations showed a significant improvement in symptomatology in case of depression (0,000) and catatonia (0,042) after ECT. No significant results were found between memory performance before and after ECT, between subjective complaints before and after ECT. Moreover, no significant associations were observed between subjective memory assessments and objective measures of the cognitive side effects of ECT.
Conclusions: Our findings showed an improvement in psychopathological features and no alterations in memory performance. However, patients still complain of subjective memory disturbancies. Holding that as true and valid, we can so justify the use of ECT as a relevant therapeutical choice within the treatment of psychopharmacological resistent patients. There is no evidence of post ECT memory impairment and the meaning of subjective memeory complaints needs further evaluations. One limitation of the present study was the relatively small number of investigated patients.

P-47-009
Influence of right frontal repetitive Transcranial Magnetic Stimulation (rTMS) on the affective picture perception

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Objectives: Brain models of emotion processing hypothesize that positive emotions are lateralized towards the left, whereas negative towards the right hemisphere (valence hypothesis). Event related potentials (ERP) as useful tools for bioelectrical measurements of emotionally arousal result in differences when viewing affective or neutral pictures. Since fast (> 5 Hz) rTMS have shown to enhance cortical activity, a facilitation of the stimulated brain region during emotional stimulation, replicated by higher ERP responses, should be expected. Slow (inhibitory) rTMS, however, should cause the opposite phenomena.
Methods: 14 healthy women (age: 22.7 ± 1.5 years) received 1 or 10 Hz rTMS over the right dorso-lateral prefrontal cortex (DLPFC) versus a sham stimulation on two different days. Immediately after rTMS, ERPs were recorded during the presentation of negative, positive and neutral pictures (International Affective Picture System). Mean area under the curve of the ERPs were analysed from frontal, central and parietal regions for the late positive potential (LPP, 400-700 ms). Separate repeated measurement analyses of variance (ANOVA) with a 2 (real vs. sham stimulation) x 4 (high and low negative, neutral, positive pictures) x 2 (hemisphere) design and LPP change as dependent variable were calculated.

Results: Compared to the sham stimulation, the 10 Hz rTMS resulted in higher LPP answer exclusively over the right frontal cortex (side of stimulation) for high-negative emotionally arousal only ($F=4.2$; $p<0.05$). No other effect reached statistical significance and no such effects appeared after 1 Hz rTMS.
Conclusions: Real high frequency rTMS of the right DLPFC results in hemispheric specific reactions during negative emotionally stimulation in healthy women and seems to enhance the right frontal activation during negative emotions. These data provide support for the influence of rTMS on processing of emotionally stimulation in the prefrontal cortex. In further studies effects of rTMS on the left DLPFC should investigate.

P-47-010
Changes in brain activities evoked by masked traumatic stimuli in patients with Posttraumatic Stress Disorder (PTSD): A functional MRI study

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Objectives: Posttraumatic stress disorder (PTSD) is an anxiety disorder associated with changes in neural circuitry involving frontal and limbic systems. The rapid development of the field of functional neuroimaging have allowed researchers to uncover the neural networks believed to be involved in the pathophysiology of PTSD.The purpose of our study is to detect dysfunctional areas to posttraumatic stress disorder (PTSD), especially related to the major symptoms of marked fear associated with traumatic experiences. Masked images were presented for a very short period, which was below the cognition threshold, and measurements were performed by functional MRI with high temporal resolution.
Methods: Participants are composed of eight patients with PTSD and nine subjects of control. Masked images were presented for a very short period, which was below the cognition threshold, and measurements were performed by functional magnetic resonance imaging employing the method visual stimulation. We analyzed differences in brain activation between the PSTD and control groups.
Results: In control group, activation associated with the masked stimuli was observed in the right inferior frontal gyrus and the left cerebellum. In the PTSD group, significant activation was not observed in these areas, but significant deactivation was observed in the right ventromedial prefrontal cortex (vmPFC) and the right anterior cingulated gyrus (ACC). In analyzing the differences in activation between the PTSD and control groups, the PTSD group also showed marked deactivation in the right vmPFC and the right ACC.
Conclusions: In PTSD, ACC with adjacent medial and ventral frontal cortical areas show to play a critical role in extinction of learned associations to aversive stimuli, therefore hyper-reactivity in PTSD patients is accentuated by deactivated and insufficient inhibition by these areas.

P-47-011
The effect of repetitive transcranial magnetic stimulation (rTMS) on fear extinction in rats

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Objectives: Fear extinction is the diminishing of learned fear responses that normally occurs when a conditioned stimulus (CS) is repeatedly presented in the absence of the aversive unconditioned stimulus (US). Facilitating the fear extinction is of clinically importance to improve the efficacy of current exposure therapies for the treatment of anxiety disorders such as post-traumatic stress disorder (PTSD). The aim of this study was to examine whether repeated transcranial magnetic stimulation (rTMS) paired and unpaired with exposure to CS facilitate fear extinction of rats or not.
Methods: Thirty five rats were conditioned to the tone CS by pairing with an electric foot shock as an aversive unconditioned stimulus (US). On the following day we administered rTMS of high frequency (10 Hz) before fear extinction and rTMS paired with CS during extinction to two rat groups, respectively. Fear responses (the level of freezing to tone) of the rats were estimated to compare between the rTMS and the corresponding sham groups.
Results: We found no differences in the level of freezing to tone between the unpaired rTMS group and sham group. More significantly, rats given rTMS paired with CS during extinction showed significantly less freezing behavior than the sham group, and this enhancement of fear extinction remained after 24 hours without further stimulation.
Conclusions: We suggest that high-frequency rTMS paired with trauma-reminding stimuli enhances fear extinction and that rTMS in conjunction with exposure therapy is potentially useful for facilitating extinction memory for PTSD.

P-47-012
From psychopathology to psychosurgery – leaving the localisationist rationale behind?

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Objectives: A critical review of the historical and conceptual foundations of psychosurgery as ablative functional neurosurgery shall shed light on questions that will arise in today's context of new techniques in functional neurosurgery as deep brain or cortical stimulation in the treatment of psychiatric disorders and shall elucidate the general problem of localisationism against connectionism as the neuroscientific frame of psychopathology.
Results: The debate connectivity against localization theory of higher mental functions found its expression already at the beginnings of experimental demonstration of localisation marked by the dispute between Flourens and Gall. Empirical lesion studies by Broca, Wernicke, Charcot and Pitrés and stimulation studies by Fritsch, Hitzig and Ferrier led to narrow-localisationist-diagramms in Galls tradition. Gottlieb Burckhardt, a Swiss psychiatrist, was the first to attempt at a therapeutic application in the domain of psychiatry. Leaving Moniz' model of ‚fixed synaptic connections' behind Freeman and Watts presented a traditional localisationist foundation of psychosurgery. Thinking that psychosurgery is based on a flawed and impoverished vision of the relationship between brain tissue and psychological disorder some psychiatrists criticised if neurosurgery for mental disorder should not better be allowed to disappear. Some have already started to shift attention and not to focus on an ideal singular target but to search for means of modulating an entire neuronal circuitry: a neuropsychiatric disorder might be more like a neurocircuitry-dysregulation than a simple hypo- or hyperfunctioning of a single brain area.
Conclusions: A cortical area might be specialized for some aspects of cognitive processing but the cortical infrastructure supporting a specific behavioural function may involve many specialized areas whose union is mediated by the functional integration among them. So, a 'mild' connectivist model that differentiates between behavioural, computational and neuroanatomical levels might be the best theoretical frame for research in psychopathology.

P-47-013
Instantaneous and complete suppression of motor tics and obsession and compulsions with unilateral thalamic deep brain stimulation in Tourette - Syndrome

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Objectives: The case report presents a 30-year-old male with compulsory left hand pounding of the chin leading to chronic ulceration of the skin, loss of teeth and mandibular fractures accompanied by several milder left and right motor (e.g. touching the nose) and a single mild vocal tic (sniffing) who had also frequent obsessions and compulsions.
Methods: Stimulation leads were placed bilaterally in the centromedian-parafascicular (cm/pf) complex of the thalamus. One week after surgery test stimulation was performed showing an instantaneous suppression of the violent tic, the other motor tics as well as the vocal tic after activation of the right electrode. Consequently, stimulation was started unilateral right. Treatment of a concomitant apparently essential tremor of the right hand was effectively initiated after two weeks by activating the left electrode.

Results: The violent tic as well as the obsessions and compulsions remained completely suppressed until 10 month after treatment initiation. After 1 year suddenly hyperkinetic symptoms with multiple motor tics and the vocal tic reappeared, accompanied by sweating and deep distress. Testing of electrodes revealed dysfunction of the distal contact of right electrode (unipolar 4-). Switching the stimulation to the next contact (unipolar 5-) suppressed the symptoms immediately.
Conclusions: This case provides further evidence, that treatment-resistant violent motor tics and comorbid obsessions and compulsions may effectively be treated by deep brain stimulation to the thalamus.

P-47-014
Repetitive transcranial magnetic stimulation postpartum depression treatment neurocognitive and behavioral symptomatology therapeutic effects

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Objectives: Double-blind, controlled, randomized study to investigate antidepressive efficacy of Repetitive Transcranial Magnetic Stimulation (rTMS) in Postpartum Depression.
Methods: SCID – DSM IV;40 patients; 18 - 36 years old; Depressive symptoms 1 – 6 months postpartum; Drug free (except clonazepan 1mg); Randomly assigned to 4 weeks of daily treatment: active rTMS x sham rTMS; Follow-up: 2 weeks; Parameters: Intensity 120% MT, Left Dorsolateral Prefrontal Cortex, 5 Hz, 10 seconds on, 20 seconds off, 25 trains/day, 20 days; Scales (before rTMS, 2 – 4 and 6 weeks follow-up): Hamilton Depression Rating Scale – HAM-D 17, Edinburgh Postnatal Depression Scale – EPNDS, Hamilton Anxiety Scale – HAM-A, Social Adjustment Scale – Self-Report, SF-36, Clinical Global Impression, GAS, Neuropsychological Tests
Results: On data collection (results to be presented at the WFSBP/2009)
Conclusions: To our knowledge this is the first double-blind-controlled study to evaluate rTMS in postpartum depression. If the results show rTMS efficacy it could become the first option for treatment in this population; being safe for patients and the baby. Neurocognitive and behavioral skills of the mother to look after the baby, as well as guarantee the benefit of breastfeeding and also caters for the social welfare and wellbeing of the family.

P-47-015
Predictors of response to electroconvulsive therapy obtained using the three - factor structures of the Montgomery and Åsberg Depression Rating Scale for major depressive disorders in Japanese patients

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Objectives: Electroconvulsive therapy (ECT) is most effective in the treatment of refractory major depressive disorders. In spite of several studies concerning with predictors of the response to ECT, the symptomatological predictors based on depression rating scale have not been studied.
Methods: This study included 24 Japanese patients who fulfilled the Diagnostic and Statistical Manual of Mental Disorders (DSM)-IV criteria for the diagnosis of major depressive disorders and whose score on the Montgomery and Åsberg Depression Rating Scale (MADRS) was 21 or higher. The three-factor model of MADRS was used for analysis: the first factor was defined by 3 items, the second factor was defined by 4 items, and the third factor was defined by 3 items representing dysphoria, retardation, and vegetative symptoms, respectively. ECT was performed two times a week for a total of 6 sessions with THYMATRON-DGx device using the brief –pulse technique. A clinical response was defined as a 50% or greater decrease in the pretreatment total MADRS score.
Results: No significant differences were observed in the age, the number of previous episodes and the duration of current episodes between the responders and non-responders. The mean factor 1 score of the responders (n=17) at pretreatment was significantly higher than that of the non-responders (n=7). Significant difference of the mean factor 3 score between the responders and non-responders was firstly observed at one week later after 6 sessions of ECT.
Conclusions: This study suggested that a high factor 1 score at pretreatment was a good predictor of the response to ECT in major depressive patients.

P-47-016
Abnormalities in cortical and trans-callosal inhibitory mechanisms in subjects at high-risk for alcohol dependence: A TMS study

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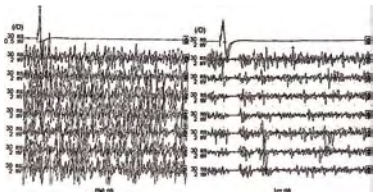
Objectives: Central Nervous System (CNS) disinhibition and a resulting state of behavioral undercontrol, has been postulated to underlie the vulnerability to early-onset alcohol dependence (AD). High family loading of early onset AD confers on these individuals a 'high-risk' to develop AD. Cortical inhibitory systems modulate the balance between excitatory and inhibitory systems and can be evaluated by transcranial magnetic stimulation (TMS). The aim of this study was to explore differences in functioning of motor cortical and transcallosal inhibitory systems, in subjects at high-risk (HR) and low-risk (LR) for AD, and to examine the relationship beween CNS disinhibition and behavioral undercontrol.
Methods: Right-handed, HR (n=15) and LR (n=15) male subjects, matched for age, gender, height, weight and education were assessed for psychopathology and family-history of alcoholism, using the Semi-Structured Assessment for the Genetics of Alcoholism and the Family Interview for Genetic Studies. Following single pulse TMS, electromyogram (EMG) recorded from the right opponens pollicis muscle was used to measure the silent periods. Contralateral silent periods were recorded at 110%, 130% and 150% of the resting motor threshold while ipsilateral silent periods were recorded at 75% and 100% of the stimulator output. Twelve trials were obtained at each stimulus intensity.
Results: HR subjects had significantly shorter cSP and iSP and a relatively higher prevalence of "absent" iSP. They had significantly higher mean Externalizing Symptoms Scores [ESS] than LR subjects and there was a significant negative correlation between iSP duration and ESS. Subjects with absent iSP at 75% SO also had significantly higher ESS than in those who displayed iSP.
Conclusions: These preliminary findings suggest that HR subjects have relative impairments in cortico-cortical and transcallosal inhibitory mechanisms. The consequent state of CNS hyperexcitability may be etiologically linked to the excess of externalizing behaviors observed in this population, which is thought to be a predisposition to a higher risk of developing early onset alcoholism.



P-47-017

Effect of augmentative repetitive transcranial magnetic stimulation in resistant obsessive - compulsive disorder: A preliminary study

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Objectives: Only few patients with OCD ever experience a complete remission of symptoms and treating resistant OCD remains a clinical challenge. Prefrontal mechanisms are implicated in OCD. There are some reports of the beneficial effects of right dorsolateral prefrontal cortex repetitive transcranial magnetic stimulation in OCD. This ongoing open label multicentre naturalistic clinical study evaluates the effect of rTMS augmentation in resistant OCD with mixed obsessions and compulsions. Preliminary findings are being reported.

Methods: 21 patients fulfilling the criteria of resistant OCD on fixed doses of medication were taken up in an open label multicentre naturalistic study at three centers in India. High frequency rTMS at 90% of motor threshold using MagPro R30 device was applied to the right dorsolateral prefrontal cortex for 15 days, 5 days a week for three weeks, following standard guidelines. Assessments were done using Hamilton Depression Rating Scale, Yale-Brown Obsessive Compulsive Scale and Clinical Global Impressions scale at baseline, weekly for three weeks and at one month follow up.

Results: Preliminary data suggests that right dorsolateral prefrontal cortex rTMS has beneficial effects on obsessions and compulsions in patients of resistant OCD receiving usual medication. Detailed results shall be presented on completion of the study.

Conclusions: Further studies with larger sample size are needed to substantiate the findings of this study that rTMS is beneficial in patients of OCD resistant to medication.

P-47-018

Transcranial direct current stimulation (tDCS) in therapy - resistant depression: A double-blind, placebo – controlled study

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Objectives: Direct current stimulation for modulating membrane potentials is known since the 1960s. Recently, tDCS has been rediscovered in motor cortex neurophysiology. Based on the role of the dorsolateral prefrontal cortex in the pathophysiology of depression and previous studies with repetitive transcranial magnetic stimulation in depression Fregni and co-workers investigated anodal tDCS of the left DLPFC in three consecutive trials yielding promising results. However, no data are available in therapy-resistant depression. We report preliminary findings from a double-blind, placebo-controlled trial in therapy-resistant depression.

Methods: 20 patients with moderate to severe major depression (DSM-IV criteria) were included in a four weeks cross-over trial. All patients had undergone at least two ineffective antidepressant trials. Patients received tDCS after not responding to a stable antidepressant treatment over 3 weeks and were randomized to active (1 or 2 mA) or placebo tDCS for two weeks each in random order. The anode was positioned over F3 and the cathode over the contralateral supraorbital region. For placebo tDCS an undistinguishable sham device was used. Severity of depression was assessed by HAMD, BDI, CGI and CORE scales and raters were blind to treatment conditions.

Results: Clinical improvement showed no significant difference between active and placebo tDCS. Group 1 (N=10) receiving 1mA intensity showed a reduction of baseline HAMD scores by 9.6 % during active and 12.2 % during placebo tDCS. Group 2 (N=10) receiving 2 mA tDCS showed a decrease of baseline HAMD scores by 18.7 % during active and 17.2 % during placebo tDCS. 1 mA and 2 mA tDCS were not significantly different regarding HAMD, BDI and CGI ratings.

Conclusions: Neither 1 mA nor 2 mA tDCS were superior to placebo treatment and previous findings from studies in less severely depressed and less therapy-resistant patients were not replicated in our sample. However, tDCS may have to be applied over a longer period at different stimulation parameters.

P-47-019

The use of transcranial laser stimulation for treating developmental language deficits in the preschool period

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Objectives: One of the key issues in clinical psychiatry is developing new methods for treating speech pathologies of different origin. The use of transcranial laser stimulation is discussed as a promising method in this field.

Methods: For utilizing the biological effect of coherent low intensity monochromatic laser radiation a helium-neon laser with the density of the power flow of 3mW in the continuous generation mode and with the wave length of 633 nm was used. 80 children participated in the study. The experimental group comprised 65 children, which were divided into four groups depending on the severity of speech dysfunctions. All the children were subjected to non-invasive transcranial scanning laser stimulation of the brain language zones during 5 minutes. The control group consisted of children who were treated by conventional drugs.

Results: After the treatment 12 children of the experimental and 12 children of the control groups were examined by computer electrical encephalography, and their temperature was taken. In the experimental group after the use of transcranial laser stimulation the following effects were observed: the increase of the amplitude of oscillation of action potentials in the language zones, increase in body temperature by 0,5 C, increase in speech activity, better understanding of speech, increase of vocabulary, better articulation, decrease of speech mistakes. The positive effect from laser stimulation was noticeable from 30 minutes to 2 hours. The best results in comparison with the control group were observed 1,5-2 ,months after the treatment.

Conclusions: The use of scanning transcranial laser stimulation facilitates the development of speech in preschool children due to the local stimulation of biological processes in the language zones, activation of the microcirculation system of nonspecific reaction of cells. This is a safe method, which is more effective in the complex therapy of language deficits.

P-09
Genetics I

P-09-001
Cis-acting regulatory influences on the schizophrenia candidate gene RGS4 in human brain

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Objectives: Regulator of G-protein signalling 4 (RGS4) is a strong candidate susceptibility gene for schizophrenia. RGS4 regulates the effects of neurotransmitter-receptor interaction in many systems implicated in schizophrenia, such as those utilizing dopamine, serotonin and glutamate. Expression of RGS4 both at the RNA and protein level has been reported to be altered in schizophrenic brains. Genetic association observed between non-coding SNPs in the RGS4 gene and schizophrenia suggests that altered expression may partly reflect genetic risk factors, and therefore constitute a primary aetiological mechanism in the disorder. We sought to determine whether RGS4 contains common variation affecting its expression in human brain, and, if so, in which regions these effects are manifest.
Methods: We assessed relative allelic expression of RGS4 across 7 brain regions in 14 individuals. Significant departure from the expected 1:1 ratio of the two alleles indicates the effect of heterozygosity for cis-acting regulatory variation.
Results: We observed significant departure from the expected 1:1 ratio of allelic expression, indicating that RGS4 is indeed subject to common cis-acting regulatory influences in brain. Furthermore, we found that, within individuals, these effects vary between brain regions.
Conclusions: RGS4 contains common regulatory variation, which potentially mediates reported genetic associations with schizophrenia. Regions where the effects of cis-acting regulatory variation are greatest may constitute areas of focal genetic pathology in the disorder.

P-09-002
Maltreatment, MAOA, and delinquency: Sex differences in gene-environment interaction in a large population-based cohort of adolescents

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Objectives: To investigate a possible interaction between a functional polymorphism in the MAOA gene promoter (MAOA-VNTR) and childhood maltreatment in the prediction of adolescent male and female criminal activity.
Methods: A cohort of 1 825 high school students, 17-18 years old, completed an anonymous questionnaire during class hours which included questions on childhood maltreatment, sexual abuse, and criminal activity. Saliva samples were collected for DNA isolation, and analyzed for the MAOA-VNTR polymorphism.
Results: Self-reported maltreatment was a strong risk factor for adolescent criminal behavior. Also, the MAOA genotyp showed a significant effect when controlled for maltreatment. Boys with a short variant and girls with one or two long variants of the polymorphism showed a higher risk for criminal activity when exposed to maltreatment.
Conclusions: Our results from a large population, including both sexes, confirm previous findings of an interaction between the MAOA-VNTR polymorphism and self-reported maltreatment. Results for boys and girls differ according to MAOA-VNTR genotype and direction of phenotypic expression.

P-09-003
BDNF gene polymorphisms and susceptibility to schizophrenia in the Cluj schizophrenic population of Romania

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Objectives: To investigate associations between brain-derived neurotrophic factor (BDNF) gene polymorphisms and schizophrenia in the Clj population of Romania.
Methods: BDNF genotyping was performed using polymerase chain reaction and RFLP techniques in 231 patients with schizophrenia and 191 healthy controls.
Results: The distribution of the BDNF rs6265 GG, GA, and AA genotypes was 61.3%, 35.1%, and 3./% in controls and 67.5%, 27.3%, and 5.2% in cases respectively. The distribution of the BDNF rs6265 A allele was 21% in controls and 19% in cases. The distribution of the BDNF C270C, C270T, and T270T genotypes was 88.0%, 11.5%, 0.5% in controls and 91.8%, 7.4%, and 0.9% in cases. The distribution of the BDNF 270T allele was 6% in controls and 4.5% in cases.
Conclusions: In conclusion, the BDNF rs6265 (G to A) and C270T polymorphisms were not associated with schizophrenia (X2=3.248;P=0.197 and X2=2.298, P=0.317 respectively). However, the BDNF AGCT compound genotype was found to be protective against schizophrenia in the Cluj population of Romania(X2=4.702,P=0.030,OR=0.134,95%CI=0.016-1.123).

P-09-004
Is the MTHFR A1298C and COMT val158met polymorphisms associated with schizophrenia in the Cluj Napoca population of schizophrenics in Romania?

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Objectives: To investigate associations between methylenetetrahydrofolate reductase (MTHFR) gene A1298C and COMT val158met polymorphisms and schizophrenia in the city of Cluj Napoca in Romania.
Methods: MTHFR A1298C and COMT val158met genotypings were performed using polymerase chain reaction and RFLP techniques in 231 patients with schizophrenia and 191 healthy controls.
Results: The distribution of the AAHL, AAHL, AALL, ACHH, ACHL, ACLL, CCHH, CCHL, CCLL genotypes was 10.0%, 24.2%, 10.4%, 11.3%, 23.4%, 10.0%, 0.9%, 6.5% and 3.5% in cases and 7.9%, 20.9%, 15.7%, 15.2%, 20.4%, 9.4%, 2.6%, 6.3%, and 1.6% in controls.
Conclusions: In conclusion, it appears that threre is no interaction between MTHFR A1298C polymorphism and COMT val158met polymorphisms in the Cluj Napoca population in Romania.

P-09-005
Methylenetetrahydrofolate reductase gene polymorphisms and susceptibility to schizophrenia in the city of Cluj Napoca in Romania

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P-09-006

The role of gene-gene and gene-environment interactions in individual variations of personality traits

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Gulnaz Faskhutdinova, Darya Gaysina, Elza Khusnutdinova

Objectives: We aimed to examine whether interaction effect of neurotransmitter system genes and demographic factors contributes to variation in personality traits in healthy individuals and to observe the models accounting for the largest proportion of variance in each trait.
Methods: The present study sample consisted of 652 healthy individuals (men-222, women-430) of Caucasian origin (Russians-233, Tatars-419) from Russia (mean age: 19.53±2.24 years) without any history of psychopathologies. Personality traits assessment was performed under TCI-125 (Cloninger et al., 1993). Genotyping of 18 polymorphic markers of the following candidate genes: 5-HTT, HTR1B, HTR2A, HTR2C, TPH1, SLC6A3, DRD2, DRD4, NET, ADRA2A, MAOB, COMT has been performed using PCR. Gene-gene and gene-environment interaction effect on personality traits was detected under multiple regression (MR) analyses (SPSS 13.0).
Results: While conducting MR analyses the best models explaining variation in personality traits were observed: 4.9% of variance in Novelty Seeking was caused by SLC6A3*ethnicity*gender*order of birth interaction (P<0.0001), 4.8% of variance in Harm Avoidance – by 5-HTT*TPH1*NET*ethnicity *gender interaction (P<0.0001), 1.3% of variance in Reward Dependence – by 5-HTT*DRD4*ethnicity interaction (P<0.0001), 1.2% of variance in Persistence – by 5-HTT*SLC6A3 interaction (P=0.009), 0.5% of variance in Self-Directedness – by 5-HTT*DRD4*MAOB*ethnicity interaction (P=0.001), 1.6% of variance in Cooperativeness – by 5-HTT*TPH1*DRD4*ethnicity interaction (P<0.0001), 4.0% of variance in Self-Transcendence – by HTR2A*smoking status*place of residence interaction (P<0.0001).
Conclusions: Our findings indicate that genes of different neurotransmitter systems can influence multiple personality traits.

P-09-008

Association between infant irritability, 5-HTT and a putative functional polymorhpism located in TFAP2B

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Objectives: In the present study we investigated the possible involvement of 5-HTT and TFAP2B gene polymorphisms in infant temperament. To test this hypothesis, we investigated polymorphic variants in the 5-HTT and TFAP2B in a cohort of Caucasian newborns. Besides, we also tested if a 4 pair base indel located in intron 2 of TFAP2B gene could be functional.
Methods: An association study was conducted on 114 Caucasian newborns. Their temperament was evaluated using the Brazelton Neonatal Assessment Scale 48 hours after birth. Several polymorphisms in the 5-HTT (5-HTTLPR, rs25531, Stin2), and the TFAP2B indel were genotyped. Linear regression was performed to analyze data, and Bonferroni corrections were applied. Dual-Reporter gene assays and transient transfection using pGL3 vectors (which carry the luciferase reporter gene and can have and SV40 promoter and/or an enhancer region) was performed to test the functionality of the TFAP2B indel polymorphism, using a a mouse cortical neural progenitor cell line
Results: A significant association was found between the 5-HTTLPR and 5-HTTLPR + rs25531 polymorphisms with State Organization cluster, related with infant irritability (p= 0.04 and p=0.01, respectively). TFAP2B indel polymorphism was also associated with State Organization (p-value=0.03). In addition, a gene-gene interaction between the 5-HTT rs25531 and TFAP2B indel polymorphisms was found (p-value=0.006). A 30% increase in the luciferase levels produced by the construct containing the TFAP2B long allele compared with the short allele was found using a pGL3 vector carrying a SV40 promoter but without enhancer sequences. This difference was statistically significant (p=0.03).
Conclusions: This study supports the role of the 5-HTT and TFAP2B genes in the infant temperament, in two different ways: as single gene effect and as gene-gene interaction. The contribution of these genes to this trait is in agreement with previous findings. Our data additionally suggest a potential functional effect of the TFAP2B polymorphism on transcription in vitro.

P-09-009

Genetic interaction of alpha-7 nicotinic acetylcholine receptor and brain-derived neurotrophic factor polymorphisms in Alzheimer's disease

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Objectives: Several genetic and environmental factors influence the susceptibility to Alzheimer's disease (AD). The partially duplicated variant (CHRFAM7A) of the $\alpha 7$ nicotinic acetylcholine receptor ($\alpha 7$nAChR) subunit gene can be a strong candidate gene for AD. A 2bp deletion polymorphism in CHRFAM7A results in a stop codon therefore a truncation in the putative gene product. A functional polymorphism of the brain-derived neurotrophic factor (BDNF Val66Met) has major impact on the intracellular trafficking and regulated secretion of pro-BDNF. BDNF induces a decrease in $\alpha 7$nAChR mediated neuronal response in hippocampal interneurons. Alterations on BDNF levels and disruption of $\alpha 7$nAChR function in the hippocampus can be involved in cognitive deficits in AD.
Methods: The study included 155 AD and 152 healthy control (HC) probands. The diagnosis of probable AD was based on NINCDS-ADRDA criteria. The genetic analyses were performed by PCR amplifications. Genotype frequencies were compared by Pearson chi-square test. A logistic regression model was used to test for the interaction between the BDNF Val/Val and the CHRFAM7A wild genotype (without the 2bp deletion allele).
Results: The frequency of the CHRFAM7A wild genotype was significantly higher in AD compared to HC group (AD: 35.9%, HC: 23.7%; p=0.010). The BDNF Val/Val genotype was significantly over-represented in AD compared to HC group (AD: 57.4%, HC: 32.2%; p<0.0001). The simultaneous occurrence of the CHRFAM7A wild genotype and the BDNF Val/Val genotype was significantly higher in AD than in HC group (AD: 25.2%, HC: 6.6%; p<0.0001).
Conclusions: We suggest that the CHRFAM7A wild genotype and the BDNF Val/Val genotype itself and in combination with each other could be a risk factor for AD. These findings support the involvement of CHRFAM7A and BDNF in the etiopathogenesis of AD.

P-09-010

Detection of stable reference genes for real-time PCR analysis of the dorsolateral prefrontal cortex in schizophrenia and bipolar disorder

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Objectives: Gene expression studies in post-mortem human brain are a common tool for studying the etiology of psychiatric disorders, such as schizophrenia and bipolar-disorder (BPD). Quantitative Real-time-PCR (qPCR) is an accurate and sensitive technique used for gene expression analysis, in which the gene expression is quantified by normalization to one or more reference genes, thought to be stably expressed in the examined samples. Accurate data normalization is critical for the validity of results obtained using qPCR. This study aimed to identify genes which may serve as reference in post-mortem dorsolateral-prefrontal cortices (DLPFC) of patients with schizophrenia, BPD, and control subjects.

Methods: RNA from post-mortem DLPFC, BA 46 samples, was obtained from the Stanley Foundation Array Collection. In the exploratory stage of the analysis samples of 4 BPD patients, 2 schizophrenia patients, and 2 control subjects underwent reverse-transcription and was were submitted to qPCR using the TaqMan® Low Density Endogenous Control Panel (TLDA), containing assays for 16 genes commonly used as endogenous controls. In the next stage, 6 of these genes: TFRC, RPLP0, ACTB, POLR2a, B2M and GAPDH were quantified by qPCR in 12 samples of each clinical group. The expressional stability of the genes was analyzed by GeNorm and NormFinder.
Results: TFRC and RPLP0 were found to be the most stably expressed genes. The least stable genes were 18S, POLR2a, and GAPDH, whereas TBP, HMBS, and YWHAZ were poorly expressed in the examined samples. Therefore, these 6 genes should not be used as reference in expression studies in DLPFC, particularly when conducted in BA 46.
Conclusions: This study illustrates the importance of examining the stability of candidate reference genes in the specific sample collection to be analyzed.

P-09-011
Polymorphisms in the GABRA6 gene influence coping style in healthy adults and show evidence for a gene-environment interaction with life events

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Objectives: Dispositional coping styles are important moderators of the stress response. They are shaped to some extent by environmental influences, but also heritable factors seem to be involved. The major constituent of the physiological stress response is an activation of the sympathetic nervous system and the hypothalamus-pituitary-adrenocortical axis, which are both under control of GABAergic neurons. Several polymorphisms of the GABAAα6 receptor subunit gene (GABRA6) have been shown to affect both the physiological response to stress as well as personality traits that are discussed as potential stress moderators. Based on this evidence we selected the GABRA6 gene as a promising candidate to investigate if GABRA6 polymorphisms are associated with coping styles or whether such an association is moderated by the individual level of life stress.
Methods: For this reason we analyzed five single nucleotide polymorphisms tagging the GABRA6 gene region in a sample of 366 healthy Caucasians and assessed stressful life events with an adapted version of the Social Readjustment Rating scale (R-MEL). Coping styles were assessed with the German Stress Coping Questionnaire SVF78.
Results: Two SNPs (rs3811992 and rs3811995) in complete Linkage disequilibrium showed an allelic effect on the coping factor Distraction. More importantly, multiple linear regression analysis revealed significant interactions between GABRA6 SNPs and life events, with the strongest interaction effect emerging for the SNP rs3911991: Homozygous carriers of the minor allele report higher scores on the coping factor Control if exposed to a high life stress level (GG vs TT x LEs: $\beta = -0.42$, $p = 0.002$, TG vs TT x LEs: $\beta = -0.56$, $p = 0.0001$).
Conclusions: Our findings provide first evidence for a gene-environment interaction between GABRA6 SNPs and the level of life stress on positive coping styles.

P-09-012
Association among aggressiveness, neurocognitive function, and the Val66Met polymorphism of brain-derived neurotrophic factor (BDNF) gene in male schizophrenic patients

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Objectives: The purpose of this study was to investigate the association among aggressive behavior, neuropsychological function, and the Val66Met functional polymorphism of brain-derived neurotrophic factor (BDNF) gene in male schizophrenic patients.
Methods: We examined 51 male patients with schizophrenia who had committed homicide (i.e., H-SCZ), 50 male patients with schizophrenia who had not committed homicide (i.e., NH-SCZ), and 50 healthy male controls. Patients were evaluated using the Positive and Negative Syndrome Scale (PANSS), Life History of Aggression (LHA), and the Overt Aggression Scale (OAS). In addition, patients were given additional neurocognitive function tests, including Korean-Wechsler Adult Intelligence Scale (WAIS) short form, the Korean version of the Rey memory test, the Stroop test, and the Wisconsin Card Sorting Test (WCST). Val66Met polymorphism of BDNF gene was also genotyped in all schizophrenic patients.
Results: We observed no significant differences between patients in the H-SCZ and NH-SCZ groups, with regards to PANSS scores. Total LHA ($P < .01$) and OAS scores for the most severe episode ($P < .01$) or for recent one month ($P < .05$) was higher in the H-SCZ group than in the NH-SCZ group. There were no significant differences in the genotype distribution or allelic frequency of the Val66Met polymorphism between the schizophrenic groups. In addition, we observed no significant differences between H-SCZ and NH-SCZ groups with regards to performance on neuropsychological tests. The Met allele of the Val66Met polymorphism was associated with poor Intelligent Quotient (IQ), Memory Quotient (MQ), learning, and delayed recall, in the H-SCZ group. However, genotype did not appear to influence neurocognitive function in schizophrenic patients who had committed homicide.
Conclusions: The neurocognitive tests used in our study were unable to distinguish between violent and non-violent schizophrenic patients. Furthermore, the Val66Met polymorphism was not associated with aggressiveness in patients with schizophrenia.

P-09-013
SMAD4 gene is associated with psychosis in the Cost Rican population

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Objectives: In a previous linkage disequilibrium analysis of subjects with psychotic disorders from the Central Valley of Costa Rica (CVCR) we found evidence of association with psychosis in three regions of chromosome 18. We identified TGIF as a candidate gene for psychosis in 18p11.31. In 18q12.3 we identified an association with the microsatellite markers D18S473 and D18S474. Fine mapping of this region showed the strongest association for the marker rs8096092 on SMAD4 gene. Smad4 interacts with tgif in the regulation of expression of genes related with neuronal development and survival. In this study we sought to study the association of SMAD4 with psychosis.
Methods: Family based association test (FBAT) was used to analyze the association of 3 SNPs in SMAD4 gene and the microsatellite marker D18S474 in 152 families (376 subjects, 151 with history of psychosis) from the CVCR. Immunoprecipitation of SMAD4 with TGIF was performed to analyze if a mutation in TGIF associated with psychosis affects the interaction of these two proteins.
Results: Association analyses revealed that all 3 SNPs tested in SMAD4 showed independent association to the phenotype of psychosis (rs2688949: p=0.0005; rs22274384: p=0.003; rs16189870: p=0.01). Linkage disequilibrium (LD) analysis showed that D18S474 is in complete LD with the 3 SNPs tested within SMAD4 (D'=1.00). The haplotype of all 4 markers showed evidence of association (global P value=0.0005) to psychosis. The mutation in TGIF did not affect the interaction of tgif with smad4.
Conclusions: SMAD4 is associated with psychosis in the CVCR population. The interaction of smad4 with tgif is not affected by a mutation in TGIF. Further analyses are required to identify causal polymorphisms in SMAD4 and to study a possible alteration of the interaction of these two genes. Altogether, our results point to the possible involvement of SMAD4 in the pathophysiology of psychotic related disorders.

P-09-014
Multifactor dimensionality reduction reveals gene – gene interactions associated with Antisocial Personality Disorder in Colombia

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Objectives: Identify and characterize high-order gene to gene interactions in antisocial personality disorder (ASP)
Methods: Participants for case–control study were selected from inmate male population in Bellavista prison from Medellin-Antioquia. The study included, 310 ASPD subjects with ASPD and 200 no ASPD; diagnoses were made according to a best-estimate procedure based on a semi-structured interview (DIGS 3.0), Genomic DNA was collected in each individual from buccal swab, and Genotyping some single nucleotide polymorphisms (snps) in candidate genes with main serotonin pathway effects. A $\chi 2$ -test was used to assess whether the genotypes were in Hardy–Weinberg equilibrium (HWE) and to compare the genotype and allele frequencies between case and control subjects. As well as logistic regression model was used to calculate odds ratios and their 95% confidence intervals. The gene–gene interaction was examined using the multifactor dimensionality reduction (MDR) method version 2.0.alfa; We assess model sizes of 2 and 3 loci and counted the number of replicates that contained the causal loci in the final best model that was identified using 10-fold cross-validation.
Results: We find epistatic interaction with COMT (Catechol-O-Methyl Transferase), 5-HTR2A and HTR1B (serotonin receptors) with ASPD. this data supports an important role of polymorphism in serotonin receptors and Low enzime activity of COMT for susceptibility to ASPD.
Conclusions: this study suggest that funtional variants in COMT, 5-HTR2A and HTR1B gene would be associated with ASPD and influence the dopamine rewards pathways and modulate serotonin levels in ASPD.

P-09-015
Chromosomial abnormalities in some cases with schizophrenia

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Objectives: Schizophrenia is a common complex mental disorder. The etiology is still unknown despite decades of intensive study. Genetic factors play an important role in the etiology of schizophrenia. It is generally believed that schizophrenia is a polygenic disease with an interplay of environmental factors and genetic susceptibility. Cytogenetic analysis might identify chromosomal aberrations associated with schizophrenia, interesting regions which may harbor susceptibility genes.
Methods: We investigated cytogenetic 20 patients with schizophrenia. Peripheral blood lymphocytes stimulated by phytohemagglutinin were cultured for 72 hours at 37ºC. The karyotyping were performed by using G banding. For chromosomial analysis between 25 and 50 metaphases were examined.
Results: We have detected 4 karyotypes with chromosomial abnormalities:
- karyotype 46,XX, 22qdel
- karyotype 46,XY, 6p21:, 9qdel
- karyotype 46,XX fra7q22
- karyotype 46,XX 14qdel

The chromosomial regions involved, contain one or more susceptibility genes: COMT (22q11), PRODH2(22q11), DTNB1(6p22), GRM3(7q21-22), Akt1(14q22-32).Our findings suggest that these regions are of interest in that they may harbor important genes for schizophrenia.
Conclusions: The identification of such chromosomal abnormalities associated with schizophrenia might provide important implications for further research for the chromosomal location of major genes in this disease.

P-09-016
Genetic association study with dysbindin gene: Common genetic factors for schizophrenia and bipolar disorders?

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Objectives: It has been suggested that there is a phenotypic and genetic overlap between schizophrenia and bipolar disorders. Recent reports have postulated that dysbindin gene would be a common genetic risk factor for both disorders. The objective of this study is to carry out a genetic association analysis of dysbindin gene with both schizophrenia and bipolar disorders in a Chilean admixed population. This paper will present the results found in the association study between the dysbindin gene and schizophrenia.
Methods: A case-control and schizophrenic family samples, according to DSM-IV criteria, were studied. Five hundred and sixty individuals were included in the analysis. Ten SNPs, described to be associated with dysbindin gene, were genotyped. In order to analyse the Chilean population structure, ten ancestry informative markers were analysed. Unphased program was used for the statistical analysis. Population stratification was studied using L-POP software. A structured association analysis was carried out with WHAP program.
Results: No single marker and haplotype associations were detected. The Chilean samples showed the same pattern of allele frequencies and LD described for ethnically diverse samples. The analysis of population structure found two ancestral populations. The structured association analysis of dysbindin gene, did not detect possible spurious findings in the Chilean case-control sample.
Conclusions: No association between dysbindin gene and schizophrenia was found. An appropriate interpretation of the results must consider all possible limitations, including false results, due to insufficient statistical power, allelic heterogeneity, and clinical heterogeneity of schizophrenia, among others.

P-09-017
Ethnic difference in pharmacogenetic result in major depression: The result of meta-analysis

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Objectives: Major depressive disorder is a severe and increasingly important disease for its high prevalence and association with serious consequences and substantial negative impact on social health. The genetically determined investigation of pharmacological responses would be much helpful to evaluate the best therapeutic tool for each patient. However, heterogeneity across the studies could also make it difficult for these candidates to be translated into treatment recommendations. Among others ethnicity could play an important role as confounder in pharmacogenetic result. Therefore we investigated pharmacogenetic effect of possible candidate variants such as 5-HTTLPR, HTR1A C-1019G, HTR2A, TPH1 and Gbeta3 in both Japanese and Italian population and also performed meta-analysis of these genes with consideration of assessment procedure, duration of treatment and type of antidepressant to detect the difference of genetic influence on antidepressant response between Asian and Caucasian.
Methods: Studies were included in the current meta-analysis if they evaluated the association between response/remission rate or intolerance rate to antidepressants treatments and genetic polymorphism in adult patients diagnosed with major depressive disorder and analyzed by RevMan analysis 1.01.
Results: Clearly different results between ethnicities were observed with HTR1A, HTR2A -1438A/G (102T/C) and TPH1 A218C independent from efficacy of type antidepressant possibly due to efficacy of other polymorphisms, different allele frequency, differential effect depending on specific symptoms, and cultural or social differences between Asians and Caucasians. As for 5-HTTLPR, inconsistent result could not be observed between ethnicities but SSRIs prescribed study and others.

Conclusions: Ethnicity was found to play an important role as a confounder in pharmacogenetic result and therefore we should pay attention to ethnicity when we deal with these variants as possible clinical predictor, however heterogeneity of protocol in each study also make it difficult for us to know actual impact of such variants.

P-09-018
5-HT1A gene polymorphisms contributed to antidepressant response in major depressive disorder

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Objectives: Variability in antidepressant response is due to genetic and environmental factors. Among genetic factors, the ones controlling for availability of the drug at the target site are interesting candidates. Rs6295C/G SNP in the 5-HT1A gene (HTR1A) has been found to affect the expression and function of HTR1A. In fact rs6295C/G is in strong linkage disequilibrium with other polymorphisms of HTR1A suggesting that those functional effects could be associated with polymorphisms other than or together with the synonymous rs6295C/G. In the present study we examined the possible association of a panel of markers in strong linkage disequilibrium of the HTR1A with SSRI/SNRI response.
Methods: 137 Japanese major depression subjects were evaluated at baseline and bi-weekly thereafter until week 6 using the HAM-D.
Results: We observed a significant association of better response to antidepressant in rs10042486C/C ($p<0.0001$), rs6295G/G ($p<0.0001$) and rs1364043T/T ($p=0.018$) genotype carriers (minor allele homozygotes), independently from clinical variables. Furthermore minor allele homozygous carriers in all these 3 SNPs were associated with treatment response by various assessment such as HAM-D score change over time ($p=0.001$), week 2 ($p<0.0001$), 4($p=0.007$), and 6($p=0.048$) as well as response rate ($p=0.0005$) and remission rate ($p=0.004$). We also pointed out the genotyping mis-definition of rs6295C/G in the previous four papers.
Conclusions: In conclusion, this is the first study that reports a significant association of antidepressant response with rs10042486C/T and rs1364043T/G variants of HTR1A and also with rs10042486-rs6295-rs1364043 combination. This finding adds an important information for the pathway of detecting the genetics of antidepressant response even if results must be verified on larger samples.

P-09-019
Escitalopram modulates the panic response to choleystokinin tetrapeptide in healthy men depending on 5-HTTLPR genotype

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Objectives: Selective serotonin re-uptake inhibitors, such as escitalopram, are currently the treatment of choice for patients with panic disorder. The panic response to intravenous cholecystokinin tetrapeptide (CCK-4), a potentially useful paradigm for volunteer translational studies, has so far not been investigated in healthy man after respective pre-treatment.
Methods: In a double-blind, placebo-controlled, randomized, within subject cross-over design thirty healthy young men, fifteen each with the long/long or short/short genotype for the serotonin transporter linked polymorphic region, were pre-treated with 10 mg/d of escitalopram orally for six weeks and then challenged with 50 µg of CCK-4. The primary outcome measure was the increase of Acute Panic Inventory ratings by cholecystokinin tetrapeptide.
Results: A significant treatment by genotype effect on the increases of Acute Panic Inventory ratings ermerged - panic induced by CCK-4 was significantly more pronounced in the short/short genotype subjects under escitalopram versus placebo pre-treatment. Contrary to our expectation, no inhibitory effect of escitalopram upon panic symptoms elicited by CCK-4 could be demonstrated in healthy men.
Conclusions: These findings do not support the potential usefulness of this panic model for proof-of-concept studies in healthy human volunteers. (Spported by Deusche Forschungsgemeinschaft - DFG, Ke 595/7-1)

P-09-020
The defence mechanism in biology

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P-27
Genetics II

P-27-002
Assessing the Pharmacokinetics of Venlafaxine Extended Release 75 mg and Desvenlafaxine 50 mg in CYP2D6 Extensive and Poor Metabolizers

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Objectives: The primary goal of this study was to evaluate the impact of CYP2D6 extensive metabolizer (EM) or poor metabolizer (PM) genotypes on the pharmacokinetics of single doses of venlafaxine extended release (ER) and desvenlafaxine (administered as desvenlafaxine succinate) in healthy adults.
Methods: In this open-label, crossover study, subjects received single doses of venlafaxine ER 75 mg and desvenlafaxine 50 mg in a randomized sequence. CYP2D6 genotyping was performed using internally developed and commercially available assays. The geometric means for area under the plasma concentration-versus-time curve (AUC) and peak plasma concentration (Cmax) were calculated. Comparisons between EMs and PMs on these outcomes were made using a 2-tailed Wilcoxon exact test.
Results: No carry-over effect was observed between treatment sequence groups. The AUC and Cmax of desvenlafaxine in subjects receiving desvenlafaxine 50 mg were comparable between EMs (n=7; 2455 ng*h/mL and 83 ng/mL) and PMs (n=7; 2702 ng*h/mL [P=0.38; EMs vs PMs] and 101 ng/mL [P=0.26; EMs vs PMs]). However, significant differences ($P<0.05$) in the AUC and Cmax of desvenlafaxine were observed between EMs (2534 ng*h/mL and 90 ng/mL) and PMs (465 ng*h/mL and 17 ng/mL) receiving venlafaxine ER 75 mg. In addition, the ratio of desvenlafaxine:venlafaxine on AUC and Cmax for subjects receiving venlafaxine ER 75 mg were significantly higher ($P\leq0.001$ for both comparisons) for EMs (7.5 and 4.0) than PMs (0.5 and 0.4).
Conclusions: These results indicate that the pharmacokinetics of desvenlafaxine 50 mg is not significantly impacted by CYP2D6 metabolic polymorphisms, whereas PMs receiving venlafaxine 75 mg had significantly lower desvenlafaxine plasma concentrations.

P-27-003
Association between Tryptophan hydroxylase-2 gene variations and the personality traits of novelty seeking and harm avoidance

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Objectives: Personality traits have been related to central serotonin system. Tryptophan hydroxylase is the rate-limiting enzyme in the serotonin biosynthesis responsible for the regulation of serotonin levels. A newly identified second isoform of the tryptophan hydroxylase gene (TPH2) was found to be solely expressed in the brain. We hypothesized that variation at the TPH2 gene and its 5' upstream region may be associated with personality traits.
Methods: Two hundred thirteen Korean healthy individuals (80 males and 133 females) participated in the present study. We analyzed three SNPs polymorphisms (rs11178997, rs4570625, rs7305115) of 5' upstream region and the TPH2 and four haplotypes (TGA, TGG, TTA, TTG) and their association with personality traits, as measured with the Temperament and Character Inventory (TCI).
Results: The rs4570625 and the rs7305115 was associated with Novelty Seeking ($F=6.9$, $p=0.001$; $F=12.5$, $p<0.001$) and Harm Avoidance ($F=7.0$, $p=0.001$; $F=10.3$, $p<0.001$) in the Korean healthy subjects. Moreover, haplotype showed an association with Novelty Seeking ($F=7.9$, $p<0.001$) and Harm Avoidance ($F=8.5$; $p<0.001$) respectively.

Conclusions: Our findings suggest that TPH2 SNPs and haplotypes may modulate personality traits in Korean healthy subjects, but further studies are required.

P-27-004
Possible association between Serotonin transporter Gene Polymorphism (5-HTTLPR) and SSRI (Sertraline) treatment response in post traumatic stress disorder

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Objectives: Objectives: This study examined the relationship between the serotonin transporter promoter polymorphism and the treatment response in PTSD patients receiving sertraline
Methods: A total of 87 outpatients diagnosed for PTSD using DSMIV criteria and treated with a fixed dose 100mg sertraline/day were genotyped for 5HTTLPR polymorphism. Weekly assessment was done by examining the change in the total score from base line to end point on CAPS2 which served as the primary outcome variable and rates of response for global improvement on CGI scale.
Results: Subjects homozygous for l allele showed a significant increase in response both statistically and clinically as compared to the patients with ss genotype. A 23.9% reduction in CAPS -2 scores in the subsets homozygous for the l allele compared to only 17.1% in those heterozygous or homozygous for s allele.. A significant increase in the number of CGI –I responders in the LL genotype on sertraline was noticed at week 1 and week 2 (p =0.01 at both time points). At week 1, 14.5% of the 29 subjects homozygous for the long allele showed a good response in relative to 1.2% of the 66 subjects heterozygous or homozygous for short allele. At week 2, 32.2% of the 29 subjects belonging to the l group were responders in comparison to 7.6% of the 66 subjects belonging to the s group. There was an increased percentage of CGI responders in the LL group at weeks 4, 8 and 12, although it did not reach statistical significance. On clinicians administered PTSD scale, CAPS- 2 assessment the change in the scores from baseline to endpoint was significantly greater for the l group compared to the s group
Conclusions: The study suggests that the genetic variation in the serotonin transporter gene may have an influence on the effectiveness of SSRI treatment in PTSD.

P-27-005
Polymorphisms of 5-HTR2A and 5-HTT genes in patients with neurotic, stress-related and somatoform disorders

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Objectives: To study T102 and A-1438G polymorphic variants of the 5-HTR2A gene and polymorphisms VNTR-17 and 5'-HTTLPR of the 5-HTT gene in patients with neurotic, stress-related and somatoform disorders.
Methods: Patients with dissociative (conversion) disorders (60 persons, ICD-10, F44), patients with adjustment disorders (43 patients, ICD-10, F43.2) and 85 mentally healthy persons were investigated. The examined people considered themselves ethnically Russians and were not in consanguinity. The distribution of 5-HTR2A and 5-HTT genotypes was compared in the groups of patients and controls.
Results: Significant differences in frequencies of A1A1 and A1A2 genotypes (T102C polymorphism) were found between patients with adjustment disorders and control (χ2=4,26; df=1; p=0,04). The distribution of genotypes AA and GG (A-1438G polymorphism) of gene 5-HTR2A in patients with dissociative disorders differs from that in controls at a trend level (χ2 =2,1; df=1; p=0,07). We have observed statistically significant differences between frequencies of genotypes AG and GG in patients with dissociative disorders and control (χ2 =3,3; df=1; p=0,03). For patients with dissociative disorders and adjustment disorders the trend toward a significance level (χ2=1,4; df=1; p=0,12) was observed for genotypes 10 10 and 10 9 (VNTR-17 polymorphism). The distribution of genotypes LL, LS and SS (5'-HTTLPR) in patients with dissociative disorders did not differ from distribution of these genotypes in patients with adjustment disorders.
Conclusions: The T102C polymorphism of the 5-HTR2A gene is associated with adjustment disorders, the A-1438G is associated with dissociative (conversion) disorders.

P-27-006
Familial depression associated with two novel T8310G and T8311A mtDNA mutations

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Objectives: Psychiatric problems, including bipolar affective disorder and schizophrenia, are common in mitochondrial diseases (MD) and frequently precede the diagnosis of mitochondrial dysfunction. However, they are rarely the only persistent manifestation of a MD and they are usually associated with other multisystemic involvement. Here, we describe a Hungarian family with novel heteroplasmic T8311A and T8312G mtDNA mutations, in which, depression recurred over several generations in the absence of other major signs of mitochondrial dysfunction.
Methods: In this family a 39 year-old woman (proband), her mother, brother and her two affected children have been investigated. Psychiatric and neurologic course as well as a detailed neuropsychologic profile of the proband has been depicted. Genetic analysis of the mitochondrial DNA has been carried out on these five patients and on 820 healthy controls.
Results: The proband has been having affective complaints in variable intensity for 20 years. Beside psychiatric symptoms, such as changeable, depressive mood, decreased initiation, anxiety, permanent symptoms of exhaustion, she has intention hand tremor, mild limb and truncal ataxia. Her mother has diabetes mellitus, hypertension and chronic ischemic heart disease and depressive symptoms. Her brother has major depression with suicidal intention. The 19 year-old son was a hyperactive child and now has anxiety and depression. The 13 year-old daughter has psychosomatic tendency with proneness to anxiety and mood lability brought about by stress. Neither the brother, nor the children have any coexisting disorders. MtDNA analysis revealed novel T8311A and T8312G mutations in all affected family members, which were absent in normal (n=820) controls.
Conclusions: In patients with positive family history of psychiatric problems, the possibility of MD should be kept in mind, even in absence of other canonical features of mitochondrial encephalomyopathies. In this family we assume that the T8311A and T8312G mutations segregating in all symptomatic family members are responsible for the psychiatric symptoms.

P-27-007
Stress associated changes in the nitric oxide signaling cascade in a genetic animal model of depression

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Objectives: Affective disorders are widely distributed illnesses with severe social and economic effects. Several studies suggest that stress is a key mediator in both the precipitation and progression of affective disorders. In addition, there is accumulating evidence that the neurotransmitter nitric oxide (NO) acts as a neuromodulator, influencing sub-cellular processes underlying cellular memory and neuronal toxicity.
Methods: The aim of the present study was to investigate the Flinders rat (FSL/FRL), a genetic animal model of depression, with regards to responses of the hippocampal nitrergic system following exposure to an escapable-stress/inescapable stress (ES-IS) stress paradigm.

Results: Hippocampal tissue from naïve FSL/FRL rats and those exposed to sub acute stress were studied with respect to hippocampal Nitric Oxide Synthase (NOS) activity and protein expression, as well as transcript expression of upstream regulatory proteins in the N-methyl-D-aspartate (NMDA)-NO signalling pathway, including NMDA-R1, nNOS, CAPON, PIN and PSD95. In ES-IS naïve animals, no differences in hippocampal nNOS activity and expression were evident in the FSL and FRL rats, although transcripts for NMDA-R1 and CAPON were increased in FSL rats. Stress increased nNOS activity and expression in FSL rats, together with an increase in nNOS and PSD95 transcripts, and a reduction in PIN. NMDA-R1 and CAPON compared to FRL rats.
Conclusions: Although FSL and FRL rats are similar with respect to hippocampal nNOS activity and protein expression under basal conditions, ES-IS induced pronounced changes in the NMDA-NO cascade in genetically vulnerable FSL rats, thereby affirming its importance as a vulnerability factor in the depressive phenotype of the FSL rat.

P-27-008
Association of polumorphisms of TPH2 gene with risk for bipolar disorder and suicidal behavior

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Objectives: Bipolar disorder (BD) is a severe psychiatric illness characterized by the occurrence of elevated mood alternating with depressive episodes. Lifetime prevalence for this disorder was estimated from 0.4 to 1.6% using DSM-IV criteria for BD. It is also known that bipolar disorder patients are at great risk for suicidal behavior. In these patients suicide rates average approximately 1% annually, about 60 times higher than the international population rate of 0.015% annually. Disturbance of the central serotonergic system has been associated with the pathophysiology of affective disorders and suicidal behavior. Tryptophan hydroxylase (TPH2) gene, which transcripts a rate limiting enzyme in the serotonin biosynthetic pathway, is considered an important candidate gene for psychiatric disorders. Thus, we addressed if there is an association between TPH2, BD and suicidal behavior..
Methods: Our sample consisted in 527 subjects (303 with a bipolar disorder diagnosis and 224 health controls) which were genotyped for eight TagSNPs covering the whole gene of human THP2. Statistical analyses were performed by UNPHASED version 3.0.12 and Haploview.
Results: One significant haplotype was observed only in controls suggesting the presence of a protective genetic factor on this haplotype; and two significant haplotypes observed in patients with BD suggested the presence of a genetic risk factor localized on these haplotypes. Two haplotypes differed significantly in their distribution between patients that experienced suicidal attempts when compared with a group without suicidal attempts.
Conclusions: The significant haplotypes observed in patients that had experienced suicidal attempts suggested the presence of a genetic risk factor localized on these haplotypes, however they also had not survived after permutation. Therefore, we demonstrated that the TPH2 gene variants might be involved in the predisposition to BD diagnosis and suicidal behavior.

P-27-009
Association study between Tryptophan Hydroxylase type II gene and late onset depression

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Objectives: Several studies suggested that early onset depression and late onset depression have many different clinical and genetic aspects. Some variants of the tryptophan hydroxylase type II gene (TPH2) have been associated with many psychiatric disorders in special with major depression and suicide attempts. The main objective of our study was to investigate the association between late onset depression and the TPH2 gene.
Methods: In the present study, one hundred and sixty-three individuals were included, being 84 patients with diagnosis of late-onset depression (69 women and 15 men, mean age of 79.2) and 79 individuals belonging to the control group (55 women and 24 men, mean age of 75.4). We genotyped eight tag-SNPs in the TPH2 gene to investigate a possible association of the gene TPH2 and late-onset depression.
Results: The presence of haplotype A-A (rs11179000 and rs7955501) confered 2.7 times higher-risk to develop late-life depression events. After permutation (1000) test for rs11179000 the adjusted p-value was 0.025 and chisq= 7.79. On the other hand, carriers of haplotype C-T-T (rs4565946, rs11179000 and rs7955501) seems to have a protector factor (OR= 2.0 nominal Padjusted = 0.01). When haplotype T-C-T-T (rs4448731, rs4565946, rs11179000 and rs7955501, respectively) showed a high protection factor (OR= 5.3 nominal P = 0.02, Padjusted = 0.003). In the sample of Brazilian population tested in this study, haplotype T-T-T (rs4565946, rs11179000 and rs7955501) and T-T-T-T (rs4448731, rs4565946, rs11179000 and rs7955501) seem to have an important protection effect for depression events (table 4). The presence of two positive markers prompted us to examine their interaction, leading to identification of a two locus (rs4565946 and rs11179000) associated with 63% increase in risk.
Conclusions: Our findings suggested that the TPH2 gene may be involved in the etiology of late onset depression.

P-27-010
Post partum depression: Association study with Val66Met polymorphism of BDNF gene

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Objectives: Postpartum depression, both because of its significant prevalence and repercussions in parturient and the infant, has been the target of an increasing number of scientific researches. Brain Derived Neurotrophic Factor, BDNF, has been largely studied and there is now a large body of evidence showing its possible association with mood disorders. The Val66Met polymorphism of BDNF gene is the most studied polymorphism of the BDNF. The main objective was to study the possible association between post-partum depression and this polymorphism.
Methods: We included 245 female individuals who gave birth in a private maternity hospital in the city of Belo Horizonte. They were assessed with a semi-structured to obtain epidemiologic and clinical data, a Edimbourg post-partum depression scale (EPDS) and a structured interview for major depression diagnosis (MINI-PLUS). All the interviews were held in the family context, where 5 ml of blood were collected for molecular analysis.
Results: No association was found between the Val66Met polymorphism and the postpartum depression diagnosis by MINI-PLUS or by the use of EPDS. We nevertheless found association between postpartum depression and the following factors: previous depression background, obstetric complications during pregnancy, stress during pregnancy, presence of depressive symptoms during pregnancy, anxiety symptoms during pregnancy, complications in the patient or in the infant in the postpartum, lack of support in the postpartum care, financial difficulties in the postpartum, stress due to child care in the postpartum, previous background of depressive or anxiety symptoms in the premenstrual period, depressive symptoms in the postpartum.
Conclusions: The identification of possible factors associated to the disease is important for the understanding of its pathophysiology, the establishment of strategies of prevention and precautious diagnosis. This is the first study, as far as we are acquainted, on the relation between this polymorphism and postpartum depression, and others are necessary to clear up a possible association.

P-27-011

Association analysis of 44 candidate genes with depressive and anxiety symptoms in post-partum women

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Objectives: The aim of this work was to further explore the genetic-vulnerability hypothesis of depression using post-partum depression (PPD) as a model since parturition may be considered an important risk factor for depression.

Methods: We analyzed the common variability present in 44 genes at candidate pathways putatively related to the etiology of PPD; such as genes involved in the HPA axis, the effects of stress in the prefrontal cortex, or the regulation of sex hormones. Five hundred and eight SNPs were genotyped in a multicentric cohort of 1804 women from Spain. Participants completed two scales at 2-3 days post-partum, 8 weeks, and 32 weeks, the Spanish version of the Edinburg Post-partum Depression Scale (EPDS) and the Spielberger State-Trait Anxiety Inventory (STAI). Those women who scored 9/10 in EPDS were evaluated for major depression using the Spanish version of the Diagnostic Interview for Genetics Studies (DIGS) adapted for PPD. Population substructure was discarded using 40 European informative markers. Association with major depression was assessed using likelihood ratio tests under a codominant genotype model. Association with scale scores was tested using linear mixed models for each SNP to take into account that individuals are measured repeatedly over time.

Results: Several SNPs at ESR1 and PRKCB are associated to PPD (P values < 0.01). Post-hoc analysis at the unphased haplotype level revealed an association with a combination of three SNPs at PRKCB, significant after multiple testing correction (global P = 0.0001596). In addition, two intronic SNPs, one at SLC6A4 and another at DDC, were significantly associated to STAI anxiety scores after multiple testing correction (P = 0.0000513 and 0.000097, respectively).

Conclusions: Thus, we confirmed the role of SLC6A4 in depression vulnerability after stressful events, and revealed new putative associations involving DDC and PRKCB. Therefore, these two genes deserve more specific studies to confirm these results.

P-27-012

Stimulated gene expression profiles as a blood marker in drug-naive major depressive disorder patients

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Objectives: Major Depressive Disorder (MDD) is a highly heritable disorder with high lifetime prevalence. At present, laboratory blood tests to support MDD diagnosis are unavailable; these blood tests could allow biological classification of patients for a better prediction of both disease course and treatment outcome. Here we classify MDD patients based on whole blood gene expression profiles.

Methods: We used a classifier approach on gene expression profiles in LPS-stimulated blood of drug-naive patients and controls selected from the Netherlands Study of Depression and Anxiety (NESDA) and determined expression of genes predicting disease state. 35 unmedicated, antidepressant-naïve MDD patients and 37 healthy controls, aged 20 to 63 years were enrolled. To overcome variation in basal blood gene expression levels and to reveal quiescent differences related to disease state, we applied a powerful ex vivo stimulus, i.e. incubation with lipopolysaccharide (LPS; 10 ng/ml blood). Gene expression was measured using whole genome microarrays, and results were validated using quantitative polymerase chain reaction (qPCR).

Results: We identified a molecular marker set (7 genes) for MDD in 42 subjects based on stimulated blood gene expression that was superior to that from basal blood. The MDD-marker was confirmed in an independent set of 25 subjects. In addition, using qPCR, subjects from both sets were classified according to disease state. All genes in the marker set are known to be expressed in both brain and whole blood.

Conclusions: We provide first evidence to classify drug-naïve MDD patients based on LPS stimulated whole blood gene expression profiles. To determine specificity for MDD our marker is currently being tested in anxiety disorder cases.

P-27-013

Personality traits and genetic polymorphisms of healthy Ugandans and Japanese

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Objectives: Personality traits and genetic polymorphisms related to the neurotransmitter system were investigated in unrelated healthy Ugandan (n=99) and Japanese nurse students (n=105).

Methods: Personality traits were evaluated using the Temperament and Character Inventory (TCI) v9 English version (Cloninger, et al., 1994) or its Japanese version (Kijima, et al., 1996). Genetic polymorphisms in the serotonin 1A receptor (5-HT1AR –1019C/G), serotonin 2A receptor (5-HT2AR –1438G/A) and a microsomal enzyme cytochrome P450 2C19 (CYP2C19 *2, *3 and *17) were investigated. The mean score of the seven subscales of TCI (Harm Avoidance, Novelty Seeking, Reward dependence, Persistence, Self-directedness, Cooperativeness and Self-transcendence) were compared between the populations or among the genotype groups.

Results: Positive findings were 1) Harm avoidance was considerably higher in Japanese than in Ugandans, 2) Self-transcendence was substantially lower in Japanese than in Ugandans, 3) Reward dependence was significantly higher and persistence and self-directedness is lower in Japanese than in Ugandans, 4) Ugandans with the A/A genotype of 5-HT2AR showed higher harm avoidance score than the A/G and G/G genotypes, 5) Ugandans with enhanced activity of CYP2C19 enzyme, namely, subjects with the CYP2C19*17/*17 or *1/*17 genotype, showed higher novelty seeking score than those with other genotypes, 6) Japanese with the G/A genotype of 5-HT2AR showed higher self-directedness score than those with the A/A and G/G genotypes.

Conclusions: These results might indicate a marked difference in personality traits between Ugandans and Japanese, partly due to the difference in genetic background. To reveal the underlying mechanism furthermore, other genes as well as psychosocial factors should be investigated.

P-27-014

Diras2 is associated with adult attention-deficit / hyperactivity disorder

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Objectives: Attention-deficit/hyperactivity disorder (ADHD) is a clinically heterogeneous childhood behavioral neurodevelopmental disorder which is highly persistent into adulthood. Twin and family studies showed heritability up to 80%. Linkage analyses and genome-wide association studies (GWAS) identified several susceptibility loci for this genetically complex disorder. Further fine-mapping of candidate regions however is needed to detect the underlying genes contributing to the genetic risk towards ADHD. In previous studies, our group could delineate the 9q22 region by both linkage and GWAS as a candidate locus for ADHD (Lesch et al., 2008; Zhou et al., 2008). This region harbours the DIRAS2 (MIM: 607863) gene, a Ras GTPase expressed in the basal ganglia and the cerebellum. The function of the gene product is still unknown but might include the regulation of cell morphogenesis.

Methods: We thus conducted a case-control association study using the Sequenom iPLEX® system in 624 patients suffering from adult ADHD and 424 controls.

Results: Six SNPs located in or near DIRAS2 (from 14 tested) were associated with ADHD, with nominal p-values ranging from p= 0.0098 to p= 0.04. Furthermore, within each of the two haploblocks there was one associated haplotype.

Conclusions: These results indicate that DIRAS2 may play a role in the pathomechanisms of ADHD. Replication studies, re-sequencing of the gene as well as functional studies are now required to further explore the role of DIRAS2 in ADHD.

P-27-015
Serotonin transporter and BDNF genes variants in borderline personality disorder

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Objectives: Borderline personality disorder (BPD) is a psychiatric condition characterized by a pervasive pattern of instability in the regulation of emotions, interpersonal relationships, self-image and impulse control. BPD affects 1-2% of the population and it is associated with high levels of suffering and impairment and a significant increase in the suicide risk. Genetic factors participate in the risk of developing BPD as twin studies show a heritability of 42%. Genetic variants involved in this disorder are not currently known, but candidates for other psychiatric disorders, such as 5HTTLPR polymorphism of the serotonin transporter gene and Val66Met of the BDNF gene are of interest. The objective of this work is to examine the allelic frequencies of these two polymorphisms in a sample of BPD patients and to compare them with two different samples: one made up of control individuals where Axis I and Axis II pathologies have been ruled out and another one extracted from general population.
Methods: Sample sizes were: BPD patients n=90, control individuals n=38, general population n=186. DNA obtained from blood samples was used to genotype the individuals through PCR and RFLP when needed.
Results: Allelic frequencies of the whole sample were: for BDNF, A=0.26; G=0.74. For 5HTTLPR, L=0.42; S=0.58. We identified no significant differences between allelic frequencies of the three groups evaluated. No interaction between these two markers was detected.
Conclusions: Further studies should be carried out that consider larger samples, more variants, and more accurate endophenotypes of the disorder.

P-27-016
Effect of the alpha 2A-adrenergic receptor gene polymorphisms on antidepressant response in major depressive disorder

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Objectives: The alpha 2A-adrenergic receptor (ADRA2A) plays a central role in the regulation of systemic sympathetic activity. Recently, the functional defect of ADRA2A has been implicated as a cause of depression, attention deficit hyperactivity disorder, and Tourette syndrome. In this study, the effect of genetic variants of the ADRA2A gene on the response to selective serotonin reuptake inhibitors (SSRIs)/serotonin norepinephrine reuptake inhibitors (SNRIs) was examined in depressed patients.
Methods: Ninety-three Japanese depressed patients were recruited in the present study, assigned randomly to paroxetine or milnacipran, and assessed by HAM-D scoring every two weeks before and after drug administration. The ADRA2A C-1297G polymorphism was considered in the association analysis with the efficacy of antidepressants.
Results: There were significant differences in the HAM-D score change over time (P= 0.019) among C/C, C/G, and G/G of the ADRA2A C-1297G polymorphism in the total subjects. The C allele carriers of the ADRA2A C-1297G polymorphism showed a significantly better improvement than G/G subjects at week 2, 4, and over time (P= 0.037) in the milnacipran group.
Conclusions: Our findings suggest that ADRA2A plays an important role in depression therapy. The level of ADRA2A expression could be associated with the efficacy of SSRIs/SNRIs, especially milnacipran, although the functional change brought about by C-1297G polymorphism has not yet been fully identified in vivo and in vitro. The ADRA2A polymorphism could be a reasonable candidate to predict the response to milnacipran. Our results are still preliminary and a large sample size will be required to confirm our findings.

P-27-017
De novo Alu-mediated mutations of endoplasmic reticulum stress-related genes in schizophrenia

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Objectives: Human retroposon Alu induces various kinds of constitutional mutations such as insertion, deletion, non-allelic homologous recombination (NAHR), and copy-number variants (CNVs), resulting in human diseases and genomic instability. Genomic instability is one of the biological characteristic observed in schizophrenia. We hypothesized that excessive mutation mediated by Alu might be affecting the gene responsible for schizophrenia. In previous reports, we performed the combinatorial experiment with Alu-specific PCR and array-CGH assay to detect Alu-mediated mutations in schizophrenia. In analysis of case-parent trios, we detected the fluctuations of endoplasmic reticulum stress-related genes in the patients. To further investigate the effects of Alu in these genes, we have performed another combinatorial experiment.
Methods: DNA samples were obtained from eight pairs of case-parent trios for schizophrenia. The Alu-specific PCR and TaqMan assay were performed to detect the Alu-mediated mutations in endoplasmic reticulum stress-related genes. This study was done under the approval of the Ethical Committee for Genetic Research, Teikyo University School of Medicine.
Results: By comparing the results of the parents and the children, we have identified fluctuations of endoplasmic reticulum stress-related genes in five patients.
Conclusions: These results suggest that Alu-mediated mutations of endoplasmic reticulum stress-related genes might be the risk factor for schizophrenia. Malfunction of endoplasmic reticulum stress response is also reported to be involved in the pathogenesis of neurodegenerative disorders and bipolar disorder. Analysis of Alu might help us identify the risk genes and elucidate the pathogenesis of schizophrenia.

P-27-018
Family association study of candidate genes in schizophrenia

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Objectives: The aim of the study was to estimate the transmission of eight candidate genes alleles (according to dopaminergic and serotonergic hypothesis of schizophrenia) by parents to their children with schizophrenia. The genes under investigation were the following: DRD1 (polymorphism -48A/G), DRD2 (polymorphism -141C ins/del), DRD3 (polymorphism Ser9Gly), DRD4 (polymorphism -521C/T), DAT (polymorphism VNTR w 3'-UTR), COMT (polymorphism Val108(158)Met), 5HTR2A (polymorphism T102C), SERT (polymorphism 5-HTTLPR).
Methods: There were 116 families in the group under investigation (sick person and his/her both parents). The patients and their parents were examined by two psychiatrists using SCID (Structured Clinical Interview for DSM-IV Axis I Disorders). No mental disturbances were found with all the patients' parents. All the persons included in the study were of the Polish origin. The statistical analysis of the frequency of tansmission of alleles was carried out by TDT (Transmission Disequilibrium Test) method.
Results: According to the results obtained no connection between analysed polymorphism of genes: DRD2 (-141C ins/del), DRD3 (Ser9Gly), DRD4 (-521C/T), DAT (VNTR), COMT (Val108(158)Met), 5HTR2A (T102C), SERT (5-HTTLPR) and schizophrenia was stated. In case of polymorphism -48A/G of gene DRD1 a trend was observed towards a more frequent transmission of allel A of gene DRD1 by parents to their children with schizophrenia (p=0,091).
Conclusions: his trend should be interpreted very carefully. Previous reports on the role of the above metioned polymorphism in the etiopathogenesis of schizophrenia have been relatively few and mainly negative. Thus it seems advisable to carry out further examinations of the role of this polymorphism in schizophrenia by means of TDT method and classical association method.

P-27-019
Determination of emotional endophenotypes: A validation of the Affective Neuroscience Personality Scale

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Objectives: The contribution of the identification of emotional endophenotypes in mental illnesses could be twofold: 1) to better understand their underlying mechanisms and reduce the gap between genes and behaviour; 2) to increase the effectiveness of therapeutic practice, both psychological and somatic, by setting-up tailored therapeutic approaches focusing on the impaired socio-affective skills (Gottesman & Gould 2003). Within this framework, Panksepp and collaborators have used the emerging knowledge from affective neuroscience and the characterization of six basic cerebral emotional systems - which include distinct substrates for seeking, anger, fear, caring, sadness, and playfulness -, to guide the construction of a self-report questionnaire assessing temperamental variability related to the activity in these systems: the Affective Neuroscience Personality Scale (ANPS) (Davis et al. 2003; Panksepp 2006).
Methods: To estimate the ANPS's psychometric properties, data from 830 normal young adults (studying or working in various areas; mean age=20.6±2.1; 55.1% of women) and individuals with a current psychiatric disorder (30 eating disorders, 20 personality disorders, 20 autism spectrum disorder) were collected. The participants also completed self-report questionnaires measuring depression (BDI), anxiety (State-Trait STAI), positive & negative emotionality (EPN31), anger (MAI), emotional awareness (BVAQ), emotional intelligence (TTSM), interpersonal reactivity (IRI, EQ) and social desirability (SD).
Results: The ANPS showed adequate internal consistency (cronbach's alphas and intercorrelations) and factorial structure, and a good convergent and discrimant validity. The expected gender differences were confirmed, except for anger. The clinical groups obtained greater negative emotion scores (fear, anger, sadness) and lower positive emotion scores (seek, care, play) than the healthy group. In addition, preliminary results from an ongoing study linking ANPS scores and emotional stimuli processing (facial and body expressions of emotion) further support the ANPS convergent validity.
Conclusions: In sum, used in conjunction with emotion processing paradigms, the ANPS could be particularly informative for understanding the emotional underpinnings of psychiatric disorders.

P-27-020
S100B as a marker of inflammation in chidren and adolescents with first episode psychosis

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Objectives: Knowledge of how inflammation affects the development of schizophrenia remains limited but several studies have identified inflammatory markers in all stages of disease: acute psychosis, chronic schizophrenia and residual schizophrenia. No studies have evaluated a possible link between inflammation and psychosis in children or adolescents. The purpose of this study is to assess inflammatory markers in a group of psychotic children and adolescents age 12- 18 years old and correlate these findings with clinical variables.
Methods: 30 patients and 30 healthy controls have been included in the study. Psychotic patients were diagnosed by a consensus of 2 child psychiatrist independently. Diagnosis included Psychosis NOS, Schizophrenia, schizophreniform disorder, and schizoaffective disorder following DSM – IV TR criteria. To participate in the study, a patient must have one of 3 core psychotic symptoms (hallucinations, delusions or peculiar fantasies) at admission. To measure the severity of symptoms the standardized SAPS for positive symptoms, the SANS for negative symptoms, and the Brief Psychiatric Rating Scale–Children version has been used. The CGI-Schizophrenia was also used to assess improvement
Results: In children experiencing and diagnosed with a psychotic episode, S100Beta levels were significantly elevated $p < 0.05$ compared to normal controls. Levels of IL1 B and IL 6 were correlated with severity of the symptoms in psychotic children.
Conclusions: We provide for the first time a link between psychiatric illness, sterile inflammation and BBB disruption. The latter was demonstrated by serum analysis for S100Beta, a peripheral marker of BBB function. It therefore appears that regardless of the triggers involved these cytokines and BBB failure are common features of several CNS disorders, and now there is a link with psychosis. Abnormalities of neurons and synapses have been the main focus of attention. Our results strongly support the "inflammatory theory" of schizophrenia formulated over a 100 years ago and recently reviewed

P-27-021
Functional polymorphism of matrix metalloproteinase-9 gene in major psychoses

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Objectives: Matrix metalloproteinase–9 (MMP-9) plays a role in many pathological conditions. MMP-9 gene was mapped to chromosome region 20q11.2-q13.1 and the -1562C/T polymorphism of this gene was shown to exert a functional effect on gene transcription. The studies of this polymorphism in cancer and heart disease showed, that carriers of T allele have an increased risk or more severe progression for some types of cancer, and increased severity of coronary arteriosclerosis. Recently, MMP-9 has been implicated in various aspects of brain functions (e.g. neuroplasticity and epileptogenesis) and thus, we hypothesized that MMP-9 gene may be associated with schizophrenia and/or bipolar mood disorder.
Methods: The study was performed in 442 patients with schizophrenia, 416 patients with bipolar mood disorder, and in 558 healthy control persons. A functional -1562C/T polymorphism of MMP-9 gene was genotyped in all subjects.
Results: Significant preponderance of C/C genotype and C allele of 1562C/T polymorphism of MMP-9 gene, in schizophrenia compared to healthy control subjects was found. On the other hand, patients with bipolar mood disorder had significant preponderance of T allele vs C allele of 1562C/T polymorphism of MMP-9 gene, compared to healthy control subjects.
Conclusions: The results may provide the evidence for an involvement of MMP-9 gene in the pathogenesis of schizophrenia and bipolar mood disorder. They may also contribute to explaining genetic connection between major psychoses and cancer and cardiovascular illness (decreased severity of these illnesses in schizophrenia and increased in bipolar illness). We hypothesize that the MMP-9 gene may be a common susceptibility gene to major psychoses with different allelic variants occurring in schizophrenia and bipolar illness.

P-36
Genetics III

P-36-001
Serotonin transporter promoter gene polymorphism and response to antidepressant treatment

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Objectives: This study investigated the relationship between serotonin transporter linked polymorphic region (5-HTTLPR) and different response to antidepressant treatment in clinical practice
Methods: Ninety Caucasian patients with Major Depresive Disorder, regardless comorbidity or associated medications, were evaluated for response to antidepressant treatment,in a naturalistic study. The severity and improvement of depression were assessed with the Beck scale. The genotypes of 5-HTTLPR in the patients were determined using PCR.

Results: During the treatment of antidepressants, a favorable response to treatment was also significantly more frequent in carriers of the l/l genotype than in those with the s/s or l/s genotype. The response in carriers of the l/l alleles were (44,4%) to serotonin-specific reuptake inhibitors (SSRIs) and (75%) to Serotonin-norepinephrine reuptake inhibitors (SNRIs). In patients carriyng the short alele (s/s and l/s) the antidepressant response was lower (31.9%) with SSRIs, and rise to (69.9%) with SNRIs antidepressants.
Conclusions: These findings indicates that patients with depressive disorder homocygote to ll genotype may exhibit a better response to SSRIs and SNRIs antidepressants, and those possessing the 5-HTTLPR short allele, exhibit a minor global response to antidepressant and lower in SSRIs treatment than SNRIs treatment

P-36-002
Electroconvulsive seizures regulate gene expression of neurotrophic, angiogenic and antidepressive signaling pathways

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Objectives: To test the hypothesis that ECS induced regulation of angiogenic, neurotrophic and antidepressive factors in brain we selected 8 genes (Creb1, Fgf2, Htr2c, Maoa, Nrn1, Ptgs2, S100b, Vegfa) to have their expression analyzed on an ECS model (single versus repeated treatments). Previous studies have shown that ECT affects other brain regions than hippocampus; so we decided to investigate hippocampus, cerebellum and cortex from animals that received acute and chronic seizures.
Methods: In the accomplishment of the study two ECS treatments had been considered: acute (one shock) and chronic (8 shocks over the period of 16 days). Animals were killed for collection of cerebellum, cortex, and hippocampus after each treatment at 0h, 48h, 7, 30, 60 and 90 days after last seizure. The expression of selected genes was determined by real-time PCR.
Results: In the chronic treatment, the modulation of the expression is more accented. Also, the effect of the ECT seems to be more evident in hippocampus than cortex or cerebellum. Arriving to reach increases in the gene expression of the order of 700 times more for the Ptgs2 and 100 times for the Nrn1 in hippocampus and could be drawn out for up to 90 days.
Conclusions: We evaluated the relative efficacy of ECS treatment in inducing gene expression changes in specific brain region. Each treatment (ECS acute and chronic) affected the analyzed brain areas differently. ECS affected the largest number of evaluated transcripts in the hippocampus and the lowest number of transcripts in the cerebellum, with the following order: hippocampus > cortex > cerebellum. Specifically, chronic ECS appear more effective in producing transcriptional changes in the hippocampus compared to acute ECS. We suggest that Ptgs2, Htr2c and Nrn1 genes could have an important role on molecular mechanisms underlying ECT.

P-36-003
The impact of CYP2D6 and CYP2C19 on antidepressant therapy for major depression

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Objectives: The enzymes of cytochrome P450 (CYP), mainly CYP2D6 and CYP2C19 are known for metabolizing approximately half of the 200 more often prescript medications. The CYP2D6 enzyme by itself is responsible for the metabolism of approximately 25% of these medications, especially antidepressants (SSRIs e TCAs). This study aimed to explore the influence of variation in CYP2D6 and CYP2C19 genes on treatment response to antidepressants in a Brazilian sample of patients with Major Depression.
Methods: Up to now 73 samples of patients with Major Depression and 90 control samples were genotyped for the following alleles: CYP2D6*1, *2, *3, *4, *6, *9, *10, *15, *17, *29, *34, *35, *40, *41, and CYP2C19*1, *2, *3, and *17. Genotyping was performed by real-time PCR allelic discrimination. The CYP2D6*5 allele and the number of copies of the gene CYP2D6 were identified by Real-Time PCR. The Hamilton scale of evaluation for depression (HAM-D) was used to determine the clinic course of response to the treatment and the adverse affects were also registered.
Results: As have been described in other studies in different populations alleles CYP2D6*1 and CYP2D6*2 were the most frequent in our sample (42,8 e 24.31%, respectively), followed by the alleles CYP2D6*4 (11,64%) and CYP2D6*41 (5,82%). For the CYP2C19 gene, our the allele CYP2C19*1 is the most frequent (60%), followed by the allele CYP2C19*17 (24%) and the CYP2C19*2 (16%). To our knowledge the CYP2C19*17 allele was evaluated in a Brazilian population for the first time.
Conclusions: We have found positive correlations genotype-phenotype although possible jeopardized because there was heterogeneity among medications. Future research directions are suggested. The future of 'personalized prescription' in psychiatry requires consideration of pharmacogenomic testing and environmental and personal variables that influence pharmacokinetic and pharmacodynamic drug response for each individual drug used by each patient.

P-36-004
The C (-1019) G serotonin 1A polymorphism is associated with comorbid anxiety and depression

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Objectives: Serotonin 1A receptors are key regulators of the serotonin activity and their dys-regulation might be involved in the pathology of major depression (MD) and generalized anxiety disorder (GAD). We aim to clarify the putative role of the C(-1019)G serotonin 1A polymorphism in the aetiology of comorbid MD with GAD, and of MD or GAD adjusting by one another
Methods: DSM-IV MD and GAD diagnoses were ascertained using the Composite International Diagnostic Interview and the Primary Care Evaluation of Mental Disorders Patient Health Questionary, respectively. 1059 sujects who took part in the PREDICT-GENE study (Cervilla et.al 2006) were included for molecular analyses using Sequenom platform. SPSS package was used to perform univariant and multivariant analyses.
Results: Carrying the G allele of the C(-1019)G polymorphism was associated with MD (OR = 1.67, 95%CI = 1.14 - 2.44, p = 0.008) but this association became non significant after adjusting by presence of GAD (OR = 1.43, 95%CI = 0.958-2.141, p = 0.080). Similarly, when exploring the association with GAD (Crude: OR = 2.54, 95%CI = 1.28-4.861, p = 0.003), adjusting by MD rendered results no longer significant (OR =1.97, 95%CI = 0.991-3.910, p =0.05). However, we found a solid significant association between carrying the G allele and comorbid MD and GAD (OR =3.41, 95% CI = 1.444-8.048, p = 0.005) which remained robust and statistically significant after adjusting by sex, age and family history of psychological problems (OR =2.82, 95%CI = 1.177-6.772, p = 0.020).
Conclusions: The C(-1019)G serotonin 1A polymorphism confers a risk for comorbid MD and GAD but not for either of these disorders alone after adjusting by presence of one another.

P-36-005
Variation at the 5-HT2A receptor gene is associated to panic syndrome

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Objectives: Dysfunction of the serotonin system has been hypothesized to play an important role in panic syndrome (PS). Genetic variation at the 5-HT2A receptor (5HTR2A) has been extensively studied in relation to depression, suicide or PS without conclusive results. We aimed to explore the potential association between 5-HT2A gene variants and PS.
Methods: Our sample consisted of 890 primary care attendees (72 cases and 818 controls) who took part in the PREDICT-Gene study (Cervilla et.al. 2006). Seven polymorphisms (rs6311, rs6313, rs6314, rs12863574, rs10507544, rs2770296, rs985933) spanning the 5-HT2A receptor gene were included in the present analysis. Those markers were selected according to functionality, heterozygosity and locus position. Molecular analyses were performed using Sequenom platform. We calculated odds ratios for panic syndrome. Haplotype frequencies were estimated with the Unphased program.
Results: Independent analyses between each 5-HT2A polymorphism and panic syndrome did not show any significant association, although a trend for an association between PS and variation at the rs6314 locus was found. Thus, homozygous for the C allele tend to be more frequent in patients than in controls (OR= 1.51 95%CI = 0.93 - 2.48, X2 = 3.01 p= 0.08). Haplotype analysis revealed a risk rs6314-rs12862574 haplotype for panic syndrome in the 5-HT2A gene. Particularly, the C–A allele combination in these loci was found to be significantly more frequent in patients with panic syndrome than in controls (OR = 1.57, 95%CI = 1.10 - 2.26, X2 =6.63 p = 0.010).
Conclusions: Our results suggest that genetic variability at the 5-HT2A gene may constitute a genetic substrate of vulnerability for panic syndrome.

P-36-006
Analysis of dopamine receptor D4 gene and serotonin receptor 2C gene polymorphisms in patients with alcoholism and opioid addiction from Russia

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Objectives: Family, twin and adoption studies have provided evidence of genetic component (40-60%) in the origin of addictive disorders. It is also known that both serotoninergic and dopaminergic systems dysfunction is associated with addictive disorders. We designed a classical case–control association study for two polymorphisms in genes encoding proteins of dopaminergic and serotoninergic systems; namely – 120bp VNTR polymorphism in the 5'-regulatory region of the dopamine receptor D4 gene (DRD4) and Cys23Ser polymorphism in the serotonin receptor 2C gene (HTR2C). Population stratification and ancestry differences within populations may compromise the success of association studies. Therefore analysis of genes in homogeneous ethnic groups is of great importance.
Methods: 303 men with diagnosis of alcoholism (112 Russians, 91 Tatars, 100 Bashkirs), 168 men with diagnosis of opioid addiction (94 Russians, 74 Tatars) and matched control groups (132 Russians, 112 Tatars, 100 Bashkirs) were typed for the above-mentioned gene variants using PCR-RFLP technique.
Results: Analysis of the 120-bp VNTR polymorphism in the DRD4 gene showed significant association of DRD4*S/*S genotype with alcoholism (p<0.05, OR=2.89) and opioid addiction (p<0.05, OR=2.28) in Tatar population. In Russian population the frequency of individuals carrying the DRD4*S allele was significantly higher in the group of alcoholics compared to the healthy controls (p<0.05, OR=2.95). Analysis of the Cys23Ser polymorphism in the HTR2Δgene revealed in Russians a significantly increased prevalence of the HTR2Δ*23Ser allele in patients with opioid addiction compared to the control individuals (p<0.05, OR = 2.12). This allele also was found to be associated with alcoholism (p<0.05, OR=1.79) in Russian population.
Conclusions: Our findings are in line with a number of recent studies questioning the association between addictive disorders and polymorphisms in DRD4 and HTR2C genes. Possible implications of these findings are discussed.

P-36-007
Gene expression profiles in human peripheral blood mononuclear cells induced by sleep deprivation

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Objectives: Although the function of sleep remains elusive, prolonged sleep deprivation is stressful and has been associated with adverse consequences the ability to concentrate, alter the autonomic nerves system and the immune responses. A number of studies have now shown that sleep deprivation results in significant increases in circulating levels of inflammatory markers such as interleukin-6, tumor necrosis factor-alpha, and C-reactive protein.
Methods: We obtained human blood from the 8 healthy adults (aged 25-35) after 24 hours sleep deprivation. Using cDNA microarray (Agilent's Human whole genome 4X 44K), we have studied the gene expression profiles produced in human peripheral blood mononuclear cells (PBMCs).
Results: As a result, five genes were up-regulated and sixteen genes were down-regulated in 2-fold PBMCs of every 8 subjects. Of the five up-regulated genes, FCGR3A (Fc fragment of IgG, low affinity IIIa, receptor (CD16a)), FCGR3B (Fc fragment of IgG, low affinity IIIa, receptor (CD16b)), IL8RBP (interleukin 8 receptor, beta pseudogene) were identified and of the sixteen down-regulated genes, THBS1 (thrombospondin 1), PDE40 (phosphodiesterase 4D), PLA1A (phospholipase A1 member A), EGR3 (early growth response 3), ATF3 (activating transcription factor 3) were identified. We identified many of these genes are associated with the natural killer cell mediated cytotoxicity pathway by DAVID Bioinformatics Resources Functional Annotation.
Conclusions: In summary, identification of these genes by cDNA microarray analysis in response to sleep deprivation may provide a foundation for further studies of immune and biological function of sleep.

P-36-008
Neuropeptide Y and schizophrenia: Genetic association study in Korean population

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Objectives: Previous study showed that schizophrenia (SPR) have been changed neuropeptide Y (NPY) gene expression in the frontal and prefrontal cortex (FC/PFC). Recently, several studies with the single nucleotide polymorphism (SNP) of NPY were reported. We suggested that coding SNP (cSNPs) of NPY for a case-control study between NPY and schizophrenia in Korean population.
Methods: We examined to coding SNP (cSNPs) of NPY for a case-control study between NPY and SPR in Korean population. We examined 274 Korean patients with schizophrenia (43.2 ± 10.8 years, mean age ± SD) and 291 control subjects (39.6 ± 8.8). Each patient was diagnosed by a Diagnostic and Statistical Manual of Mental Disorders, Fourth Edition (DSM-IV). Written informed consent was obtained from each subject. The study was approved by the Ethics Committee of the Medical Research Institute, Kyung Hee University Medical Center. In the NPY gene region, 2 SNPs [rs5573(exon2) and rs5574(exon3)] were selected using human SNP websites (http://www.ensembl.org; www.ncbi.nlm.nih.gov/SNP).
Results: The genotypic distributions of 2 SNPs were consistent with HWE (P > 0.05). We could not find significant association between SPR and control subjects. We calculated LD-block by using the Gabriel method then 1 block was revealed. However, we could not found significant association findings.
Conclusions: In conclusion, two SNPs (rs5573 and rs5574) of NPY maybe not involve in the development of schizophrenia in Korean population.

P-36-009
Relations between 5-HTTLPR polymorphism, aggression, impulsivity and neuroticism in a Chilean borderline personality disorder sample (Proyecto FONDECYT 1071045).

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Objectives: Actually has a strong evidence for relating low serotonergic function to impulsiveness, depression and some aspects of personality. The borderline personality disorder (BPD) is characterized by low regulation of emotions and disruptive behaviors, core symptoms that can be understood by low serotonergic function. From this view, a portion of the clinical problems of BPD can be influenced by serotonergic genetic polymorphism. The aim of this study is to evaluate the association between impulsivity, aggression and neuroticism in BPD.
Methods: We examine 49 Chilean subjects, representative of Chilean admixture population (Amerindian people and Caucasian settlers). The subjects met the DSM-IV diagnostic criteria for BPD, and did not meet criteria for axis I diagnoses. Personality were assessed with the Eysenck Personality Questionnaire Revised (EPQ-R). The impulsivity was assessed with the BIS11, that differentiates 3 forms of impulsive behaviors (cognitive, motor, not planned). The aggressive behaviors were assessed with OAS (Overt Aggression Scale). We studied 5-HTTLPR polymorphism, and TPH1, 5HT1B, 5HT2C receptors polymorphism. The statistics analysis was performed with STATA9.
Results: All the patients showed high scores in BIS11 (mean 63.65) and in OAS (mean 38.08).The S-allele carriers, LS and SS genotype showed significant higher scores in BIS11 than LL genotype ($p<0.01$). The difference between S-allele carriers and LL in BIS11 was mostly determined by the subtype motor impulsivity. There were not differences between alleles in OAS scores. The S-allele carriers group showed higher scores in neuroticism dimensions than LL allele genotype ($p<0.01$). In a linear regression, the higher neuroticism is in strong relation with motor impulsivity. No significant association was observed between the variables and the other studied polymorphism.
Conclusions: The conclusions are: 1) the motor impulsivity in BPD is related with 5-HTTLPR polymorphism, 2) the personality dimension Neuroticism is a good predictor of motor impulsivity in this borderline sample.

P-36-010
A Microarray analysis of gene expression following Lithium-induced Euthymia in Bipolar disorder type 1 patients and resultant synaptic plasticity

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Objectives: To investigate gene expression pre- and post- Lithium treatment in Bipolar disorder type1.
Methods: Ten patients were recruited from the acute Psychiatry ward of the Johannesburg Hospital in South Africa. Bloods were taken pre- and post-Lithium treatment. RNA was extracted from the lymphocytes in the peripheral blood. The preparation of probes, hybridization and scanning of images and analysis of human microarrays were performed using the Research Genetics Microarray Protocol. Gene expression changes between the manic and euthymic states were calculated as ratios between colour images.
Results: The identified genes overexpressed 100 times after Lithium treatment were Integrin Linked Kinase, Splicing Factor3a120,Metal regulatory factor 1, GTP-GDP dissociation factor. Other genes overexpressed 50 times after Lithium treatment were Fatty acid amide hydrolase, Cytoplasmic Antiproteinase, Cartilage specific homeodomain protein, Microsomal glutathion S-Transferase and Gamma Interferon Inducible Protein 30.
Conclusions: After a preliminary analysis of the data, it was decided that genes such as Integrin Linked Kinase were paving the way for a further exploration of the wnt pathway. The wnt/Beta-catenin pathway directs neuronal differentiation and migration of neural precursor cells, and this would indicate that Bipolar disorder is a neuronal migration disorder.

P-36-011
RGS4 in pathophysiology of schizophrenia

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Objectives: Genetic mechanisms of schizophrenia are studied largely with the aim to find genes mutations associated with this illness. There is evidence to suggest an association between genetic variation at the regulator of G-protein signalling 4 (RGS4) and schizophrenia. Studies related to the association between schizophrenia and RGS4 however suffered from the lack of consistency, which is often a problem with the majority of other implicated candidate genes. In this study, we have silenced expression of RGS4 in vitro with the goal to assess the influence of RGS4 gene alteration on the expression of other genes.
Methods: As a model system human neuroblastoma cell line BE (2)-C was used. To silence human RGS4 we have designed 4 siRNAs covering different parts of the RGS4 coding sequence. Retroviral vector pSilencer 5.1-H1 Retro was used to ensure stable RGS4 silencing. We created stable cell lines expressing different amounts of siRNA against human RGS4 and the expression was assessed by quantitative Real-Time PCR.
Results: The established stable cell lines show different levels of RGS4 gene expression. RGS4 expression levels reached from 3.1% to 404.1% of the RGS4 expression in the parental cell line. The aberrant overexpression of genes caused by siRNA has been described as a unique, nevertheless existing phenomenon caused by the interaction of specific siRNA and its target sequence. Wide interval of RGS4 expression levels is a useful tool to study effect of different amount of RGS4 in the analysed cell line. As the next step, microarray expression profiling will be employed to study the effect of differential RGS4 expression levels in the model cell line BE (2)-C.
Conclusions: Phenotypical and molecular differences resulting from the down-regulation of RGS4 gene may be useful to better understand the role of this gene in the pathophysiology of schizophrenia.

P-36-012
The role of recent adaptative selection on schizophrenia susceptibility genes

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Objectives: The aim of this study was to test if the existence of common susceptibility alleles to schizophrenia may be explained at least in part by recent natural selection, as commonly suggested.
Methods: First, we selected functional candidate genes based on its role in synaptic transmission, neurodevelopment, differential expression in schizophrenia, or interaction with DISC1 from databases (Panther, Gene Ontology, Synapse DB, Schizophrenia Gene) and bibliography. Then, we searched for signals of recent positive selection on these genes, taking data from HapMap phase II, by the use of several tests that detect haplotypes with an extension of linkage disequilibrium larger than expected under neutral evolution in regard to its frequency. Finally, we searched for association of the selected haplotypes with schizophrenia in a sample of 300 schizophrenic patients and 659 controls from Spain.
Results: Our analysis suggests that 13 of 1694 selected candidate genes present strong signal of recent selection. Among these, there are one haplotype in PTPN13, gene putatively over-expressed in prefrontal cortex of schizophrenics, that is over-represented in controls (allelic test P value = 0.0077, OR 1.46, 95% CI 1.10 – 1.94; dominant genotypic model P value = 0.0086). Another haplotype in the synaptic transmission gene SNTG1 is marginally significant at the allelic level (P = 0.0710), and it reaches significance under a recessive genotypic model (P = 0.0188). Nevertheless, these results do not remain significant after multiple testing correction.
Conclusions: It seems that natural selection plays a role in the evolution of some candidate genes for schizophrenia susceptibility, affecting their current variability. Nonetheless, the common variants subject to recent natural selection do not confer any clear risk to schizophrenia, although results at PTPN13 and SNTG1 are pending of replication analysis to totally discard (or alternatively confirm) any role in schizophrenia risk.

P-36-013

Study of association between tryptophan hydroxylase-2 and depression of late - onset

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Objectives: Depression is one of the most common psychiatric diseases, being considered late-onset depression when only happens after 60 years. The population above this age has increased significantly in Brazil and it is estimated that will reach in the year 2025, about 32 million of elderly people. The depression in this population has been worsening in the course of other diseases and also has a great negative social impact. Several lines of research have shown that depressive symptoms are associated with changes of the serotonin system. Thus, the genes involved in the synthesis, transport and degradation of serotonin have received special attention in the effort to discover the genetic basis of depression. Tryptophan hydroxylase-2 is an enzyme involved in the biosynthesis of serotonin in the brain and polymorphisms in this enzyme can interfere in the synthesis of the neurotransmitter. Some variants of TPH2 have been associated with various psychiatric disorders, especially major depression and suicide, but few studies have investigated the role TPH2 gene polymorphisms and susceptibility of the late-onset depression. Our objectives are analysis the frequencies of polymorphisms in a group of elderly patients with late-onset depression and investigate whether the frequencies of polymorphisms are associated with depressive events.
Methods: Our sample were recruited in the Reference Center for the Elderly Professor Benjamin Caio Dias. The case sample consisted of 84 elderly patients with late-onset depression and 84 controls. The DNA was isolated from whole blood. We are investigating eight TagSNP's of gene TPH2. We genotyping using the Real-Time PCR with probe TaqMan.
Results: Data showed an association between the genotype c/c of the polymorphism located in the intronic region of the TPH2 gene (rs1487275 p= 0.026) and the presence of late-onset depression.
Conclusions: The result strengthens the hypothesis of neurobiological involvement of serotonin system in the etio-pathogenesis of depression in the late-onset depression.

P-36-014

Polymorphisms in GRM3 and HOMER1 genes and their possible role for early treatment response in schizophrenia

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Objectives: Recently, the major role of glutamate and metabotropic glutamate receptors (GRM) in schizophrenia has been confirmed. Also, HOMER proteins as intracellular structural proteins regulating the activity of GRM can be traded as important in the aetiology of schizophrenia. This is why possible associations between polymorphisms in the GRM3 receptor and Homer1 gene with early treatment response were analysed in schizophrenic patients.
Methods: 308 schizophrenic patients were genotyped for 5 SNPS in the GR3M and HOMER1 genes. The patients comprised 2 different samples: 70 were recruited within the German Research Network on Schizophrenia throughout and 238 of them consecutively at the psychiatric department of the Ludwig-Maximilians-University. PANSS ratings were performed weekly from admission to discharge. Statistical analyses with ANOVA repeated measurements were performed using the SPSS version 15.0.
Results: 308 schizophrenic patients (187 male, 121 female, mean age 33,10 years [±11,85], mean number of hospitalizations 2,49 [±2,43]) were treated either in a naturalistic setting (n=70) with multiple drug regimes or in monotherapy using different atypical antipsychotics. 4 of the 5 GRM3 polymorphisms revealed results with marginal significance concerning response of positive symptoms (ranging from p=0,02-0,06). In contrast, 2 SNPs of the HOMER1 gene could be associated with high significance with early treatment response of positive symptoms (F=5,065, p=0,007), mainly within the first 3 weeks.
Conclusions: Our results underline the importance of the glutamatergic system in aetiology and treatment of schizophrenia and propose a significant impact of its regulating protein HOMER1 on early drug response. Future analysis with larger sample sizes and control groups are warranted.

P-36-015

Association between D2 Dopamine Receptor (DRD2) Gene Polymorphism and Posttraumatic Stress Disorder in Vietnam War Veterans of Korea

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Objectives: Evidences from recent studies supports the role of genetic factors in the development of Posttraumatic Stress Disorder (PTSD). The primary aim of this study is to investigate the association between the dopamine D2 receptor (DRD2) TaqI A polymorphism and PTSD. The second aim is to examine the association between the DRD2 TaqI A polymorphism and clinical symptoms in patients with PTSD.
Methods: We recruited 189 Vietnam veterans for participation in this study, among whom 99 were PTSD patients and 90 were control subjects. The presence of the DRD2 TaqI A polymorphism was determined by polymerase chain reaction (PCR). Several standardized research scales were used in the clinical assessment of PTSD, including the Combat Exposure Scale (CES), Clinician Administered PTSD Scale (CAPS), Beck Depression Inventory (BDI), and Clinical Global Impression (CGI).
Results: There was no significant difference in the distribution of the DRD2 genotype, frequency and prevalence of the A1 allele, or the frequency of heterozygotes between the patients with PTSD and the controls. In the PTSD group, the patients with the A1 allele (A1A1, A1A2) scored higher on the CAPS-total (p=0.044), CAPS-avoidance symptoms(p=0.016) and BDI (p=0.024) than those without the A1 allele (A2A2).
Conclusions: We could not find an association between the dopamine D2 receptor (DRD2) TaqI A polymorphism and PTSD. However, the A1 allele of DRD2 seems to influence avoidance symptoms in patients with PTSD.

Table 4. Comparisons of CES, CAPS, BDI, CGI-PTSD scores between PTSD patients with 'A1/A1+A1/A2' and 'A2/A2' genotype of DRD2 gene

	A1+ (A1A1+ A1A2) (N=57)	A- (A2A2) (N=42)	p-value
	mean±SD		
CES	19.6± 4.7	21.2± 4.8	0.098
CAPS			
Total	82.2± 26.4	71.7± 23.6	0.044*
Reexperience	22.0± 7.4	19.3± 6.3	0.060
Avoidance	21.5± 11.6	16.2± 9.3	0.016*
Hyperarousal	21.2± 7.4	19.5± 8.4	0.287
BDI	26.4± 12.3	21.2± 9.2	0.024*
CGI-PTSD	4.4± 1.2	4.2± 1.0	0.251

Comparisons made by t-test
SD : Standard deviation
CES: Combat Exposure Scale
CAPS: Clinician Administered PTSD Scale
BDI: Beck Depression Inventory
CGI-PTSD: Clinical Global Impression-PTSD Symptoms
* : P<0.05
** : P<0.01

P-36-016

The role of 677C>T genetic polimorphism of the methylenetetrahydrofolate reductase gene in schizophrenia

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Objectives: To evaluate the presence of the 677 C>T polymorphism in 44 patients with schizophrenia and its relationship with the risk of schizophrenia, the clinical picture and the responsiveness to the antipsychotic treatment.

Methods: 44 patients diagnosed with schizophrenia according to ICD 10 criteria were assessed by psychiatric examination and scalar evaluation. The presence of the 677 C>T genetic polymorphism was evaluated by DNA analysis in the 44 patients and 35 control subjects.
Results: The presence of the 677 C>T mutation was found in 28 (66,7%) of the patients, compared to 11 (34,3%) of the control subjects. The intensity of the positive, negative and general symptoms was higher in the patients presenting the T allele, compared to the patients with normal genotype. The mean age of onset did not differ between the two patient groups. The responsiveness to the antipsychotic treatment was similar in patients with the normal genotype, compared to the patients presenting the T allele.
Conclusions: Our study confirms the role of the 677C>T MTHFR gene mutation in the aetiology and pathogenesis of schizophrenia.

P-36-017
The MAO-A gene, adverse life events and adult ADHD

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Objectives: Attention deficit hyperactivity disorder (ADHD) is a disorder characterized by inattention, hyperactivity and impulsivity. ADHD has been linked to the dopamine, serotonin and norepinephrine system which are partly regulated by Monoamine Oxidase A (MAO-A). Our group has previously shown an interaction between the serotonin transporter gene, adverse early life events and severity of adult ADHD. (Mueller et al 2008) In this study we extend the hypothesis that genetic variations in the functional polymorphism (rs6323T/G) of the MAO-A gene show a similar effect.
Methods: A total of 110 Caucasians were diagnosed with adult ADHD (71 males and 39 females) according to DSM-IV criteria. Adult ADHD diagnosis and severity was assessed using the Wender Utah rating scale (WURS) and the Brown Attention Deficit Disorder Scale (BADDS). Genotypes, adverse life events (ALE) and age were included in MANCOVA and linear regression analyses. Since MAO-A is located on the X-chromosome, we performed sex-specific analyses.
Results: We found a significant positive correlation between total BADDS score and ALE (P=0.021). Within the males, the total BADDS scale (T vs G allele, Mean =88.5 +/- 17.7 vs Mean =73.8+/-18.5; p=0.03) and two of its subscales ("sustaining attention and concentration" and "working memory and accessing recall") were significantly higher in T-allele carriers. However, after correction for ALE and age, our observations become non significant. Within the females, we did not observe any difference across the genotypes in BADDS.
Conclusions: Our study support the hypothesis that the MAO-A gene is associated with severity of ADHD. However, this association has only been observed in males and became insignificant after correction for age and ALE. Furthermore, no interaction was observed with ALE and genotype. These observations need to be confirmed in a larger sample size. We are currently investigating further variants in the MAO-A gene.

P-36-018
A family study of the association of the dopamine gene polymorphisms with temperament and behavioral problems

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Objectives: Recent research suggest that the variability of dopaminergic genes may be involved in the development of temperament and children's behavioral problems. The objective of the presented study was to investigate possible associations of DAT1, DRD2, DRD3 and COMT variants with behavioral outcomes in children aged 4-10 years.
Methods: We performed family-based association study by genotyping five SNPs (rs4680, rs6280, rs27072, rs463379, rs1800497) in the set of 153 parent – child trios of Polish origin. Temperamental characteristics were measured using the Temperament Inventory for Children (TIC), and behavioral problems using the Child Behavior Checklist (CBCL). Family-based association analysis was performed using FBAT package.
Results: The COMT polymorphism was significantly related with temperament trait of briskness (over-transmission of the Met allele in the dominant model, Z=2.01, p=0.04). One of the DAT1 polymorphisms (rs463379) was associated with temperament traits of sensory sensitivity (over-transmission of C allele in the dominant model, Z=2.76, p=0.006) and emotional reactivity (under-transmission of both alleles in the dominant model, for G Z=-2.07, p=0.04, for C Z=-2.06, p=0.04).We also found significant association of rs463379 with somatic complaints scale of the CBCL (under-transmission for G allele in the dominant model, Z=-2.06, p=0.04) and with aggressive behavior scale (under-transmission for C allele in the dominant model, Z=-2.5, p=0.01). Another SNP in DAT1 gene (rs27072) was significantly associated with attention problems scale (under-transmission of C allele in the dominant model, Z=-2.76, p=0.006) and with aggressive behavior scale (under-transmission of C allele in the dominant model, Z=-2.26, p=0.02).
Conclusions: These findings suggests that DAT1 and COMT variability may be related to the temperament and some behavioral problems in a Polish population.

P-36-019
Specific gene expression in the periaqueductal grey predicts a rats preference for a proactive, reactive or shifting emotional coping style

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Objectives: Chronic neuropathic pain is characterised by both sensory and affective changes. We have shown that following sciatic nerve constriction injury (CCI), 30% of rats develop persistent changes in behaviour (social interactions, sleep-wake cycle and motivated behaviours) identical to the disabilities seen in chronic neuropathic pain patients. We have also shown that a rat's intrinsic coping style to physical and/or psychological stressors predicts the development disability following CCI. Rats, which fail to adopt a consistent coping style (i.e., either proactive or reactive), termed "shifter" animals, are most vulnerable to the development of disability after CCI. The periaqueductal grey region (PAG) of the midbrain, is critical for the expression of emotional coping behaviours, in these experiments we aimed to determine whether rats with "shifting" coping styles were characterised by specific patterns of gene expression in the PAG.
Methods: Rats (N=32) were characterised either as proactive, reactive or shifter using 25 indices, in a well characterised behavioural test battery. 24 genes were identified as having significantly different expression levels between the behavioural groups using Affymetrix GeneChips. RT-PCR was then used to compare expression levels of the identified genes in the PAG of rats with defined coping styles against a "control" un-tested population of age/weight/strain/litter matched rats (N=32).
Results: Significantly higher expression levels of Cd200, Col1a2 and Pde1b and significantly lower levels of Bax/Bcl2 and Tph2 characterised shifter rats. Rats with a shifting coping style did not differ significantly from the "control" population for genes known to be selectively regulated by CCI: Camk2b, Cck, Cnr1, Gfap.
Conclusions: Taken together with the earlier observation that it is "shifter" rats who show vulnerability to developing disabilities, the patterns and magnitudes of gene regulation in the PAG triggered by CCI is much more dramatic than first appreciated.

P-36-020

Association between Thrombospondin 1 (THBS1) gene polymorphisms and schizophrenia in Korean population

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Objectives: Thrombospondins are a family of matrix glycoproteins that regulate cell-matrix and cell-cell interactions. Thrombospondin 1 (TSP1, THBS1) is a potent inhibitor of angiogenesis and tumor progression. Recent research revealed that immature astrocytes expressed THBS1 and THBS2, and THBSs promoted synaptogenesis in vitro and in vivo. Synaptic pathology plays critical roles in brain development, synaptogenesis, and synaptic plasticity of schizophrenic patients. In this study, we examined whether single nucleotide polymorphisms (SNPs) of the THBS1 gene are associated with schizophrenia in Korean population.
Methods: A total of 217 schizophrenic patients [female 96, 43.0 ± 11.0 years (mean ± sd); male 121, 41.8 ± 10.3] and 378 healthy adult controls (female 186, 44.3 ± 6.7; male 192, 44.4 ± 6.3) were examined. Four SNPs were selected from the THBS1 gene region: two intronic SNPs (rs2236741, rs11070220) and two exonic SNPs (rs2228261, rs3743125). Genotyping was carried out by using direct sequencing. For the analysis of genetic data, SNPstats, HapAnalyzer 1.0, SNPAnalyzer, and Helixtree were used.
Results: No significant deviations from the Hardy-Weinberg equilibrium were observed for 4 SNPs ($P > .05$). Three SNPs (rs11070220, rs2228261, and rs3743125) were significantly associated with schizophrenia. The rs11070220 had associations in the codominant ($P = .044$) and recessive ($P = .017$), rs2228261 in the codominant ($P = .006$) and recessive ($P = .002$), and rs3743125 in the codominant ($P = .009$) and recessive ($P = .003$) models, respectively. In haplotype analysis, the CCCC haplotype showed a significant association with schizophrenia in the dominant model ($P = .019$). The TTTT haplotype was also significantly associated with the risk of schizophrenia in the recessive model ($P = .031$).
Conclusions: In conclusion, our findings suggest that THBS1 might be one of genetic factors for the development of schizophrenia.

P-19
Neuroimaging I

P-19-001
FDG - PET imaging of patients with amnestic mild cognitive impairment with and without depression

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Objectives: Mild cognitive impairment (MCI) may represent an early or a transitional stage of Alzheimer's disease (AD), allowing in many instances a pre-syndromic identification of patients who will develop AD. However, not all individuals with MCI progress to dementia. The frequent comorbidity of depression in patients with MCI suggests that depression may be a risk for subsequent dementia in individuals with MCI.
Methods: In this pilot study, we investigated differences in brain activity in individuals with MCI with (N=4) and without (N=3) depression as compared to a group of patients with probable AD (N=8) and healthy controls (HC; N=16) using [(18)F]fluorodeoxyglucose (FDG) positron emission tomography (PET) in amnestic MCI individuals 55 years of age and older. All subjects performed a learning task during the uptake period.
Results: Results indicate that patients with AD and MCI with and without depression share a common and widely replicated decrease in relative glucose metabolic activity in the temporal (F3, 27=4.45, p=.012) and parietal lobes (F3, 27=4.35, p=.013). In contrast, in the frontal lobe, a disassociation was seen with increased activity in the AD group in medial and orbital cortex (and to a lesser extent in the anterior and dorsolateral frontal cortex), which possibly represents compensatory activation. However, patients with MCI and depression showed an orbital and dorsolateral decrease, often reported in affective disorder, which was dissimilar to the AD and MCI without depression comparison groups (Diagnosis x AMOD Effect: F9, 61=2.58, p=.014), suggesting that depression may modulate or prevent frontal compensation for temporal lobe deficits.
Conclusions: Depression is associated with cognitive difficulties, with some studies indicating improvement in cognitive abilities following treatment. Our findings suggest that antidepressant treatment in MCI with depression may be important for cognitive improvement and that some patients with MCI and depression may represent a subgroup of individuals who will not progress to AD.

P-19-002
Using Effective Connectivity as a marker for Depression Vulnerability

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Objectives: Converging evidence suggests that dysfunctions within emotion brain networks might reflect behavioral correlates of depression vulnerability. Further support stems from studies demonstrating that genetic risk factors impact on the coupling between regions critically involved in emotional processing. However, prior studies only utilized correlative measures, which do not allow inferences about causal interactions between different regions of the brain. Advances in neuroimaging are now providing the framework to estimate such causal interactions by the use of measures of effective connectivity. In contrast to functional connectivity, effective connectivity utilizes a priori knowledge of anatomically networks, which has been detailed over the last decade. The goal of our study is to investigate such differences of effective connectivity within emotion brain networks in a large sample of remitted Major Depressive Disorder (MDD) patients by the use of functional Magnetic Resonance Imaging (fMRI).
Methods: We will present preliminary data of an ongoing long-term study investigating vulnerability markers for depression including at least 40 remitted and drug-free MDD patients as well as 80 normal controls without any previous history of psychiatric symptoms. All subjects underwent anatomical and functional scanning as well psychometric assessment. Dynamic causal modeling (DCM) will be utilized as measure of effective connectivity. In addition to intrinsic regional connectivity DCM also enables stimulus-induced changes in connectivity allowing for important insights on the functional integration between different brain regions.
Results: This study will expand on our previous DCM studies and now include networks of emotion processing in this specific sample of remitted MDD patients and healthy controls. Anatomical assumptions will be based on available anatomical literature as well as structural connectivity analysis.
Conclusions: Since information on causal interactions within emotion brain networks in normal controls is sparse and unavailable in remitted MDD patients, we will provide timely results in the field of depression research.

P-19-003
Volitional saccades and prefrontal cortical activation in young people at ultra-high risk of psychosis

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Objectives: The antisaccade task is a well-characterised cognitive task requiring inhibition of a reflexive response to a visually-presented target, and generation of a saccade to an area the same distance away from the fixation point, but in the opposite direction. Antisaccade errors (considered to be reflecting a behavioural failure of inhibition) have been found to be consistently and reliably higher in psychotic illness, and often higher in those at risk of such illness. This study aims to use the antisaccade task to investigate prefrontal BOLD activation in a group at ultra-high risk (UHR) of psychosis, and in matched controls. It is predicted that UHR participants will display an increased antisaccade error rate in addition to otherwise normal eye movement characteristics, and altered levels of BOLD activation in areas associated with executive function (such as the dorsolateral prefrontal cortex).
Methods: 23 UHR and 9 control participants perform visually-guided and antisaccade tasks both in a laboratory setting, and while undergoing event-related BOLD fMRI at 3T. Eye movements are recorded during scanning with an iView X MRI-LR infrared system.
Results: UHR participants demonstrated, as predicted, a significantly higher rate of antisaccade errors (38.3% vs 25.3%, p = 0.039), and no difference in reflexive saccade parameters or in speed of saccade generation. Preliminary fMRI results indicate subtle differences in BOLD activity in the prefrontal regions between groups. In particular the high-risk participants demonstrated a greater reduction of activation in Brodmann Area 10 (at the frontal pole) during the performance of antisaccades.
Conclusions: The increased antisaccade error rate and differences in prefrontal activity of the UHR participants is evidence that processes affecting the frontal areas in psychotic illnesses may be active before the onset of clinical psychosis, and may yet form a basis for understanding the factors involved in the development and treatment of psychotic symptoms.

P-19-004
Dissociation of neural networks for anticipation and consumption of social and non-social rewards

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Objectives: Comprehending the mechanisms underlying the processing of reward is of essence for the understanding and treatment of addictive disorders. Reward processing can be dissected into phases of reward anticipation and reward consumption. It is currently a matter of debate whether these processes are mediated by the same or different neural networks. Previous research has identified the ventral striatum as key structure in reward anticipation. However, its role in reward consumption is disputed. Here, we examined the neural basis of reward anticipation vs. consumption in healthy participants in an incentive delay task offering either money or social approval.
Methods: In both conditions (money task and social task) participants (N=28) were given a cue indicating potential reward. In order to receive reward, a target button had to be pushed within a certain time window (adapted for individual reaction time). Reward (pictures of coins or approvingly smiling faces) was presented for 1650 ms 300 ms after target time onset. Monetary or social conditions were alternated sessionwise. Magnet resonance imaging was performed on a 1,5 Tesla Siemens scanner in an event-related design.
Results: Anticipation of reward resulted in activation of mesolimbic brain structures, including the ventral striatum, independent of incentive type. In contrast, consumption of monetary or social reward resulted in individual activation patterns, neither of which included the striatum. Among other structures, monetary reward specifically activated the thalamus, while social reward specifically activated the amygdala.
Conclusions: Our results corroborate the role of the ventral striatum as modality-independent mediator of reward anticipation but cast doubt on its importance for reward consumption. Moreover, the findings implicate that the neural mechanisms underlying reward consumption are more modality-specific than those for reward anticipation.

P-19-005
The pathophysiology of schizophrenia: Evidence by Voxel-Based Morphometry and Diffusion Tensor Imaging

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Objectives: A growing body of evidence supports the hypothesis that major cognitive disturbances in schizophrenic patients are the result of a functional disconnection in both local neural circuitry and among several brain areas. Deficits of myelinization in relevant neuronal structures indicate an anatomical disconnection between brain regions which may be involved in the disorder. Sensitive MRI methods such as voxel-based morphometry (VBM) and diffusion tensor imaging (DTI) can detect macroscopic as well as microstructural cerebral alterations in vivo.
Methods: 3D-T1 and DTI (25 directions) were performed in 20 schizophrenic patients and 23 age-matched control subjects on a 1.5 T GE-scanner. Group comparisons of gray matter density maps, fractional anisotropy (FA), and the apparent diffusion coefficient were performed using t-tests.
Results: Compared with controls, patients showed significant less gray matter density in the medial prefrontal cortex, the temporal lobes, cingulate gyrus and dorsolateral prefrontal cortex bilaterally ($p < 0.05$, corrected). Additionally, DTI revealed a decreased FA in the anterior corpus callosum and the white matter of the right lateral prefrontal cortex.
Conclusions: The findings of our study define structural brain alterations in patients with schizophrenia. Using DTI analyzed on a voxel-by-voxel basis, our results consistently show abnormalities in white matter structures (e.g. corpus callosum) which form a major basis of cortico-cortical connections. Correlations of microstructural alterations with PANSS scores will be discussed.

P-19-006
Progressive MRI findings in schizophrenia

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Objectives: Early MRI studies were interpreted in such away to support that schizophrenia was a purely neurodevelopmental disorder, which means that after a certain age limit (different for the various brain regions) there were no progration of MRI lesions. The aim of the study was to investigate if the hypothesis that schizophrenia is a purely neurodevelopmental disorder is correct by critically review recent MRI studies.
Methods: Rresearch in Medline using as key words: schizophrenia, change, longitudinal, progressive, duration, cross-sectional, follow up.
Results: The design of each study affects the outcome and decisive conclusion should be cautiously made. The studies are either longitudinal or cross-sectional. The former type is easier to complete and hence longitudinal studies are three fold more common in literature, but still their results are difficult to interpret. Medication is considered to have controversial effects. Studies have focused on specific brain areas, such as gray matter, the lateral ventricles volume and hippocampus volume. We included only studies that lasted more than two years and examined more than thirty subjects of each group. We also present advantages and limitations of the two imaging procedures: Region of Interesy (R.O.I.) and Voxel Basede Morphometry (V.B.M.)
Conclusions: Brain should not be considered as a lifeless organ, sometimes static in volume and other times with volume reduction but as a throughout life changing formation. Pure neurodevelopmental or neurodegenerative forms of schizophrenia are rarely (if ever) found usually there is a combination of both forms.

P-19-007
Cortical activations during auditory and non-auditory hallucinations: An fMRI study in childhood- and adult-onset schizophrenia

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Objectives: Brain-imaging has been extensively used to evidence the underlying mechanisms of hallucination in schizophrenia, even if little is known about reproducibility of these results. In the present study, we present brain-mapping of the hallucinatory phenomenon taking into account the group-level, the age of onset and extra-auditory experiences.
Methods: 15 adults and 15 children, with a positive diagnosis of schizophrenia (DSM-IV-TR) and suffering from refractory hallucinations were included in this study. They all benefited from a 30-min. rest fMRI examination (Philips Intera Achieva 1.5T) after which they were accurately interviewed about their psycho-sensory experiences during scanning. Using cortex-based Independent Component Analysis (ICA), BOLD signals related to the hallucinatory experience were extracted at the subject level. The ICA decompositions obtained from the data-sets of each subject were submitted to self-organizing-group ICA (sog-ICA) procedure to extract clusters at the group level, on the basis of a pure spatial similarity matrix.
Results: 10 adults and 9 children experienced hallucinations during scanning. Our results highlighted auditory, visual, somesthetic and multisensory hyperactive-clusters in both groups after decomposition by sog-ICA (threshold fixed at $|Z|=2.2$, $p< 0.01$). Multisensory networks were more significantly recruited in childhood-onset schizophrenia than in adult subjects. In the 5 adults and 6 children who did not experienced hallucinations, sog-ICA identified a common parietofrontal component reflecting the so-called "default-mode" network.
Conclusions: Data-driven analysis methods for rest fMRI-data allowed evidencing the neural correlates of auditory and non-auditory hallucinations in subjects with schizophrenia. Despite inter-individual variability, associative cortical areas seem regularly involved in this pathological process. These regions constitute good candidate to guide innovative dimensional treatment of hallucinations like rTMS.

P-19-008
Groupage A.B.O, phenotype, rhesus, lewisand schizophrenia

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P-19-009
Brain activation preceding auditory verbal hallucinations

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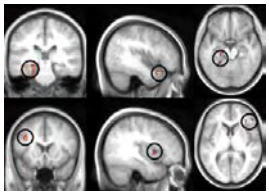
Objectives: Previous fMRI studies have demonstrated activation in a network of language-related regions during auditory verbal hallucinations. However, it has remained unclear where these hallucinations originate in the brain. Identifying brain regions that show significant signal changes preceding AVH might reveal the origin of AVH.
Methods: Fifteen psychotic patients indicated the presence of AVH during 3T fMRI scanning by squeezing a small balloon. To control for motor related activation fifteen control subjects squeezed this balloon at matched time intervals. A tailored ‚selective averaging' analysis method was used to enable analysis of brain activation from 6 to 0 seconds prior to the AVH without any apriori assumptions concerning the heamodynamic response profile.
Results: Prominent deactivation preceding AVH was observed in the left parahippocampal gyrus. In addition, significant deactivation was found in the left superior temporal, right inferior frontal and left middle frontal gyri as well as in the right insula and left cerebellum. No significant signal changes were revealed prior to the balloon-squeezing in the control subjects.
Conclusions: Auditory verbal hallucinations in psychotic patients are consistently preceded by prominent deactivation of the parahippocampal gyrus. This could imply that auditory verbal hallucinations are triggered by memory retrieval



P-19-010
Gender differences in [123I]-ADAM binding to Serotonin Transporters in patients with Major Depression before and after treatment with Citalopram

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Objectives: The aim was to determine the relation between characteristics of [123I]-ADAM binding to serotonin transporters (SERT) in several brain regions to different symptoms in patients diagnosed with major depressive disorder (MDD) and to analyze data for males and females separately. Differences of [123I]-ADAM binding in patients before and after treatment with the Selective Serotonin Reuptake Inhibitor (SSRI) antidepressant Citalopram were assessed.
Methods: 12 non medicated patients (5 females and 7 males) diagnosed with MDD were examined by SPECT with the specific Serotonin transporter radioligand [123I]-ADAM before and after treatment with the SSRI Citalopram. We administered the dose of 10 mg Citalopram per day intravenously at first day, followed by a 6 days period of oral application. After 7 days of treatment patients were examined for second time with SPECT. The relationships between [123I]-ADAM binding and different aspects of major depression represented by HAMD items, assessed twice by the Hamilton Depression-Scale (HAMD) once at baseline and second after the treatment period, were evaluated.
Results: We found significant correlations with significant gender differences between singular sub items of HAMD and indices of [123I]-ADAM binding in midbrain before and after treatment. These findings points to the need of data analysis separately in males and females. No correlations between HAMD total scores at baseline and indices were found.
Conclusions: SERT availability for 123-ADAM binding in the midbrain in drug naives as well as in treated patients with major depression disorder seems to be related to intensity of sub items in the HAMD and the outcome of treatment.

P-19-011
Structural differences of gray matter between patients with unipolar and bipolar disorders assessed by voxel-based morphometric analysis

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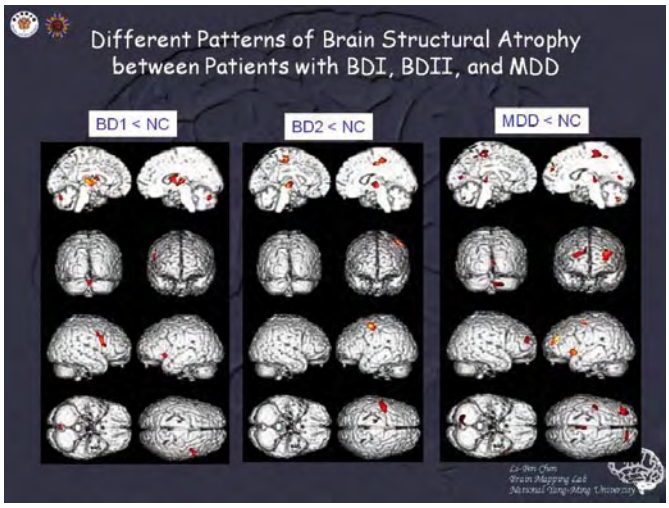
Objectives: The course of major depressive disorder (MDD) contains one or recurrent depressive episodes while bipolar disorder (BD) patients experience one or more manic/hypomanic episodes intermixed with depressive episodes. Bipolar I (BDI) and bipolar II (BDII) are two subtypes of BD characterized by the presence of one or more manic episodes (BDI) and hypomanic episodes (BDII), respectively. In this study we examined volumetric differences of brain tissues existing in patients with BDI, BDII, and MDD by using the voxel-based morphometry (VBM) approach.
Methods: Seventeen BDI, eighteen BDII, and twenty-five MDD patients during remission stage were selected from the outpatients of the psychiatry department of Taipei Veterans General Hospital. Twenty-eight healthy subjects without major medical conditions were also recruited. All subjects provided written informed consent to participate in the study according to the guidelines approved by the Institutional Committees of Medical Ethics and Radiation Safety. T1-weighted magnetic resonance (MR) brain images of all participants were acquired by a 1.5 T GE scanner. These MR images were processed by a VBM procedure for statistical inference ($p<0.001$) of the inter-group structural differences.
Results: BDI patients present decreasing volume in the thalamus and the right inferior frontal and right precentral cortices. BDII patients present decreasing volume in the thalamus and left precentral cortex. Compared to BD patients, MDD patients present decreasing volume in more areas, including the left superior temporal pole and the left middle frontal, right superior frontal, and left precentral cortices.
Conclusions: We found that the atrophic regions presented in BDII patients are also presented in MDD patients, except the thalamus, which matches the phenomenon that early stage BDII patients are often wrongly diagnosed as MDD. The results also suggest that the amount of volume decrease of the thalamus might be relevant to manic and hypomanic episodes in BD patients.



P-19-012
Longitudinal changes in brain structure following the first episode of psychosis

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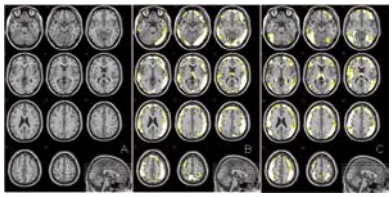
Objectives: We expected patients with first episode schizophrenia psychosis (FESP) and first episode affective psychosis (FEAP), to be differentiated by diagnosis-related reduction from the early stage of the disease and by different trajectories over time compared to controls.
Methods: Adolescent patients with first episode psychosis (n=22) were scanned using MRI at presentation and 3 years later. An age-matched group of healthy volunteers (n=17) was scanned at the same time points. Within-group and between-group changes in grey matter volume were examined using voxel based morphometry.
Results: There was a longitudinal decrease in total grey matter volume in controls (p=0.034) but not in patients, although the group by time interaction was not significant. At the regional level, there were differences between patients and controls in the frontal, temporal, parietal, cerebellar cortex and in the thalamus, mainly reflecting longitudinal volumetric reductions in the healthy controls. Subdivision of the patient group revealed that while there were similar longitudinal changes in patients with affective psychoses to controls, there were no volumetric changes in patients with schizophrenia.
Conclusions: Schizophrenia may be associated with a delay or a loss of longitudinal reductions in grey matter volume that occurs during brain development in normal adolescence and in patients with affective psychoses.



P-19-013
Working memory dysfunction in obsessive - compulsive disorder: A neuropsychological and functional MRI study

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Objectives: Previous neuropsychological studies indicate that OCD subtypes such as checking rituals might be associated with a working memory deficit. On the other hand, functional neuroimaging studies found functional abnormalities of the frontal cortex and subcortical structures in OCD. Combined with functional imaging method, we applied neuropsychological batteries to demonstrate a working memory deficit in OCD by comparison with normal controls. In addition, working memory and brain activation were further examined with symptom-based analysis.
Methods: Forty patients with OCD and 25 normal controls were examined using neuropsychological tests including the WAIS-R, WCST, WMS-R, and R-OCFT and functional MRI (fMRI) during the N-back task including 0 and 2 back task. On fMRI, the brain regions activated during the performance and the differences in the activation between patients and controls were identified. Additional analyses of severity and subtypes were conducted by using Y-BOCS severity score, symptom-checklist and Leckman's 4-factor model, respectively.
Results: On the neuropsychological tests, the OCD patients had significantly lower scores on the delayed recall section of the WMS-R and the immediate recall section of the R-OCFT compared to the controls. On fMRI, the patients showed greater activation in the right dorsolateral prefrontal cortex (DLPFC), left superior temporal gyrus (STG), left insula, and cuneus during 2-back task compared to the controls. Right orbitofrontal cortex activity showed a significant positive correlation with Y-BOCS scores in OCD. Furthermore, patients with obsessions/checking rituals (n=10) showed severer memory deficits and decreased activity in the postcentral gyrus than patients with cleanliness/washing rituals (n=14).
Conclusions: We found neuropsychological dysfunction and brain abnormalities in OCD. Furthermore, our results suggested that symptom severity and symptom subtype such as obsessions/checking might affect neuropsychological dysfunction and related brain activities.

P-19-014
Disruption of white matter integrity in generalized anxiety disorder: A diffusion weighted imaging study

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Objectives: In this study, a diffusion weighted imaging (DWI) approach was used to explore white matter microstructure in patients with generalized anxiety disorder in comparison with healthy controls (HC), expecting disrupted white matter organization.
Methods: Thirteen DSM-IV patients with generalized anxiety disorder and 15 HC were studied using a 1.5 T scanner. DWI images were obtained by applying the following sequence parameters: TR=3200 ms, TE=94, flip angle=90°, slice thickness=5 mm, number of averages=4, FoV=230, matrix=192x192, number of slices=19, distance factor=30%. Diffusion values were determined by manually placing regions of interest on cortical lobes and corpus callosum's subregions. An analysis of covariance (age and gender as covariates) was performed to compare diffusivity between patients and HC.
Results: Significantly increased diffusivity was detected in patients compared to HC in left frontal lobe, right parietal lobe and right splenium (analysis of covariance, $p<0.05$). No correlation was observed between diffusion values and clinical measures (partial correlation analyses, controlling for age, $p>0.01$).
Conclusions: To our knowledge, this is the first study investigating white matter integrity in patients with generalized anxiety disorder. Alterations occurring in fronto-parietal and callosal white matter may sustain functional disturbances of both intra-hemispheric and inter-hemispheric neural circuitries critically involved in cognitive functioning and social intelligence, which are often compromised in anxiety disorder patients.

P-19-015
Six months follow-up study of brain levels of γ-aminobutyric acid, glutamate, and glutamine in the first episode schizophrenia patients

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Objectives: Dysfunctions in γ-aminobutyric acid (GABA) and glutaminergic neurotransmission might be involved in the pathophysiology of schizophrenia. In the present study, we measured brain concentrations of GABA, and a composite measure of glutamate (Glu) and glutamine (Gln) in patients with the first episode of schizophrenia used MR spectoroscopy at 3T.
Methods: Enrolled in the study were 18 patients in the first episode of schizophrenia (9 males, 9 females; age range 13-52 y) and sex- and age-matched 18 healthy controls (9 males, 9 females; age range; 15-49 y). [1H]-MRS was used to measure GABA, and Glu+Gln in the frontal lobe, basal ganglia, and parieto-occipital lobe before and 6 months after the treatment. We also examined serum BDNF levels in the patients. This study was approved by the Ethics Committee of the University of Occupational and Environmental Health and all participants gave written informed consent to participate in the study.
Results: The concentrations of GABA/Cr and Glu+Gln/Cr in the left basal ganglia, but not in the frontal or parieto-occipital lobe, differed significantly between the first episode schizophrenia patients and the healthy controls. No differences were found in serum BDNF level between the two groups. Treatment with atypical antipsychotic drugs for 6 months did not change GABA/Cr levels, however, decrease Glu+Gln/Cr levels at any three regions.

Conclusions: These results suggest that dysfunction of GABAergic and glutaminergic neurons exist in early stage of first episode schizophrenia patients and the treatment with atypical antipsychotic drugs influence those systems.

P-19-016
The neural basis of inhibiting one's own perspective in psychosis proneness: An fMRI study

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Objectives: Previous research on functional and neural basis of perspective taking showed that the prefrontal cortex and the temporo-parietal-junction play a role in this 'Theory of Mind' (TOM) capacity. TOM capacity can be subdivided into two components: self-perspective inhibition and other-perspective taking (Samson et al., 2005, Brain). In this study, we examined differences between psychosis prone (PP) and healthy control (HC) subjects in TOM networks, using fMRI.
Methods: The task consisted of short movie-clips differing in self-perspective inhibition and other-perspective taking demands. Conditions with similar other-perspective taking demands, but differing self-perspective inhibition demands were compared.
Results: In HC we found left IFG activation for self-perspective inhibition, also found in simple response inhibition (Rubia et al., 2001, Schizophrenia Research). Furthermore, we found MTG activation in the other-perspective taking versus baseline contrast. This confirms the subdivision of TOM into self-perspective inhibition and other-perspective taking. No behavioural differences between groups were found, however PP showed stronger activation in left IFG, DLPFC, MTG and SFG in self-perspective inhibition. Thus, in order to perform as well as HC, PP excessively addressed self-perspective inhibition networks. Finally, we found PCC and mPFC deactivation in false belief reasoning versus baseline, which was stronger in HC than in PP. Possibly the IFG inhibits self-perspective by deactivating mPFC and increasing TPJ activation, implying that less deactivation in mPFC reflects more difficulty in this inhibition process.
Conclusions: The results suggest that PP - to equal the HC behaviourally - compensate by excessively activating TOM networks. This paradigm could be interesting in psychotic patients lacking illness insight. They may have difficulty inhibiting their own perspective, resulting in more difficulties in other-perspective taking. Being unable to observe themselves through the eyes of others and reviewing their own behaviour, might result in problems in adapting their own self-image to reality, namely that they suffer from a psychotic disorder.

P-19-017
Attentional bias and vulnerability for depression: An fMRI study

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Objectives: Past studies have reported that depressed individuals display an attentional bias by either avoiding positive stimuli, or favoring negative stimuli. This bias has been discussed as being associated with a dysregulation of the prefrontal cortex. These phenomena may thus be linked to vulnerability for depression. However, no studies are available that have investigated neural correlates of attentional bias in a population vulnerable for depression. Therefore, in the present study, we recruited healthy college students who displayed depressive tendencies.
Methods: Sixty healthy college students (30 males) were recruited. Based on the scores on Beck Depression Inventory (BDI), the subjects were assigned to either a control group (BDI≤9) or a subclinically depressed group (10≤BDI≤18). The participants underwent three functional runs during which they completed the dot-probe task employing happy, sad and neutral faces. For this purpose, we adapted the classical dot-probe task for the neuroimaging environment.
Results: Analysis is currently ongoing, and the results will be presented at the conference. We hypothesize that the control subjects will show the attentional bias towards happy faces, while the subclinical participants will divert their attention away from the positive information. Further, we expect to observe deactivation in dorsolateral prefrontal and orbitofrontal cortex, and lower levels of activation in anterior cingulate cortex in subclinical compared to control subjects.
Conclusions: Understanding the neural processes of attentional bias in individuals vulnerable for depression may contribute to the development of preventive measures and improved treatments for subjects diagnosed with depression.

P-19-018
The gray matter volume would predict the symptoms change in the patients with major depressive disorder: Mirtazapine vs SSRI

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Objectives: Recent functional neuroimaging studies have suggested that dysfunction of emotional process and limbic-cortical network were associated with cortical, subcortical defect in major depression. We hypothesized that gray matter volume would be altered in prefrontal, temporal lobe in the patients of major depression and the differences of GM volume would predict the response of antidepressant treatment.
Methods: Twenty three patients with major depression who visited ChungAng university hospital were recruited. Fourteen of them was given mirtazapine and nine of them was given SSRIs(paroxetine, fluoxetine, escitalopram). Patients of two groups underwent MRI scans before using medication.(3.0T Philips Intera Achieva, 150 coronal slices, voxel size 0.94mm×0.94mm×2mm, FOV 240mm x240mm, TR 20msec, TE 4.1msec, FA 30°) We evaluated depressive symptoms with Beck Depression Inventory scale at admission, eight weeks later and compared the difference of BDI score changes. VBM images were analyzed with MATILAB6.5.1 and SPM2, the association of brain region and BDI change was analyzed with regression analysis.
Results: Both groups showed the reduction of GM volume in right frontal lobe, right temporal lobe, middle temporal gyrus, right cerebellum. While the changes of depressive symptoms in SSRI group were associated with just frontal region, those in mirtazapine group were related with frontal(left middle frontal gyrus, right middle frontal gyrus) and temporal lobe(right inferior temporal gyrus). The difference of BDI score change from at admission to after eight weeks between two groups had no significant differences.
Conclusions: Current study showed that GM volume was associated with the symptom change in patients with major depression. The GM volume of frontal lobe and temporal lobe may predict the improvement of symptoms of major depression. Differently activated regions of brain between mirtazapine and SSRI groups may be associated with norepinephrine system in pharmacodynamic of mirtazapine. Mirtazapine is known to occupy not only serotonin but also norephineprine receptor controlling emotional learning, memory, and cognition.

P-19-019
The neurocircuits in the social anxiety spectrum: A voxel-based investigation

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Objectives: The diagnostic frontiers of social anxiety disorder are still controversial, since this disorder could be the extreme of a continuum of severity rather than a qualitatively distinct condition. The present study aims to investigate possible differences among subjects along the social anxiety spectrum.

Methods: The sample was composed by randomically selected university students aged between 18 and 30. We included patients with generalized SAD (n=25), subjects with subclinical SAD (with fear of a social situation without avoidance or impairment; n=14) and healthy controls (n=22). The interventions were the application of the Simulated Public Speaking Test and the acquisition of MRI data across the three groups. Clusters in a priori regions were reported as significant only if including voxels with Z values of > 3.09 (corresponding to the two-tailed p < .001 level, uncorrected for multiple comparisons). The significance threshold p<0.01 (uncorrected) was adopted in the correlations.
Results: In the Simulated Public Speaking Test findings showed that avoidance and functional impairment were due to a negative self-evaluation in the test and not to the level of anxiety experienced (p< .001). When all groups were pooled together, there was a positive correlation between levels of anxiety and volume of the right amygdala. The negative self-evaluation of performance in the Test was associated with a reduction in the volume of the anterior cingulate complex only in the social anxiety group.
Conclusions: These results suggest that the association between anxiety and amygdala volume may be part of a continuum of social anxiety. The association between the negative self-evaluation of performance and decreased volume of the ACC in the SAD group alone is consistent with the idea that this brain area is involved in processing negative emotional assessment in SAD, but do not support the idea that this association is part of a social anxiety continuum.

P-19-020
Regional differences in validity of serotonin transporter occupancy values using PET

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Objectives: Selective serotonin reuptake inhibitors (SSRIs) reduce the activity of the serotonin transporter (5-HTT), therefore increase the serotonin level in extracellular space and decrease binding of specific radioligands to 5-HTT. Treatment-induced changes of serotonin binding to the 5-HTT and occupancy can be measured by PET and the highly selective and displaceable radioligand [11C]DASB (Meyer et al., 2004). For the assessment of occupancy data, low test-retest variability is crucial. The test-retest variability depends on the signal-to-noise-ratio that might be not suitable for occupancy measurements in cortical areas with low binding.
Methods: Eight healthy male subjects underwent two PET scans. For quantification of the 5-HTT binding potential (BP) [11C]DASB was used. BP was calculated via the graphical analysis method (Logan) (reference region: cerebellum). 48 regions of interest (ROIs) were investigated: e.g., the limbic areas expressing moderate levels of 5-HTT; and the basal ganglia expressing high levels of 5-HTT. An automatized method for ROI definition was applied. The variability of binding potentials were calculated using the algorithm: (|scan1 – scan2| / scan1) (normalized absolute differences, NAD), respectively (Wallius et al., 2008). Spearman correlation analyses (1-tailed) between the regional mean 5-HTT BPs and the variability were done with SPSS 15.0.
Results: There was a highly significant negative correlation between regional 5-HTT BP and variability (r=-0.786, p=<0.00001), surviving the statistical threshold for multiple testing (Bonferroni corrected threshold: p<0.00106).
Conclusions: In contrast to brain regions with low 5-HTT binding as extralimbic cortex, areas with high 5-HTT BPs showed an excellent test-retest variability, namely as striatum including putamen, nucleus caudatus, and thalamus. These areas with high 5-HTT binding are best suitable for occupancy studies considering occupancies about 80% across treatment with SSRIs at minimum therapeutic doses.

P-37
Neuroimaging II

P-37-001
The functional neuroanatomy of working memory in very preterm born young adults following neonatal brain injury

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Objectives: Very preterm birth (<33 weeks of gestation) and neonatal complications are often associated with working memory deficits. Periventricular haemorrhage (PVH) is the most common type of brain injury in preterm-born individuals and it may occur either in isolation (e.g., uncomplicated PVH; UPVH) or concomitant with ventricular dilatation (VD; PVH+VD). We aimed to investigate with fMRI the functional neuroanatomy of working memory in preterm born young adults who sustained differing degrees of neonatal brain injury, as detected by ultrasonography.
Methods: 11 very preterm born young adults with a history of UPVH (mean age, 25.27 years, ±1.42) and 9 with a history of PVH+VD (mean age, 25.11 years, ±1.54) were studied. An n-back verbal working memory task with three difficulty levels was used (1-back, 2-back and 3-back), and analyzed with non-parametric analysis software.
Results: Very preterm born young adults with a history of UPVH and those with a history of PVH+VD did not show differences in on-line task performance. However, the PVH+VD group showed attenuated activation in right parietal areas (BA 40) compared to the UPVH group during the 1-Back and 2-Back conditions. Attenuated activation during the 2-Back condition further included the left precuneus and the left middle frontal gyrus (BA 6). Left middle frontal and angular gyri activations were decreased in the PVH+VD group during the 3-Back condition (i.e., highest cognitive load).
Conclusions: These results suggest that despite similar performance of a working memory task with differing cognitive load, very preterm born individuals with a history of PVH+VD show attenuated neural activity in frontal and parietal brain areas compared to individual who sustained milder forms of neonatal brain injury. These findings may reflect deficits in other prefrontal and/or parietal mediated functions known to be impaired in preterm born individuals, such as episodic and semantic memory and executive functions.

P-37-002
Subjective loudness of auditory-verbal hallucinations interferes with processing in brain areas implicated in inner speech

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Objectives: One of the most influential cognitive models of auditory-verbal hallucinations (AVH) in schizophrenia suggests that AVH arise from a failure to adequately monitor the production of inner speech, leading to verbal thought being misidentified as an alien voice. Although this model has been relatively well studied using neuroimaging methods, it remains unclear which aspects of AVH relate to specific deficits in the inner speech network. We investigated the relationship between subjective perceptual characteristics of AVH and the neural substrates of inner speech, using a behaviourally controlled phonological processing task, which has been shown to activate brain regions involved in inner speech production as well as perception (Aleman et al., 2005).
Methods: 24 subjects with a DSM-IV diagnosis of schizophrenia were scanned on a 3T Phillips Intera scanner. The experimental task consisted of judging metrical stress of visually presented words. Subjective characteristics of AVH were assessed with the Auditory Hallucinations Rating Scale (AHRS). Based on literature review of inner speech processing, the following ROIs were selected, and defined based on the AAL system: inferior frontal gyrus, middle and superior temporal gyrus, SMA, insula, anterior cingulate, angular and supramarginal gyrus. Correlations were calculated between AHRS subscales measuring perceptual characteristics (reality and loudness) and activation in the bilateral ROIs. Results were FDR corrected for multiple comparisons.

Results: Significant negative correlations were observed between perceived loudness and activation in the bilateral inferior frontal gyrus (triangular part), angular gyrus and anterior cingulate cortex, and the left medial temporal gyrus and insula. No significant correlations were observed with perceived reality.
Conclusions: Perceived loudness of AVH is associated with reduced activation in a substantial part of the inner speech network, during the performance of phonological processing, suggesting that the perceptual component of AVH competes for neural resources with inner speech. AVH 'reality' rather, appears to be a secondary attribution.

P-37-003
Brain [18F]MPPF imaging in eating disorders suggests specific serotoninergic organic background

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Objectives: Serotonin (5-HT) pathway abnormalities were demonstrated in eating disorders. [18F]MPPF (4-(2-methoxyphenyl)-1-[2-(N-2-pyridinyl)-p-fluorobenzamido]-ethylpiperazine), a selective 5-HT1A receptor antagonist, provides a unique opportunity to assess changes in serotoninergic activity at central level.
Methods: We assessed by positron emission tomography the brain [18F] MPPF binding potential (BP) in 8 patients with restrictive-type anorexia nervosa (AN), 9 subjects recovered from restrictive-type AN, 7 patients with bulimia nervosa (BN) and 7 age-matched controls. Voxel-based analyses were performed to assess differences in [18F]MPPF BP between the three groups. Eating related psychopathological traits were also evaluated.
Results: Restrictive AN patients presented increased [18F]MPPF binding in a selective area of the right cortex including part of the superior temporal gyrus, inferior frontal gyrus, parietal operculum and temporoparietal junction. Striking regional similarities of increased [18F]MPPF binding were found in recovered AN. Widespread increases of [18F]MPPF BP were found in BN in amygdala-hippocampal complex and temporo-parietal cortex, symmetrically, in left insula and right dorsolateral prefrontal cortex (DLPFC). Unspecific traits such as depression co-varied with [18F] MPPF binding in large cortical and limbic areas. Positive correlation were found between [18F]MPPF binding and: body image and food concern in hippocampal-amygdala complex; food concern in left insula and temporoparital junction; emotional eating in a large area of right temporal cortex.
Conclusions: The persistent decreased serotoninergic activity in frontotemporal region of recovered AN, support the hypothesis of an organic dysfunction of this area in AN and corroborates with previous literature reports of anorexia nervosa cases induced by temporal lesions. Widespread increases in [18F]MPPF BP suggest a central breakdown of serotoninergic activity in severe BN, connected to common psychiatric abnormalities. Regional deficit in serotoninergic activities in left insula and right DLPFC could be more specifically related to eating behaviour and therefore to BN pathophysiology.

P-37-004
Neural mechanisms of empathy in boys with autism spectrum disorder and their unaffected fathers

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Objectives: Recently, it has been proposed that dysfunctions in the human mirror neuron system may underlie empathy disturbances in autism spectrum disorder (ASD). However, evidence for this assumption is still lacking, and it is unknown how familial influences might impinge on neural empathy correlates in ASD. Here, we aimed to investigate the neural mechanisms of empathy in ASD, and to explore familial contributions to empathy correlates.
Methods: Using fMRI, 15 boys with ASD, 11 fathers of boys with ASD, and two control groups matched for age and IQ (n=15 typically developing boys and their fathers (n=9)) were investigated during an empathy task. Emotional faces were presented and participants were either asked to infer the emotional state from the face (other-task) or to judge their own emotional response to the face (self-task).
Results: During the self-task, ASD subjects showed less emotionally congruent reactions and inferior frontal gyrus activity was decreased compared to controls. When attributing emotions to self and other, the ASD group showed diminished fusiform gyrus (FG) activation. Neural activity in the FG was inversely related to empathy deficits in ASD subjects. Although fathers of ASD children scored higher on a self-rating scale for autistic symptoms, their task performance was unimpaired. Neurally, fathers of affected children also showed reduced FG activation during the other-task, while inferior frontal gyrus activation during both tasks did not differ from control fathers.
Conclusions: Shared abnormalities in FG activation in affected subjects and first-degree relatives suggest that this dysfunction constitutes a fundamental deviation in ASD, which might be genetically modulated. In persons affected by ASD, FG dysfunction might lead to cascading social deficits including impaired empathy along with aberrancies in the human mirror neuron system. Compensatory mechanisms in relatives with a genetic load might prevent such cascading impairments both on the neural and behavioral level.

P-37-005
Structural covariance in the hallucinating brain modulated by hallucination severity: A voxel-based morphometry study

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Objectives: Neuroimaging findings suggest that auditory verbal hallucinations (AVHs), one of the most devastating yet poorly understood symptoms of schizophrenia, partly arise from altered activation in brain regions involved in inner speech and verbal self-monitoring. Initial structural studies using voxel-based morphometry (VBM) indicate regional deficits in inferior frontal gyrus (IFG) and temporal pole associated with AVHs. Neuroimaging studies also suggest that a number of brain regions express altered patterns of structural covariance in schizophrenia patients relative to controls. However, whether these alterations are modulated by the severity of AVHs remains unknown. This study sought to investigate the structural correlates of AVHs, and to subsequently examine structural covariance with other cortical areas dependent on hallucination severity.
Methods: Optimized VBM was applied on structural scans from 26 schizophrenia patients (13 females; mean age: 36.23 ± 12.14) with treatment-resistant AVHs. Using the General Linear Model, we designed a voxel-wise regression analysis with the individual gray matter (GM) segments, specifying severity of AVHs as predictor. Region of Interest (ROI) analysis was performed in areas previously associated with AVHs - IFG, superior and middle temporal gyri [STG, MTG], hippocampus, and insula. Next, we extracted the GM volume from the regions associated with AVHs to examine structural covariance with our ROIs.
Results: The regression analysis revealed a positive correlation between volume in the left IFG and AVHs, corrected for multiple comparisons. Furthermore, patterns of positive covariance dependent on severity of AVHs were observed between this region and the contralateral IFG, left STG, MTG, hippocampus, and insula.
Conclusions: The present study shows that GM volume of several cortical regions is modulated by severity of AVHs in the hallucinating brain. In particular, we observed positive covariance between frontotemporal areas implicated in the production and monitoring of inner speech, supporting functional neuroimaging findings, and providing new insight into the structural properties of AVHs.

P-37-006
Relationship between glutamate levels and medial temporal function in the At Risk Mental State

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Objectives: Medial temporal dysfunction and altered glutamate function are thought to contribute to the development of psychosis. We sought to examine the relationship between them in subjects with At Risk Mental State (ARMS), who have a high risk of psychosis.
Methods: 22 ARMS subjects and 16 healthy volunteers were scanned using fMRI while performing a verbal episodic memory task. Magnetic Resonance Spectroscopy (MRS) was used in the same subjects to measure glutamate concentrations in the anterior cingulate gyrus, hippocampus, and thalamus. Activation during encoding and recognition in each group was correlated with regional glutamate levels.
Results: In controls, there were no correlations between activation during either encoding or recognition and regional glutamate levels. However, within the ARMS group, glutamate levels in the anterior cingulate were negatively correlated with the BOLD response in the right parahippocampal gyrus (PHG) during encoding (p=0.042 FWE), and positively correlated with activation in the left hippocampus during recognition (p=0.049 FWE).
Conclusions: In subjects at high risk of psychosis, medial temporal function during episodic memory processing was correlated with glutamate levels in the anterior cingulate. These data are consistent with evidence that changes in medial temporal and glutamate function are critical to the development of psychosis.

P-37-007
Fronto-limbic dysfunction in borderline personality disorder: A 18F-FDG Positron Emission Tomography study

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Objectives: Different functional neuroimaging studies have demonstrated specific abnormalities when comparing borderline personality disorder (BPD) patients with controls. Abnormalities which primarily occur in fronto-limbic pathways and are known to be associated with the expression and control of two of the main behavioral dimensions of BPD: emotional dysregulation and aggressive impulsivity. The present study aimed to evaluate regional cerebral metabolism in euthymic BPD patients with similar measured levels of impulsivity by means of 18F-FDG Positron Emission Tomography (PET) during resting state, and to compare them against a control group with similar socio-geographic characteristics. The study pretends to contribute to existing literature on brain metabolism in BPD patients under resting conditions since there is no previous published study of this type in spanish population.
Methods: The present study evaluates regional cerebral metabolism in 8 euthymic BPD patients by means of 18F-FDG Positron Emission Tomography (PET) during resting state as compared to 8 control subjects with similar socio-geographic characteristics.
Results: BPD patients presented a marked hypo- metabolism in the frontal lobe and showed hyper-metabolism in the motor cortex (paracentral lobules and post-central cortex), medial and anterior cingulus, occipital lobe, temporal pole, left superior parietal gyrus and right superior frontal gyrus. No significant differences appeared in the basal ganglia or thalamus.
Conclusions: Results do reveal a dysfunction in patients' frontolimbic network at baseline conditions and provide further evidence for the importance of these regions in relation to BPD symptomatology.

P-37-008
Individual differences in socio-affective skills influence the neural bases of anger processing

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Objectives: Investigating in non clinical population the neural correlates of individual differences in emotional experiences can help to better characterize the mechanisms accounting for an individual's predisposition to develop certain mental illnesses. The present study focused on the core affective program Fear, for which Panksepp (2006) has postulated an implication in generalized anxiety disorders and social phobia. Using fMRI, we addressed the influence of individual differences in the Fear system on the neural bases of perceiving body expressions of anger. Indeed, watching angry behaviors makes the observer feel threatened and prompts him/her to prepare an adapted response and regulate his/her own behavior to the ongoing interaction (Frijda, 1986).
Methods: Subjects were scanned while perceiving body expressions of anger, ranging from low intensity to high intensity. Each video-clip lasted 2 sec. Order of stimuli was fully randomized. Subjects were asked to press a button each time an upside-down video-clip (oddball trials) appeared. After the scanning sessions, subjects had 1) to complete a battery of self-questionnaires including the: Affective Neuroscience Personality Scale (ANPS) (Panksepp 2006); anxiety (State-Trait STAI), social anxiety (ECAS) and depression (BDI); 2) to judge the intensity of the emotion.
Results: Preliminary results show that the perception of high versus low anger behaviors is associated with bilateral activations in complex MT/V5/EBA, fusiform gyrus, superior temporal sulcus (STS) extending to tempo-ro-parietal junction (TPJ), inferior frontal gyrus (Ba 45 and Ba 44) as well as dorsal premotor cortex. In sub-cortical regions, the right thalamus and amygdala were also detected.
Conclusions: Correlation analyses between brain activity and questionnaire scores (ANPS, State-Trait STAI, ECAS) suggest this approach provides useful information for a better definition of emotional endophenotypes associated with inadequacy in everyday social relations that are involved in different psychiatric pathology.

P-37-009
FDG - PET changes in a patient with neurosyphilis

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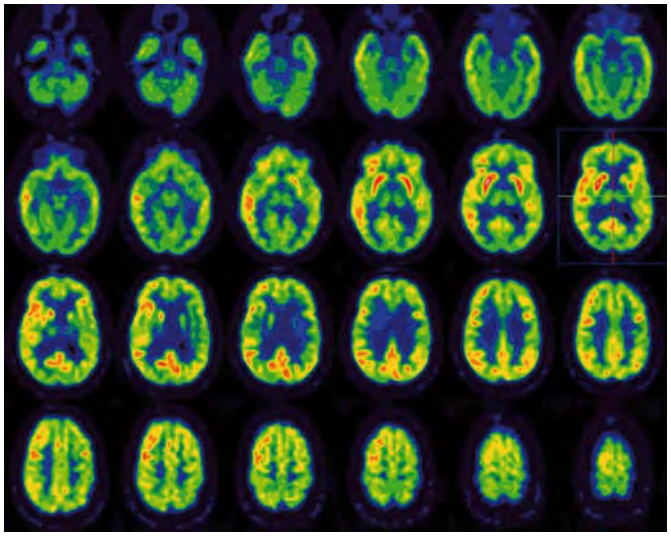
Objectives: To describe the FDG-PET changes in a patient with clinically symptomatic Neurosyphilis. There are no published reports of patterns in this population.
Methods: This is a case report of a 42 year old male who presented with acute personality changes, paranoid symptoms and some cognitive decline without a background of mental illness.
Results: The patient was found to be serologically positive for Syphilis and this was confirmed with a CSF study. FDG PET showed specific changes that included marked reduction of metabolism in the bilateral thalami and visual cortex and milder reductions of metabolism in the left frontal and left temporal lobes when compared to the right hemisphere.

Conclusions: These very unique findings are the first known FDG-PET findings in neurosyphilis. The specific changes in the thalami have not been described in any other condition. FDG-PET has shown to be a useful tool in the diagnosis of many neurodegenerative conditions. While the sensitivity of the test has been high, the patterns of changes seen so far have not been considered specific enough to warrant its use in clinical practice. Demonstration of more specific patterns will be useful in the accurate diagnosis and treatment of reversible neurodegenerative conditions and PET scanning at the moment, appears to be a step in the right direction.



P-37-010

Effect of catechol-O-methyltransferase val158met genotype on emotional intelligence and neural activation during emotional processing of words

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Objectives: The regulation of emotion is very important for human well-being. There are large individual differences in strategies of emotion regulation and ability to process emotions. The catechol-O-methyltransferase (COMT) gene has a common functional polymorphism (val158met) that has been associated with emotion processing. In the present study we wanted to elucidate the neural basis of cognitive-emotional processing associated with emotional intelligence and the role of the effects of COMT genotype on brain activation.
Methods: 39 subjects with scores ranging from low to high on the intrapersonal subscale of the EQ-i (Bar-On, 1997) performed an emotion and metrical stress task during fMRI and were genotyped for the COMT val158met polymorphism. Participants were required to evaluate the valence of subsequently presented words in one condition and they had to indicate the syllable carrying the metrical stress, in the other condition. The statistical threshold for fMRI analyses was set at $p<0.001$, $k>10$ and clusters were corrected at FDR<0.05.
Results: Number of val alleles and the EQ-i intrapersonal subscale correlated significantly ($p<0.05$). Brain activity in bilateral posterior cingulate gyrus (pCC)/medial frontal gyrus (meFG), left supramarginal gyrus/superior temporal gyrus correlated positively with number of val alleles. Individuals with higher scores on the intrapersonal subscale of the EQ-i had more activity in bilateral medial frontal gyrus extending into precentral gyrus. There were no significant overlapping clusters between EQ-i-intrapersonal subscale and COMT, although the areas in the medial frontal gyrus were neighboring each other.
Conclusions: Variation in the COMT val158met genotype was related to emotional intelligence and to neural activation during emotional processing of words. Specifically, the number of val alleles may be associated with higher levels of emotional awareness.

P-37-011

Imaging serotonin-1A receptor asymmetry in language areas using [carbonyl-11C]WAY-100635 and positron emission tomography

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Objectives: Lateralization in auditory and language processing regions (1, 2) is a well described feature of the human brain. In this study we used positron emission tomography (PET) to investigate hemispheric lateralization in the distribution of the major inhibitory serotonergic receptor subtype, the serotonin-1A receptor (5-HT1A).
Methods: 36 healthy subjects (24.81±4.9, mean age ± SD; 18 women and 18 men) underwent PET measurements using [carbonyl-11C]WAY-100635, a highly specific tracer for the 5-HT1A receptor. Regional binding (BPND) was calculated with the Simplified Reference Tissue Model (SRTM2) in a regions-of-interest (ROI)-based approach. Individual dynamic data underwent spatial normalization to fit a symmetric 5-HT1A distribution map matching the MNI space and a ROI template comprising 12 auditory and periauditory regions. Regional BPND was compared for hemispheric and gender differences in a repeated measures ANOVA and post hoc t-tests using SPSS 15.
Results: Statistical analyses showed a significant difference in 5-HT1A BPND between the hemispheres ($F12,23=7.35$, $p=0.00002$), but no significant hemisphere*gender interaction ($F12,23=1.86$, $p=0.098$). Post hoc t-tests revealed lateralization effects in the Heschl's gyrus ($T=3.131$, $p=0.0035$), superior temporal gyrus ($T=3.427$, $p=0.0016$) and the rolandic operculum ($T=3.839$,$p=0.0004$), showing higher BPND in the left hemisphere. The triangular ($T=-3.382$, $p=0.0017$) and orbital ($T=-3.410$, $p=0.0016$) part of the inferior frontal gyrus and middle frontal gyrus ($T=-4.774$, $p=0.00003$) showed higher values in the right hemisphere.
Conclusions: To the best of our knowledge, this is the first study showing significant area-specific differences of 5-HT1A receptor binding between hemispheres in vivo. The leftward lateralisation in specific areas might reflect the serotonergic influence on early cortical processing of speech (1) and syntactic speech production (3). The higher 5-HT1A BPND in distinct right-hemispheric regions might reflect serotonergic contribution to the modulation of prosody and processing of emotional communication (2). References: (1) Tervaniemi et al.,2003. Brain Res Brain Res Rev 43(3), 231-246. (2) Nishitani et al.,2005. Physiology (Bethesda) 20, 60-69. (3) Indefrey et al.,2001. Proc Natl Acad Sci USA 98(10), 5933-5936.

P-37-012

Is hypometabolism in limbic and neocortical areas a specific feature of dementia? Results from a positron emission tomography study with cognitively normal elders

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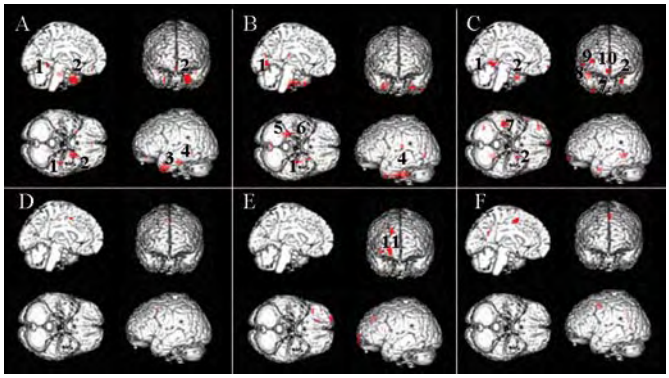
Objectives: To establish a comprehensive profile of functional brain changes in elders and to test the following hypotheses: (1) Regional cerebral metabolism in healthy elders is heterogeneous and influenced by gender and age; (2) Results from previous studies with samples across the span of life do not fit the pattern of metabolic changes in elders; (3) Hypometabolism in limbic structures is present in normal brain aging.
Methods: Voxel-based analysis of cerebral glucose metabolism was performed with the use of Statistical Parametric Mapping program in a community-based sample of 30 non-demented elders with a narrow age-range (17 males and 13 females, 67-75 years of age). The PVElab software was used to perform the atrophy correction by co-registering MRI and PET images according to the modified Müller-Gärtner method. Negative and positive correlations between age and 18FDG uptake were assessed and significant findings were reported after a family-wise error correction was made for multiple comparisons ($pFWE \leq 0.05$).

Results: There was a significant negative correlation between aging and glucose metabolism in the right cerebellum, in the left insula and in the left middle temporal gyrus in males, whereas the right hippocampus, the left parahippocampal gyrus and several frontal regions were more affected in females. A significant negative correlation in the lingual gyrus was found in both groups. The right superior frontal cortex in males was the region that manifested the lowest metabolic decrease as a function of age.
Conclusions: Our study demonstrated that elders have a specific profile of gender and age-related regional glucose metabolism changes. The increased vulnerability to aging in some limbic structures reported in our cognitively normal subjects is of high importance once some of the features previously believed to indicate neurodegenerative processes may be a part of the specific pattern of volumetric changes in the old brain.



P-37-013
Emotional salience of visual scenes enhances repetition suppression in stimulus-related brain regions

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Objectives: Repetition suppression (RS) is a fast adaptive response of cortical areas to the repeated presentation of a stimulus. A previous study investigating RS for faces suggests that RS is enhanced for emotional relative to neutral faces in the amygdala and in the fusiform face area (Ishai et al., 2004). Here we used event-related fMRI to investigate whether similar effects can be observed for natural scenes in stimulus-related brain regions, such as the lateral occipital cortex (LOC) and parahippocampal place area (PPA).
Methods: 25 young, healthy participants viewed scenes and were instructed to respond to a target image presented at the beginning of each trial. During each trial, another image was also repeated, but was irrelevant to the task. This repeated picture could be either of neutral or negative emotional content. Emotional pictures were taken from the International Affective Picture System.
Results: Both target pictures and task-irrelevant distracter pictures elicited a reliable repetition suppression response (1st – 3rd presentation) in the fusiform gyrus, in the LOC and in the PPA. Emotional distracter pictures showed a repetition-related decrement in the bilateral amygdala. A direct comparison of the RS responses to emotional versus neutral pictures revealed a stronger response decrease in the PPA, fusiform gyrus, amygdala and in the LOC, for emotional relative to neutral scenes. Notably, the emotional enhancement of RS was more pronounced for distracters rather than targets.
Conclusions: These results show that repetition suppression for scenes is enhanced by emotional content, in line with previous observations for face stimuli. Modulation of repetition suppression by emotion was observed in secondary visual areas and in higher order stimulus-related brain regions, suggesting that emotional salience facilitates neural processing, possibly by modulating both perceptual and higher-level analysis of visual stimuli.

P-37-014
Cerebral involvement in chronic hepatitis C virus infection assessed by magnetic resonance imaging

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Objectives: According to WHO estimates 170 mio. are globally infected with hepatitis C virus (HCV). Patients with chronic HCV infection have a high prevalence of depressive disorders, cognitive disturbances, reduced quality of life and chronic fatigue. The majority of HCV patients in Europe have a history of drug abuse and psychosocial stress, making the causal relationship between HCV infection and psychiatric symptoms complex. HCV have been isolated in brain tissue in HCV patients and cerebral magnetic resonance spectroscopy revealed metabolic abnormalities indicating chronic inflammation. Furthermore, a substantial number of patients develop major depression during antiviral interferon treatment. In this study, we aim to correlate neuropsychological performance and psychiatric symptoms with viral characteristics (HCV genomic sequencing from peripheral blood and cerebrospinal fluid) and magnetic resonance imaging (MRI). First, we wish to elucidate the causal relationship between chronic HCV infection, cognitive disturbances and psychiatric symptoms. Second, we would like to identify MRI markers for the development of interferon-induced depression.
Methods: An extensive MRI protocol using a 3 Tesla MRI scanner, including diffusion tensor imaging with possibility of fiber tracking, magnetization transfer sequences, regional cerebral blood flow, Fluid attenuation inversion recovery sequences, hippocampal volumetry and H MR Spectroscopy performed before and after antiviral treatment of 60 HCV patients. 40 HCV patients without pending antiviral treatment and 20 healthy subjects will serve as controls. HCV patients receiving antiviral therapy will be examined for the development of depression after 8 weeks of treatment. Extensive neuropsychological testing, psychiatric assessment (Schedules for Clinical Assessment in Neuropsychiatry) will be performed concomitant to the MRI in another study (S.G. Renvillard).
Results: Preliminary results will be presented at WFSBP 2009.
Conclusions: NA

P-37-015
Small amygdala-high aggression: On the role of the amygdala in modulating normal aggression in healthy subjects

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Objectives: Several lines of evidence suggest an association between the amygdala and the modulation of aggressive behavior. Previous morphometric brain imaging studies found amygdala volume loss in different neuropsychiatric disorders associated with aggressive psychopathology. In order to better understand the physiological role of the amygdala in modulating aggressive behavior we investigated the relationship between amygdala volumes and lifetime aggression in healthy subjects.
Methods: Morphometric brain scans were obtained from 20 healthy female, german speaking, right-handed volunteers (mean age 27.2 ± 7.59, range 20-43). Manual measurement of the amygdala followed well established procedures. Careful psychiatric and psychometric assessment was effectuated to exclude any psychiatric disorder. To assess lifetime aggressiveness an established and validated psychometric instrument was used (i.e. Life History of Aggression Assessment (LHA)) as described by Coccaro.
Results: All volunteers were psychiatrically healthy and scored in the normal range of lifetime aggression. Volunteers with higher aggression scores displayed a 16-18% reduction of amygdala volumes. There was a highly significant negative correlation between amygdala volumes and lifetime aggression (right amygdala; Pearson correlation: r = -.650, p = .003; Spearman correlation: Rho = -.672, p = .002 ; left amygdala: Pearson correlation: r = -.630, p = .007; Spearman correlation: Rho = -.737, p = .001).

Conclusions: Remarkably smaller amygdala volumes were associated with higher lifetime aggression scores in psychiatrically healthy women with a physiological extent of aggressive behavior in our sample. Our data support the assumption that the amygdala do play an important role in modulating aggressive behavior. Still our findings do need replication in larger samples of women and healthy men. This observation questions the conclusion that amygdala volume alterations in neuropsychiatry are linked with causality when being found in certain neuropsychiatric disorders. Smaller amygdala might just be an epiphenomenon of the increase in aggression present in different psychiatric disorders.

P-37-016
Pretreatment MR-scanning in OCD

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Objectives: Although the understanding of the neurophysiological background of OCD has improved considerably, many questions remain unanswered. To further approach the understanding of the function of the cortico-basal ganglia circuit in OCD, important aspects await clarification: Functional studies (Cognitive tasks, provocation and rest), which includes a. Comparison between areas of cortico-basal ganglia circuit on different cognitive tests to clarify the significance of the circuit b. Symptom provocation using visual stimuli to differentiate between anxiety related reactions in OCD and controls c. Correlation in BOLD-signal between areas in the cortico-basal ganglia circuit in a resting condition These are investigated before and after cognitive behavioural treatment to clarify the influence of the short-term effects of treatment. Opposite most studies the focus will be on neuronal circuits rather than simple anatomical localisation. The location of white matter lesions will be analysed to examine whether the OCD patients differ from the controls with respect to number or location. Special interest will be given to lesions in fibres between striatum and cortical areas.
Methods: Both Structural and functional MR-imaging will be combined to investigate the cortico-basal ganglia circuit. Functional magnetic resonance imaging (FMRI)-scans and clinical measures are after the inclusion in the clinic before the first cognitive behavioural sessions as well as on completion of the treatment approximately 20 weeks later. Clinical measures and neuropsychological tests are gathered before and after treatment.
Results: Preliminary pretreatment results will be presented at the conference.

P-37-017
A possible biological marker to differentiate between remitted bipolar I and bipolar II disorder using combined FDG-PET brain imaging and executive function assessment

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Objectives: To investigate the relationships between brain glucose metabolism and cognitive profiles in medicated remitted BD, using positron emission tomography (18F-FDG-PET), and to see if BD I is different from BD II and healthy controls.
Methods: Seventeen patients (BD1/BD2 = 9/8), out of 38 remitted BD (YMRA < 10 and 17-item HAMD-17 < 10) after a 4-week treatment, and 16 well-matched healthy controls received both 18F-FDG PET and neuropsychological tests including attention, memory and executive function. MRI-coregistrated PET data were analyzed by PMOD software.
Results: Clinical features between BD I and II are comparable in age (40s),age onset (30s), duration of illness (10s) and manic (4.5) or depressive (5) episodes as well as euthymia. There were significantly poorer executive functions (WCST) in BD I than in BD II and healthy subjects, including more % errors, more % non-perseverative errors, fewer % conceptual levels and fewer categories completed (all $p < 0.05$). No difference in attention and memory tests was found among these 3 groups. PET analyses showed diffused hypometabolism in BD I versus BD II/controls in several frontal/parietal/occipital areas. Nonparametrical correlation analyses revealed significant correlations between poor executive function and left middle frontal gyrus as well as right thalamus ($r=-0.51$ to 0.54, all $p < 0.05$).
Conclusions: BD I presented significantly worse executive function even in remitted status, while BD II was not. Abnormal regional glucose hypometabolism over left middle frontal gyrus and right thalamus could be trait markers for differentiating BD I from BD II.

P-37-018
Robust interaction of emotion and cognition in a working memory task with emotional stimuli

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Objectives: As substantiated by lesion experiments and neuroimaging studies, emotion and cognition domains are intimately linked on a brain systems level. While a top-down regulation is suggested by anatomical connections, several studies indicate the co-existence of a significant bottom-up regulation. However, due to conflicting results exact underlying brain mechanisms are still under discussion. The goal of this study was to further investigate the complex relationship between emotion and cognition domains in two large and independent samples of healthy subjects using different scanner hardware and thus minimizing hardware and sample stratification effects.
Methods: The seminal eighty-two healthy volunteers, recruited at NIMH, NIH, and so far fifty-two healthy volunteers, recruited at the Medical University of Vienna, performed two cognitive tasks composed of a 2-back working memory and a low-level control task within a mixed fMRI design using stimuli taken from the International Affective Picture System (IAPS). fMRI data were analyzed independently for both samples using a mixed-effects ANCOVA model with task, valence and gender as fixed factors and subjects as random factor. Furthermore, direction and strength of bottom-up regulation and top-down regulation were estimated using functional and effective connectivity measures. All results were corrected for multiple comparisons.
Results: A preliminary analysis indicates that emotional stimuli have a robust and significant impact on the activation of dorsolateral prefrontal cortex (BA 46/9) in both independent samples being driven by limbic regions such as amygdala and hippocampus. Effective connectivity analyses provide information on the directionality of this complex relationship.
Conclusions: Preliminary results support the notion that cortical top-down regulation may be overruled in the presence of emotion-laden stimuli. Our two independent sample approach largely eliminates the possibility of a bias related to scanner hardware, MRI sequence, and sample stratification. Hence, our study provides strong evidence of emotional regulation of cognitive processes.

P-37-019

Association between triallelic polymorphism of the serotonin transporter and [18F]MPPF binding potential over 5-HT1A receptor in healthy subjects

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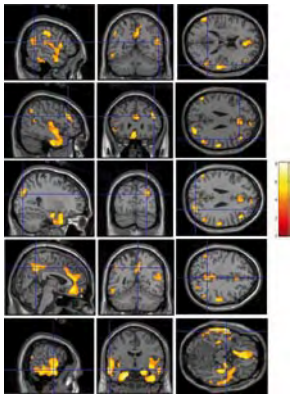
Objectives: The polymorphism of the serotonin transporter (5-HTT gene-linked polymorphic region; 5-HTTLPR) was associated with mood disorders, including depressive disorder. Previous [11C]WAY100-635 PET studies have demonstrated that the short (S) and long (L) alleles of the 5-HTTLPR polymorphism were associated with distinct patterns of 5-HT1A receptors distribution in Human. However, these studies reported discordant findings and did not take into account the recent description of two functional variants of the L allele (LA/LG). To further explore this issue, we investigated the relation between the triallelic functional 5-HTTLPR polymorphism and the avability of 5-HT1A receptors in 38 healthy volunteers.
Methods: All subjects underwent a [18F]MPPF PET and a 3D anatomical T1 weighted sequence. We used a simplified reference tissue model to generate parametric images of [18F]MPPF binding potential (BPND), and compared these data among the different genotypes using statistical parametric mapping and region of interest of the raphe nuclei.
Results: Homozygote carriers of the S allele demonstrated greater [18F]MPPF BPND than carriers of the LA allele, but this association was only found in women. Differences in [18F]MPPF BPND between women with and without LA allele were observed over large clusters encompassing the right and left temporal lobes, cingulate and perisylvian regions, as well as the right precuneus and frontal dorso-lateral cortex, and the left orbitofrontal cortex. In contrast, no difference was found between groups in the raphe nuclei.
Conclusions: The greater [18F]MPPF BPND observed in women homozygote carriers of the S allele could either reflect a greater 5-HT1A receptor density or a lower extracellular concentration of 5-HT. Our data suggest that any future PET studies of 5-HT1A receptors should incorporate the 5-HTTLPR polymorphism status of the population studied.



P-10
Psychopharmacology / Antidepressants

P-10-001
Corticotropin – releasing factor receptor 1 antagonist attenuates neurochemical responses against swim stress in the rodent brain

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Objectives: Corticotropin-releasing factor (CRF) system plays crucial roles in mediating responses to stress, and its dysregulation has been implicated in generation of stress related disorders, such as depression and anxiety disorders. Therefore, CRF receptor antagonists have been regarded as a potential antidepressant and/or anti-stress drug, although their pharmacological effect has yet to be fully understood. In this study, we assessed the effect of the CRF receptor 1 antagonist, ONO-SF-353Ms (SF-353; Ono Pharmaceutical Co., Osaka, Japan) on the neurochemical responses induced by swim stress in the rodent brain.
Methods: Experiment 1: C57BL/6J mice, pretreated with SF-353 (10 mg/kg, i.p.) or vehicle, were subjected to forced swimming test (FST), and predominant behaviors were rated. Mice were perfused with paraformaldehyde 2 hrs after onset of the FST, and then the expression of c-Fos in the discrete brain regions was examined by immunohistochemical method. Experiment 2: Using in vivo microdialysis, extracellular dopamine (DA) and noradrenaline (NA) levels in the medial prefrontal cortex (MPF) were monitored in Wistar rats, pretreated with SF-353 (10 mg/kg, p.o.) or vehicle, during acute swim stress. Effects of local injection with SF-353 into the MPF or ventral tegmental area (VTA) on the prefrontal DA and NA release were also investigated in freely moving rats.
Results: Experiment 1: FST-induced c-Fos positive cells in the MPF, paraventricular thalamic nucleus and ventral hippocampal formation were significantly decreased in SF-353 group. No significant behavioral effect was observed. Experiment 2: SF-353 pretreatment significantly attenuated the swim stress- induced increase of DA and NA levels in the MPF. Local injection of SF-353 had effect on neither DA nor NA level in the MPF.
Conclusions: While SF353, unlike conventional antidepressants, had no significant effect on basal catecholamine release, it strongly attenuated neurochemical responses to stress, suggesting possible effectiveness in the treatment of stress-related disorders.

P-10-002
Treatments patterns, resource use and related healthcare costs in depressed patients with co-morbid anxiety in a large US claims database

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Objectives: Anxiety is frequently associated with major depressive disorder (MDD). Antidepressants are approved for MDD and some anxiety disorders. However, few data exist on real-life utilisation and outcomes of antidepressant treatments in patients with MDD and co-morbid anxiety. This study aims at describing and comparing treatment patterns, healthcare resource use and associated costs in these patients.
Methods: This cohort study using the US claims database PharMetrics included adults with a first prescription of an antidepressant (escitalopram, an SSRI or venlafaxine) associated with a diagnosis of MDD in 2003-2005, and with two diagnoses of anxiety in the year surrounding this first prescription. Treatment patterns, healthcare resource use and related costs were assessed during the 6-month before and after first prescription, and compared across treatment groups.
Results: Of 18,676 patients, 69% were women, and mean age was 40. 25% of patients were prescribed escitalopram, 64% SSRIs, and 11% venlafaxine. Treatment patterns showed a 15% switch rate, a 16% combination rate and 23% of stops with no subsequent relapse (successful treatment stop). Both switch and combination rates were lower with escitalopram vs. SSRIs and venlafaxine ($p<0.001$ and $p=0.002$ respectively). Successful treatment stops were more frequent with escitalopram vs. venlafaxine ($p<0.001$). 6-month total healthcare costs after treatment initiation were not significantly different than before (US$ 4,656 vs. US$4,254), but the structure of costs differed, with more pharmacy costs (20% vs. 10%), and less inpatient care (36% vs. 51%) after treatment start. Compared with baseline costs, healthcare costs were decreased with escitalopram and increased with SSRIs and venlafaxine (- US$74 vs. + US$496 and + US$916 respectively).
Conclusions: In patients with MDD and co-morbid anxiety, antidepressant treatment was generally associated with decreased inpatient care. Compared with SSRIs and venlafaxine, escitalopram was associated with less treatment changes and with decreased costs.

P-10-003
Induction of violence by psychotropic drugs: Signal detection

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Objectives: Violence which presents as a public problem is often inadequately managed, particularly for those with mental disorders who are prescribed psychotropic medications.
Methods: We reviewed the institutional frameworks relevant to responding to and managing violence by individuals prescribed psychotropics.
Results: Violence is typically investigated and dealt with by the police and criminal justice systems. These agencies are accustomed to handling violence caused by alcohol and by abuse or illegal misuse of drugs, but are still largely unaware of the effects of prescribed psychotropic medicines. National drug regulatory agencies collect and analyse reports of adverse effects of medicines (ADRs). They need to recognise and investigate signals of potentially important adverse effects so that these can be prevented or minimised, and people can be warned about them. However, professionals and patients tend not to report violence as a suspected ADR; the police never do - they don't know when it is appropriate to suspect medicines, and hardly ever obtain an offender's full medication history.
Conclusions: Violence as a potential ADR is grossly under-reported to regulators, and there is an associated lack of understanding in the criminal justice system and among the public. New arrangements are needed for reporting, collection, investigation and analysis of these incidents. This will require alerting of professionals, training in the police and criminal justice services, and the establishment of prompt and reliable communication between these and medicines regulatory agencies.

P-10-004
Violence as a side - effect of antidepressants: Provocation by alcohol

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Objectives: Based on case-reports and epidemiological data, we reported the rare induction of serious violence by antidepressant treatment (PLoS Med 3(9): e372). Given alcohol's prevalence and tendency to disinhibit behaviour, we studied its association with SSRI-induced violence.
Methods: We analyzed some 200 cases drawn from our medicolegal practices, web-based patient discussion lists, and ADR reports to government authorities in Canada and the USA. Assessment was based on standard criteria for drug-effect causality (CIOMS), taking into account apparent sources of bias.

Results: A distinct syndrome of uncharacteristic disinhibition with alcohol was detected in 40 individuals of either sex during treatment with SSRIs or venlafaxine. Outcomes included 12 homicides (2 of which were double), suicide, serious assault, unintended sexual intercourse, and other damaging or markedly embarrassing social behaviour. In the majority of cases, memory for the episode was lacking, often completely so. For most individuals, modest or usual amounts of alcohol were involved, with evidence that these had been well tolerated before antidepressant treatment, and after its discontinuation (challenge-dechallenge). In several cases, re-exposure to the same or related antidepressant reproduced the phenomenon (rechallenge).
Conclusions: We identify a distinct and forensically important interaction between alcohol and SSRI antidepressants. Aggregated pharmacovigilance data (in preparation) corroborate the existence of this phenomenon. We suggest that antidepressant product warnings regarding alcohol, hitherto non-specific and unhelpful, will need to be reconsidered.

P-10-005
Antidepressants for prevention of interferon-alpha-induced depression: A meta-analysis

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Objectives: Many studies described major depression following interferon-alpha (IFN) treatment for determined clinical conditions, including chronic hepatitis C and melanoma. Suicide ideation and even suicide completion have been also reported during IFN treatment. In order to prevent these serious IFN-induced psychiatric effects, some studies of prophylactic antidepressants use were performed.
To perform a meta-analysis to evaluate the efficacy of current antidepressants on prevention of IFN-induced depression.
Methods: PUBMED and SCOPUS databases (limited to English and Portuguese idioms) were used and a search using the words "interferon", "depression", "antidepressants", "depressive", "prevention", "therapy", was performed.
Results: Out of 807 works, 5 were randomized, double-blind and placebo controlled studies. One of these studies did not use antidepressant, but amantadine. Four studies were included in the present meta-analysis: Morasco et al, 2007; Raison et al, 2007; Capuron et al, 2003; and Musselman et al, 2001. Paroxetine was the antidepressant in all the four studies. Paroxetine daily doses ranged from 20 mg to 50 mg. In total 149 subjects were enrolled. The meta-analysis showed that 56 out of 66 (85%) patients who used paroxetine did not develop depression. In the placebo group, 55 out of 83 (66%) patients did not evolve with depression. This difference was statistically significant (p=0.005).
Conclusions: Paroxetine seems to be effective in the prevention of IFN-induced depression.

P-10-006
Antidepressants post-receptor mechanism of action involves beta-arrestins and extracellular signal-regulated kinases

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Objectives: Beta-arrestins play a pivotal role in GPCR desensitization and down-regulation. Preliminary data from our laboratory indicates that chronic treatment with antidepressant drugs (ADs) affects beta-arrestin1 rat brain levels. This study aims at elucidating ADs mechanism of action at the post-receptor level involving beta-arrestin1&2 and their interaction with MAPK cascade components.
Methods: C6 glioma cells were treated chronically with various classes of ADs in the presence or absence of the MEK1/2 inhibitor U0126 or the translation inhibitor cycloheximide. Proteins function and levels were measured by confocal microscopy and western blotting. mRNA levels were measured by RT-PCR. One-way ANOVA followed by Dunnett was used for the statistical analyses of antidepressant drugs effects.
Results: Chronic exposure to ADs results in a significant increase in activated beta-arrestin1 while causing a major decrease in the levels of both beta-arrestin2 and functional ERK1/2 in the cytosol of the cells (for all described measurements, $P<0.001$ in comparison to control cells). Inhibition of MEK1/2 caused a significant decrease in beta-arrestin1 in both control and AD-treated cells ($P<0.001$ in comparison to control cells). Following chronic treatments, a major increase in the levels of activated ERK1/2 in the nuclear fraction of the cells was observed ($P<0.05$ in comparison to control cells). Cycloheximide overturned the elevation in beta-arrestin1 protein levels following ADs ($P<0.01$ in comparison to control cells). ADs treatment also caused an increase in beta-arrestin1 mRNA levels that was reversed by U0126 (for both experiments $P<0.01$ in comparison to control cells).
Conclusions: The data described in this report demonstrates that by reducing beta-arrestin2 protein levels ADs enables translocation of activated ERK1/2 to the nucleus, thus increasing beta-arrestin1 transcription and expression. The described findings also indicate that beta-arrestins may serve as diagnostic markers for major depression diagnosis and monitoring response to treatment.

P-10-007
A case of neuroleptic malignant syndrome induced by atypical antipsychotics

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Objectives: Miss MK was a 23-years-old girl with mental retardation and a 3-year history of an affective disorder, with psychotic features. She was admitted to our outpatient clinic with severe muscular rigidity, hypertonia of limbs and trunk, mutism and akinesia. She had a history of antipsychotic use. After 12 days of treatment with risperidone quicklet along with olanzapine velotab, both twice a day, she had high fever, muscular rigidity, loss of energy, psychomotor retardation, decrease in sleep, mutism, wounds in her mouth, and sweating. After 3-4 days, she applied to an emergency clinic, where risperidone consta 50 mg and haloperidol 5 mg was injected. Her rigidity and fever continued. She could not walk, eat or talk properly. On admission to our clinic, she had tachycardia, a subfebrile fever, incontinence, increased blood pressure and heart rate. Blood tests showed elevated (520 U/l) values of serum creatine phophokinase (CK) and leukocytosis. In accordance with the clinical symptoms and laboratory results, neuroleptic malignant syndrome (NMS) was diagnosed and she was hospitalized. In addition to supportive medical treatment, her drug therapy included dopa agonist, bromocriptine, titrated to 12.5 mg/day. Her antipsychotic medication had already been stopped for 10 days. CK levels were 470 U/l on the first, and 701 U/l on the third day. Parenteral 40 mgs of dantrolene was started, to which the patient responded well at first and her rigidity partially recovered. At the end of the 3rd day, although she showed some improvement, she did not completely recover. She was then transferred to an intensive-care unit, where she would receive both psychiatric and medical care. We aimed to present a case of NMS in a young female patient and discuss this life-threatening and often misdiagnosed condition in this particular patient. All antipsychotic drugs, typical or atypical, may precipitate the syndrome.

P-10-008
Venlafaxine-associated manic episode in a young depressive patient

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Objectives: Ms. MB, aged 20 years, presented to our clinic with a 4 weeks history of depressed mood, decreased interest in activities, worthlessness, decreased sleep and appetite, loss of energy and feelings of worthlessness. The psychiatric history revealed no previous episodes of major depressive disorder. In the family history, her father had a psychiatric disorder and use of antipychotic medication. The Structured Clinical Interview for DSM-IV Axis I Disorders performed in October 21st, 2008, gave a diagnosis of major depressive episode. The severity of the depressive episode was assessed by the Hamilton Depression Rating Scale and the total score was 20. At that assessment, there were no symptoms suggestive of a switch to a manic episode or a mixed affective state. On the 14th day of treatment, she was noticed to have excessive cheerfulness, over-activity, overtalkativeness, grandiosity and decreased sleep. These symptoms were prominent for the last 7 days. Psychiatric examination also revealed inflated self-esteem, flight of ideas, and distractibility. Young Mania Rating Scale (YMRS) was performed and the score was 23. The clinical picture was distinguished from major depressive episode by her grandiosity, flight of ideas, irritable mood, and self-report of interest in sexual activity. Drug-induced manic switch was considered, and venlafaxine was stopped. Three days later, a reduction in symptoms was observed and her YMRS score was 13. At the end of 2 weeks, she became asymptomatic. Here, a case of venlafaxine-associated manic episode is described. The presence of predisposing factors for bipolarity, such as female gender, early age of onset and a family history of psychotic disease, probably made this patient vulnerable to a switch to hypomania on taking therapeutic dosages of venlafaxine. Prior to starting any antidepressant, clinicians should attempt to obtain risk factors for bipolarity to help in early detection when a manic/hypomanic switch occurs.

P-10-009
Antidepressants inhibit microglial activation: The possibility of a novel therapeutic effect

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Objectives: Microglia has recently been regarded to be a mediator of neuroinflammation by releasing proinflammatory cytokines, nitric oxide in the central nervous system. It is well known that microglia plays an important role in the pathology of neurodegenerative disease such as Alzheimer's disease (AD) and Parkinson's disease (PD). Recent study suggested that depression may be a risk factor of AD. Furthermore, another study suggested that antidepressants may reduce cognitive decline in depressed AD patients. On the other hand, there have so far been only a few studies on the relationship between microglia and depression. Thus, we investigated whether antidepressants can inhibit microglial activation in vitro.
Methods: We investigate effects of antidepressants on the proinflammatory cytokines and nitric oxide (NO) produced by interferon-γ activated microglia (murine 6-3 cell line).
Results: Some of antidepressants significantly reduced the NO production and TNF-α production. We also found that some atypical antipsychotics, which are also used for treatment-resistant depression, had similar effects on microglial activation.
Conclusions: Our results suggest that several kinds of antidepressants have an anti-inflammatory effect via the inhibition of microglial activation, which may play an important role in the pathophysiology of depression.

P-10-010
Effect of antidepressant therapy on brain neurotrophic factors, brain ERK system and cognitive performance of rats exposed to chronic mild stress

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Objectives: Depression is associated with decreased brain neurotrophic factors levels mainly BDNF. Antidepressants therapy was reported to normalize their levels. Chronic mild stress (CMS) in rats is an established model of depression. Objectives; to evaluate the effect of CMS, and chronic therapy with: Fluoxetine (FLX) a serotonin reuptake inhibitor, (SSRI), Reboxetine (REB) a norepinephrine reuptake inhibitor (NRI) on central IGF-1and BDNF systems, and on conjunct signal transduction pathway, MAPK, in rats hippocampus and frontal cortex. and to evaluated the treatments effect on behavioral and cognitive parameters in the Morris Water Maze (MWM) and Object Recognition (OR) tests
Methods: Male rats were exposed sequentially, over a period of 4 weeks, to a variety of mild stressors. Animals received daily i.p. injections of 5mg/kg antidepressants. Control rats received the same treatment without stress. After 4 weeks of CMS animals were exposed to MWM and OR. At the end of the experiment, brains were dissected and the frontal cortex and hippocampus were separated.
Results: In the frontal cortex, FLX treatment in non stressed animals increased BDNF and p-ERK levels. REB treatment of CMS animals, increased BDNF and Trk-B expression, and decreased IGF-1R expression. CMS decreased and FLX treatment normalized p-ERK levels. In the hippocampus, CMS decreased p-ERK and BDNF expression, and both antidepressants normalized the p-ERK and BDNF levels. FLX treatment in stressed rats increased IGF-1R expression. Cognition was not affected by the different treatments except for a minor facilitating effect of FLX on non stressed rats.
Conclusions: Antidepressants (FLX and REB) stimulated the BDNF system in the frontal cortex and the hippocampus of stressed rats. Only FLX activated also the IGF-1 system. Both agents were found to induce activation of ERK which might play a role in the neurotrophic activity of the antidepressants.

P-10-011
The 5-HT2B receptor is necessary for the behavioral and neurogenic effects induced by chronic SSRI treatment

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Objectives: Chronic effects of selective serotonin reuptake inhibitors (SSRI) antidepressants are associated to an increase in hippocampal neurogenesis possibly mediated by neurotrophins. Likewise, extracellular serotonin (5-HT) levels are controlled by the 5-HT transporter, the target of SSRIs. 5-HT transporter activity has been recently shown to be modulated by 5-HT2B receptors. Our aim was to investigate the putative role of 5-HT2B receptors in the effects of a chronic treatment with two different SSRIs (fluoxetine or paroxetine).
Methods: Adult male and female 5-HT2B receptor-knockout (5-HT2BKO) and their 129/SvPas control mice were employed. Behavioural tests combined with immunohistochemistry of BrdU and Ki67, two markers of cell cycle progression, and in situ hybridization of hippocampal BDNF mRNA levels were conducted in order to address the proposed objectives.
Results: The classical response to SSRIs in the novelty-suppressed feeding test was developed by wild type mice, but not by 5-HT2BKO mice. BrdU and Ki67 labeling revealed a significant increase in the hippocampal neuron proliferation and survival in wild-type mice induced after 4 and 8 week, respectively, of SSRI treatment. Nevertheless, no neurogenic effect was observed in 5-HT2BKO mice in the same conditions. In addition, we confirmed a significant increase of BDNF mRNA levels in chronically fluoxetine-treated wild type mice, but no change was seen in 5-HT2BKO mice after the SSRI treatment. Finally, the basal response of 5-HT2BKO mice in the behavioral test as well as their basal hippocampal BDNF levels were similar to those of chronically-SSRI treated wild type mice. This particularity suggests that the absence of 5-HT2B receptors induces a "depressant-resistant like" phenotype.

Conclusions: The 5-HT2B receptors play a role in the effects of SSRI by a likely regulation of the 5-HT transporter activity. Lastly, its potential as a co-target in the treatment of depression is advocated.

P-10-012
Peripheral biomarkers are modulated by early-life stress and antidepressant treatment in a gene-environment interaction model of depressive disorder in rats

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Objectives: Availability of peripheral biomarkers for depression could aid diagnosis and help predicting treatment response. The objective of this work was analysing peripheral biomarker response in a rat gene-environment interaction model of depression. The genetically selected Flinders Sensitive Line (FSL) rats were subjected to maternal separation (MS), since early-life trauma is considered an important antecedent of depression. An open-ended approach based on a proteomic analysis of serum was combined with the evaluation of depression-associated proteins.
Methods: Rats experienced MS and chronically received Escitalopram (ESC) or Nortryptiline (NOR) in food (25mg/kg/day). Serum proteins were separated by 2Delectrophoresis, compared by image analysis, analysed by univariant and multivariant tests and identified by mass-spectrometry. Corticosterone, cytokines, BDNF and CRP were measured by immunoassays. ANOVAs and planned comparisons were performed.
Results: Comparing FSL with the control strain FRL, 25 spots were significantly modulated in proteomic maps; ApoAI and AIV, alpha1-macroglobulin, glutathione-peroxidase, complementC3 and Nf2 were identified. In FSL rats, significant increases were detected in leptin (40%), IL1alpha (400%) and BDNF (37%). CRP levels were significantly reduced (30%). The effect of early-life stress was assessed by comparing FSL+MSvs.FSL. Maps showed 17 significantly modulated spots. Apo-E, alpha1-macroglobulin, complementC3, serotransferrin and hemopexin were identified. The effect of stress in antidepressant response was then evaluated. By comparing FSL+ESC+MSvs.FSL+ESC 22 changed spots were detected on gels, among them albumin, alpha1-macroglobulin, glutathione-peroxidase and complementC3. In MS group significant reductions were detected in IL4 (70%), IL6 (60%), IL10 (90%), CRP (30%) and BDNF (20%). By comparing FSL+NOR+MSvs.FSL+NOR 19 spots showed different levels, such as ApoAIV, pyruvate -dehydrogenase, post-synaptic density protein, alpha1-macroglobulin, serotransferrin and complementC3.
Conclusions: Lipid metabolism and immunity proteins were differently expressed in FSL in comparison with FRL. Exposure to MS induced changes in inflammation and transport proteins specifically displayed in responses to antidepressant treatments. Modulated proteins could suggest biomarker studies in humans.

P-10-013
The TREK-1 potassium channel as a new antidepressant target

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Objectives: Molecular components leading to depression are poorly understood and this pathology still has a life-time prevalence of up to 20%. The neurotransmitter serotonin (5-HT) is a key element in clinically valuable treatments of depression. TREK-1 channels are expressed in regions (prefrontal cortex, hippocampus) that mediate cognitive aspects of depression such as memory impairments and feeling of worthlessness, hopelessness, guilt and suicidality. The objective of this project was to evaluate the involvement of TREK-1 potassium channels in the depression.
Methods: TREK-1+/+ and TREK-1-/- mouse behaviours were studied through five different animal models, namely the Porsolt forced swim, the tail suspension, the conditioned suppression of motility, the learned helplessness and the novelty-suppressed feeding test. The TREK-1 deletion effects on 5-HT neurotransmission were studied by electrophysiological measurements.
Results: Using TREK-1-/- mice, we show that TREK-1 might have an important role in the regulation of depression. The TREK-1-/- mice display an increased resistance to depression in the 5 different models. TREK-1-/- mice display a behavior similar to that of naive animals treated with classical antidepressants such as fluoxetine. In the Dorsal Raphe Nucleus, using unitary extracellular recording we show that most of the 5-HT neurons also express TREK-1 channels. In mutant mice these particular neurons discharge within an amplified frequency, up to 4 Hz instead of 1.5-2 Hz. TREK-1 deletion increases the efficacy of the 5-HT neurotransmission, suggesting that alterations in the functioning and/or the regulation of the TREK-1 channel might alter mood.
Conclusions: Our results designate the TREK-1 channel as a potential target for new antidepressants. Arguing for this hypothesis, we actually develop in our laboratory a new natural and endogenous compound that is able to block TREK-1 channels and behaves as an efficient antidepressant.

P-10-014
The efficacy of Desvenlafaxine 50 mg/d for improving anxiety symptoms in patients with major depressive disorder: A pooled analysis

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Objectives: This analysis was conducted to evaluate the efficacy of desvenlafaxine (administered as desvenlafaxine succinate) for improving anxiety symptoms in patients with major depressive disorder (MDD).
Methods: Data were pooled from 3 double-blind, placebo-controlled clinical trials that were conducted in outpatients diagnosed with MDD without a primary anxiety disorder diagnosis. Patients were randomly assigned to 8 weeks of treatment with desvenlafaxine 50 mg/d (n=462) or placebo (n=471). The primary outcome for this analysis was the 17-item Hamilton Rating Scale for Depression (HAM-D17) Anxiety/Somatization factor, which is the summation of items 10 (Anxiety/Psychic), 11 (Anxiety/Somatic), 12 (Somatic/Gastrointestinal), 13 (Somatic/General), 15 (Hypochondriasis), and 17 (Insight). Patients were assessed the HAM-D17 at the week 1-4, 6, and 8 visits. In addition, patients were assessed with the Covi Anxiety Scale at weeks 2, 4, and 8. Adjusted mean change from baseline scores from the final evaluation (last observation carried forward) were analyzed using analysis of covariance.
Results: Baseline scores for both treatment groups were 7.6 on the HAM-D17 Anxiety/Somatization factor and 6.3 on the Covi Anxiety Scale. Treatment with desvenlafaxine 50 mg/d was associated with a statistically significant degree of improvement compared with placebo on the HAM-D17 Anxiety/Somatization factor (4.1 vs 4.7; P<0.001). A significantly greater degree of improvement was observed on 4 of the 6 items that comprise this factor (Anxiety/Psychic [P<0.001]; Anxiety/Somatic [P<0.05]; Somatic/General [P<0.05]; Hypochondriasis [P<0.05]). Difference between the desvenlafaxine and placebo groups on the Somatic/Gastrointestinal and Insight items failed to achieve statistical significance. A statistically significant degree of improvement in Covi Anxiety total score for desvenlafaxine compared with placebo also was observed (4.9 vs 5.3; P<0.001).
Conclusions: These results suggest that desvenlafaxine 50 mg/d can effectively improve the symptoms of anxiety that are commonly associated with MDD.

P-10-015
Antidepressant psychotropic/ psychological effects in healthy subjects

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Objectives: A wide debate took place on whether antidepressant effects should be considered a general property of these agents or exclusively belong to the context of target symptoms. The aim of the present review was to summarize recent findings regarding antidepressant influences on healthy volunteers, focusing on changes in psychological and cognitive functions.

Methods: To identify studies eligible for this review we searched Medline for all available publications examining these antidepressant effects on healthy volunteers. Twenty seven articles including different classes of antidepressants (SSRIs, NRIs, SSNRIs, NaSSAs, TCAs, MAO-Is) were selected. Inclusion criteria were: 1) studies in which healthy volunteers were treated with antidepressant single dose or chronic treatment; 2) single and double blind randomized placebo-control studies; 3) case-control studies; 4) studies focused on changes in emotional and cognitive functions modulated by antidepressants. Exclusion criteria were: 1) studies in which healthy volunteers were treated with drugs different from antidepressants; 2) studies focused on changes modulated by antidepressants other than in psychological and cognitive functions.
Results: Differences were detected between single dose and chronic treatments. A single antidepressant dose was found to act in two ways: the first leading positive bias in processing emotions, while the second leading a facilitation in recognition of negative emotions, that could be linked to early antidepressant side effects. This double effect of the antidepressants was found in both SSRIs and SSNRIs, suggesting a selective serotonergic implication. Chronic treatments were found to stabilize some acquisitions induced by the single dose, such as an increase in social behaviours. On the contrary, the facilitation in recognition of negative emotions was abolished. Regarding the antidepressant modulation of affective symptomatology and personality traits contrasting results were reported.
Conclusions: Antidepressants exert a significant and detectable influence also in normal subjects. This observation leads to both research and clinical consequences.

P-10-016
Effect of the p38 MAP kinase inhibitor SB-239063 on behaviour and peripheral biomarkers in the Lipopolysaccharide (LPS) induced sickness model in rats

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Objectives: LPS administration in rats induces a characteristic syndrome termed 'sickness behaviour', including profound changes on locomotor activity (LMA) and circulating stress and inflammatory mediators, as shown in previous studies performed in our laboratory. The aim of our investigation was to evaluate whether the behavioural and peripheral biomarker responses induced by LPS could be modified by acute treatment with the potent and selective p38 MAPkinase inhibitor SB-239063.
Methods: Male Sprague-Dawley rats were treated orally with vehicle or SB-239063 (10 and 30mg/kg) 1h before intraperitoneal injection of saline or LPS 125µg/kg. Body weight (BW), food intake (FI) and LMA were assessed for 12h following LPS injection. Inflammation and stress mediators were evaluated in plasma 2, 3, 5 or 14h post-LPS. Data were analysed with ANOVA followed by LSD test or planned comparisons if $p<0.05$.
Results: BW, FI and LMA were significantly decreased by LPS over 12h time period. No changes in these parameters were observed in LPS injected animals pretreated with SB-239063 30mg/kg. IL1beta, IL6, IL10, GM-CSF, IFNgamma and C-reactive-protein levels were increased significantly by LPS but not by treatment with both LPS and SB-239063. LPS treatment significantly decreased Growth-hormone and Prolactin levels and these effects were reversed by SB-236063. TNFalpha, ACTH and corticosterone levels were significantly higher in LPS-treated rats, however SB-239063 failed to attenuate these increases.
Conclusions: These results show that SB-239063 could prevent the modifications induced on behaviour and peripheral hormones/cytokines involved in the pathophysiological effects of LPS. This activity was expressed maximally 2h post-LPS and slowly declined at later time-points, as expected from the pharmacokinetic profile of the compound. Thus, given the similarity between the syndrome induced in rodents and humans, this study suggests that p38 inhibition may be a useful strategy to normalise some major depressive disorder symptoms by dampening elevated cytokine levels reported in subsets of patients.

P-10-017
The involvement of GABAA receptor in the molecular mechanism of combined antidepressant and antipsychotic treatment

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Objectives: One of the promising drug combinations implemented in the treatment of schizophrenia is administration of antipsychotic medications with antidepressant agents from the pharmacological group of selective serotonin inhibitors (SSRIs). In this study we investigated the modulation of GABAergic components and molecular pathways associated with GABA-A receptor function by the combined treatment of SSRI fluvoxamine and typical antipsychotic haloperidol compared to atypical antipsychotic clozapine.
Methods: Frontal cortices, obtained from Sprague–Dawley rats intraperitoneally injected with the combination of fluvoxamine (10mg/kg) and haloperidol (1mg/kg), each drug alone, or clozapine (10mg/kg) for 30 min or 1h, were subjected to subcellular fractionation and consequent protein assessment by Western blot analysis. For in-vitro study we examined GABA-A receptor phosphorylation in cultured primary cortical neurons.
Results: We have found that co-administration of fluvoxamine and haloperidol, and clozapine treatment, decreased the levels of GABA-A beta3 receptor subunit at cytosolic fraction, while increasing it at membranal compartment. Fluvoxamine or haloperidol did not produce changes in GABA-A beta3 receptor subcellular localization. In addition, the combined treatment and clozapine similarly regulated molecular signaling pathways that modulate GABA-A receptor function, such as, PKC and ERK1/2. Furthermore, we demonstrated that short-term treatment (15 min) with haloperidol-fluvoxamine drug combination (but not each drug given alone) and clozapine increased GABA-A beta subunit phosphorylation. Pretreatment of the cells with GF109203X, an inhibitor of PKC pathway, abolished the effect of the combined treatment, or clozapine on GABA-A receptor phosphorylation. However, inhibiting MAPK cascade with PD98059, an ERK inhibitor, did not alter the effect of drugs on GABA-A receptor phosphorylation.
Conclusions: Together, our findings provide evidence that the combined treatment may regulate GABA-A receptor function via PKC dependent pathway. The similarity of our findings with clozapine suggests that this may be part of the mechanism mediating the neurotherapeutic effect against negative symptoms of schizophrenia.

P-10-018
A slow vs standard up-titration with Paroxetine in the treatment of panic disorder

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Objectives: Patients with panic disorder (PD) are described as quite sensitive to the stimulatory properties of some selective serotonin reuptake inhibitors, thus requiring extremely low dosages at initiation of treatment. Our objective was to verify if a slow up-titration with paroxetine was better tolerated than a standard starting dose.
Methods: We conducted an open controlled randomized multicentre study among a primary care setting. Sixty patients (44 females and 16 males) with PD with or without agoraphobia were enrolled and randomized to - a slow up-titration with paroxetine (increments of 2.5 mg/d every 2 days) or a standard one (increments of 10 mg/d every week) – until they have reached a maximum daily dose of 20 mg which was maintained during the whole follow-up period (from the day 18 to the day 42). One-Way ANCOVA model was employed and the level of significance was set in 0.5.

Results: There were no significant differences between the two groups on the tolerability. During the up-titration phase, the slow group exhibited an increased reduction in the number, severity and duration of spontaneous panic attacks when compared to the standard group (-82%, -46%, -36% vs -70%, -35%, -32%, respectively). Anticipatory anxiety was also lower in the subjects treated with the slow up-titration modality (-69% vs -58%). In the same way, the whole duration of feelings of fear related to a panic attack was lower in the slow group (-49% vs -44%). There were no significant differences between the groups on the day 42 but a trend was evidenced to a lower number of other symptoms in the slow group during the follow-up period (p=.06).
Conclusions: Our findings of a reduced symptomatology in the subjects treated with a slow up-titration may suggest a better clinical tolerability by this therapeutic schema though additional double-blind studies are necessary to confirm those results.

P-10-019
Effects of commercially available products of St John's Worth in Serbia on forced swimming and tail suspension tests in mice

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Objectives: In last couple of years use of St. John's wort products for self-treatment of depression is in constant increase in Serbia. Patients buy such products in pharmacies or in health food stores, without consulting physicians about severity of disease or adequate dosage for their condition. The aim of research was to examine the efficacy of domestic commercially available St. John's wort products by forced swimming (FST) and tail suspension test (TST) in mice.
Methods: Experiment was carried out on NMRI mice. Animals were given water solutions of domestic commercially available St. John's wort products HySD, HyD, HyK (200mcg/kg). Control substances were: imported commercially available St. John's wort product HyQ (200mcg/kg), sertraline 10mg/kg and maprotiline 10mg/kg. Substances were administrated intraperitonealy 24h, 5h and 1h before the experiment. Modified FST and TST were used in experiment, with each animal being control to itself. Animal behavior was analyzed by specially designed program.
Results: Results were statistically analyzed with paired t-test. Maprotiline 10 mg/kg significantly decreased immobilization in FST ($p<0,01$). Sertraline 10mg/kg significantly decreased immobilization in TST ($p<0,01$). HyQ statistically significant decreased immobilization in TST($p<0,01$). HySD, HyD, HyK didn't significantly decreased immobilization in FST, nor in TST.
Conclusions: According to results it is noticeable that domestic commercially available St. John's wort products didn't have significant antidepressive effects in performed tests. Depression is not a kind of disease suitable for self-treatment and St. John's wort products can interact with other drugs. For those reasons consulting physician should be obligatory before using St. John's wort in treatment of depression.

P-10-020
Escitalopram as monotherapy in major Depressive Disorder with insomnia

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Objectives: In Major Depressive Disorder common symptom is disturbed sleep, especially early morning wakening (terminal insomnia). Besides treating MDD with antidepressants, hypnotics are frequently used in this indication. The aim of this study is to confirm the efficacy of escitalopram as monotherapy in treating MDD with insomnia, comparing two groups of patients with diagnosed MDD and Insomnia, using Diagnostic and Statistical Manual of Mental Disorders (DSM-IV) criteria.
Methods: First group (n1=31) was treated with escitalopram, in dose of 10mg/day, but in second group (n2=30) has been receiving escitalopram and zolpidem, too, in dose of 10mg/day. Depression symptoms were scored on Hamilton Depression Scale (HAM- D) and severity of insomnia was assessed by Insomnia Severity Index (ISI). Results were evaluated on baseline visit, after two weeks, four and eight weeks of treatment.
Results: Among this sample after two weeks of treatment scores on HAM- D ($p=0,024$) and ISI ($p=0,000$) show statistically significant difference between these two groups and scores were lower in group with adjuvant hypnotic therapy with escitalopram- zolpidem. After four weeks of treatment there were no significant difference in HAM-D ($p=0,149$) and ISI ($p=0,521$) scores between groups. After eight weeks of treatment results were the same (HAM-D, $p = 0,854$; ISI, $p = 1,000$), when clinically was observed significant improvement in patients with symptoms of MDD with co morbid insomnia at baseline visit (HAM-D, $p = 0,001$; ISI, $p = 0,000$).
Conclusions: Results indicated that escitalopram as monotherapy has a great impact in resolving insomnia symptoms in MDD, after four partially and almost completely after eight weeks since baseline. Adjuvant therapy with zolpidem is indicated only in first week of treatment.

P-20
Psychopharmacology I

P-20-001
Mirtazapine and sertraline in pregnancy and lactation

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Objectives: Depression is one of the greatest burdens of disease worldwide. Especially in childbearing years women show a high propensity as. 12% - 16% of new mothers develop major depression (1, 2). Despite adverse effects of depression on mothers and infants, many mothers and physicians refrain from introducing antidepressant treatment in pregnancy or breastfeeding, because of insufficient data on adverse effects. There are only a few studies about treatment with sertraline and mirtazapine in pregnancy and breastfeeding so our results are relevant (5).
Methods: Case report: A 30 year old pregnant woman (week 31) with major depression after a suicide attempt by drug overdose was put on sertraline (100mg) and trazodone (150mg) later mirtazapine (30mg) and sertraline (100mg) and mirtazapine (30mg) during breastfeeding. Drug plasma levels were controlled before and after birth to adapt medication to stabilize the patient´s mood and plasma levels. During lactation sertraline and mirtazapine breast milk-levels were controlled on day 3 and day 11 after birth in fore- and hindmilk.
Results: During pregnancy plasma levels were stable; after birth sertraline increased 2.6-fold and mirtazapine 7.8-fold on day 11, indicating a lower bioavailability of the drugs in pregnancy than postpartum (Tab. 1). Postpartum mirtazapine and sertraline levels in breast milk increased after birth parallel to plasma levels (Tab. 2). Foremilk and hindmilk presented a difference in drug levels, due to the higher fat content of hindmilk. Mirtazapine levels increased more than sertraline levels (Tab. 3).
Conclusions: Plasma levels of mirtazapine in hindmilk are higher than in foremilk, because of the higher fat content of hindmilk, higher milk excretion and increased local blood flow by the end of feeding. Bioavailability of antidepressants during pregnancy is reduced in comparison to postpartum; therefore plasma levels should be controlled before and after birth to optimize dosage (3, 4).

P-20-002
Assessment of 3-methoxy-4-hydroxyphenylglycol (MHPG), cortisol and cognitive performance in patients with anxiety, neuroticism and allostatic load, under treatment with alprazolam

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Objectives: Assessment of saliva and plasma MPHG and cortisol, and cognitive performance in patients with anxiety, neuroticism and allostatic load under treatment with alprazolam.

Methods: Thirty outpatients (18-71 years), with three or more clinically or biochemically verified items of allostatic load, with anxiety levels scored by Hamilton Anxiety Scale of six or more, neuroticism on the NEO-FFI Personality scale of 18 or more, and a neuropsychological test battery monitoring operative memory, sustained attention, executive function and psicomotor performance (through Continuous Performance Test, Digit Symbol, Digit Sapn, Verbal Fluency, Five Points, Revised Taylor Complex Figure and Stroop Test), during each evaluation time point (days -7,0,7,14,28,60,90) and saliva and plasma measures of MPHG and cortisol.
Results: Significant reduction was observed in MPHG and cortisol levels by first week of treatment with alprazolam. In relation to performance-related neuropsychological processes, impact of alprazolam on reduction of anxiety appears to aid complex task performance, though improvement appears to display more evidently in long term style of functioning rather than short term memory tasks
Conclusions: Global variation of clinical, biochemical, and cognitive parameters of allostatic load under treatment with alprazolam, postulate it may favor more adaptive performance in psychological and physical responses to stress challenge

P-20-003
Cycloserine and fluvoxamine combined pharmacotherapy of refractory obsessive-compulsive disorder (OCD) among adolescents

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Objectives: The clinical observation that few patients experience a complete response to SSRI-s or dopamine antagonists suggests that other neurochemical systems are involved in the pathophysiology of OCD.
Methods: We conducted an open study of 12 adolescents (14-17 year old) with refractory OCD. Diagnosis of OCD was confirmed using the SCID-I Clinician Version for DSM-IV Axis I Disorders. Cycloserine was added after 12 weeks of treatment with Fluvoxamine (100 – 150 mg/day). Fixed Dose of Cycloserine 250 mg. was administrated. All patients did not receive any specific psychotherapy.
Results: We found significant improvement in both OCD symptomatology in 9 out of 12 patients (Total score -CY-BOCS decrease, 42 %, P= .003, as well as in overlapping depressive syndromes (average SDS index of Zung score, before was 65, after treatment: 50).
Conclusions: Efficacy of Fluvoxamine and Cycloserine combination may be explained by ability of Cycloserine (a partial agonist at NMDA glutamate receptor subtype) to enhance glutamate activity to OCD target region in brain and/or through the activation of 5-HT relies by receptors.

P-20-004
Decrease in benzodiazepine binding is a possible sign of fear and anxiety

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Objectives: One of the main challenges in pre-clinical studies of novel anxiolytics is the necessity to use several behavioral animal models due to their ambiguity. A scope of reviews mentions contradicting results obtained by different research groups in testing similar animal strains in similar experimental conditions. Thus finding universal sign of fear and anxiety for behavioral tests is necessary. It is known that in Open Field Borodin's modification test (OF) Balb/c mice show lower locomotoractivity comparing to C57Bl/6 mice and this effect is accompanied by decrease in benzodiazepine binding (BZB) at Balb/c mice brains, while BZB level in C57Bl/6 mice remains unchanged. So far it is unclear whether decrease of BZB at stress situation are attributed to genetical background of Balb/c only or OF is not stress for C57Bl/6. To answer for this question we have studied BZB after "Exposure to a cat" test (CAT) as the most dramatic anxiogenic stress for rodent animals.
Methods: Radioreceptor assay H3-flunitrazepam by synaptosomal membranes of mice brains
Results: We have observed decreasing of BZB after CAT at brains of both strains. Therefore we have supposed that the decreasing of BZB is the universal mechanism escorting anxiogenic stresses. To check this hypothesis we have performed several behavioral tests and have found that only anxiogenic stresses, such as Elevated Plus Maze, OF, Light/dark box and CAT, lead to decreasing of BZB at Balb/c mice brains, but depressiogenic test Forced Swimming, does not. Furthermore, we have studied effects on BZB of several used-in-practice anxiolytics with various mechanisms of acting such as Diazepam, Afobazol, Noopept, Gb-115 (only Diazepam is BZD-ligand). We found that these substances do not significantly change BZB at intact Balb/c and C57BL/6 mice brain and prevent decrease of BZB at their brains after CAT.
Conclusions: Decrease in benzodiazepine binding is a possible sign of fear and anxiety

P-20-005
New drugs elaboration for neurodegenerative disorders treatment based on KYNA – receptor binding mechanism

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Objectives: Kynurenic acid (KYNA) is a specific NMDAR and A7AChR antagonist. This compound is a part of tryptophan degradation pathway and is believed to serve as a basis for elaboration of new therapeutic treatments for Alzheimer's and Parkinson's diseases. Therefore the certain mechanism of KYNA-receptor binding is a problem of great importance for drug design. Several data suggest, that stacking interaction (originates from binding of two aromatic rings ϖ-electronic densities) plays alongside with hydrogen, electrostatic, Van-der-Waals and hydrophobic interactions an important role in the initial stage of ligand-receptor interaction.
Methods: Ab initio quantum chemical calculations of stacking-interaction (GAUSSIAN 03) for model systems (benzene - imidazole, KYNA dimers) were carried out.
Results: The calculated KYNA-benzene dimer stacking-interaction energy is 8.8 Kcal/mol. Consistent substitution for KYNA aromatic ring protons (positions 5 and 7) by chlorine atoms gives the increase in stacking interaction energy by 1.5 Kcal/mol. This effect leads to the strengthening of ion channel inhibition according to the experimental data. It is also shown that gradual increase in solvent permittivity leads to gradual decrease in stacking interactions energy. According to our calculations the geometry of non-polar aromatic compounds (benzene dimmer) is parallel-displaced, but for polar compounds (benzene-phenol, imidazole) it changes to T-shaped conformation with the binding energy increasing by 3.3 Kcal/mol. There are several possible conformations for imidazole dimer, the preferred one is determined by the interaction of polar groups. Similar results were obtained for KYNA-imidazole dimer. It was also shown, that stacking-interaction energy in KYNA-imidazole and KYNA-phenol dimers depends of molecules protonation state.
Conclusions: The data obtained strongly support the important role of polar residues in aromatic rings interaction. Polar interactions can affect aromatic residues position and binding energy. The data obtained seems to be interesting for investigation in protein and DNA stability and folding kinetics also.

P-20-006
Influence of Solcoseryl on immune system and inflammatory-destructive processes in central nervous system in patients with cerebral arteriosclerosis

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Objectives: To determine effects of Solcoseryl on immune system and inflammatory-destructive processes in CNS in patients with cerebral arteriosclerosis (CA).
Methods: Basic and follow-up study of immune and inflammatory indices of the blood included 15 patients suffering from with CA at age range 45 to 59 years and 10 age-matched healthy subjects. The patients were treated with Solcoseryl, 10 ml i/v daily during 10 days.

Results: Due to above treatment, the patients with CA displayed an imbalance of main lymphocyte subpopulations, specifically CD8+ and CD16+ cytotoxic cells, the high level circulating immune complexes (CIC) and the high activity of autoimmune reactions in response to neuro antigens. The intensity of such immune disturbances depended on TCD density characteristics of the CA plaques. Interestingly, the blood CIC level was higher in study patients with hypoechogenic plaques (by 1.4 times) as compared to the patients with hyperechogenic plaques and to essentially healthy persons (by 2-2.5 times). The activity of neuroimmune cell reactions decreased after Solcoseryl administration. There was decline in the activity of neutrophiles adhesion in the presence of main myelin protein and albumin that testifies to the positive effect of the drug on pathological cerebral autoimmune reactions in patients with CA.
Conclusions: The immune alterations and autoimmune reactions are associated with TCD echo density of the cerebral atherosclerotic plaques. Positive influence of Solcoseryl on immune system and inflammatory-destructive processes in CNS can be suggested as its administration leads to decrease of CIC level and to normalization of some immune indices of the blood in the patients with CA. Therefore we can recommend the differential use of Solcoseryl depending on TCD echo density characteristics of CA plaques.

P-20-007
Effect of Methylphenidate – a point of view from a cell

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Objectives: The psychostimulant methylphenidate (MPH) is the first choice of drug for treatment in Attention-Deficit Hyperactivity Disorder (ADHD). Nonetheless, the long-term neurochemical effects of MPH treatment are still unknown. Therefore, it seems to be in great importance to understand the mechanism of action of this psychostimulant and its effects on neuronal growth and differentiation. In this study we attempted to disclose whether MPH, a neurotransmitter-transporter inhibitor, also influences neuronal cell gene expression in a dose depend manner.
Methods: Using N2A neuroblastoma cells we investigated the effect of MPH on gene expression levels. N2A were cultured and treated in a dose depend manner with MPH (0/ 0.5/ 1/ 10/ 100 nM) for 2 days. On the second day, cells were trypsinized and RNA was isolated for gene expression profiling analysis. Gene expression level of synaptophysin 1 (Syp1), VAMP2, SNAP25, synaptotagmin (Syt) 1 and 4, syntaxin 1a (Stx1a), tyrosine hydroxylase (TH), acetylcholinesterase (AChE) and norepinephrine transporter (NET) were measured by using quantitative real-time RT-PCR.
Results: N2A treatment with MPH shows an effect on expression level of all investigated genes in a dose dependant manner. Especially synaptic proteins such as Syp1, SNAP25 and Stx1a show a significant decreased gene expression level. In contrast, expression level of NET mRNA is significantly increased.
Conclusions: We could show that MPH influences gene expression profiles in a dose dependant manner, which might be as a result of dopamine and norepinephrine uptake inhibition as well as via different signal transduction. This may point to diverse effects of MPH on cell metabolism, signal transduction and growth than suspected to date.

P-20-008
Comparison of milnacipran, duloxetine and pregabalin in the formalin pain test and in a model of conditioned stress-induced ultrasonic vocalizations in rat

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Objectives: Milnacipran and duloxetine, serotonin and noradrenalin reuptake inhibitors (SNRI's), and pregabalin, a α2-δ1 voltage-gated Ca2+ channel blocker, have shown efficacy in treating fibromyalgia, a condition characterized by wide-spread chronic pain and exacerbated by stress.
Methods: We compared these three compounds in a rat model of acute/inflammatory pain (the formalin test), and in a model of stress-induced ultrasonic vocalization (USV: recording of distress calls around 22 kHz following presentation of a conditioned stimulus previously associated with foot shocks).
Results: In the formalin test, milnacipran dose-dependently attenuated paw elevation and paw licking, with a minimal effective dose (MED) of 2.5 mg/kg i.p. for the latter during the late (i.e. inflammatory) phase. Duloxetine was slightly more potent (MED=0.63 mg/kg). Pregabalin was inactive up to 160 mg/kg for paw elevation, and was only active against paw licking during the late phase (MED=0.63 mg/kg). Milnacipran dose-dependently reduced USV (MED=10 mg/kg, near total inhibition at 20 mg/kg); duloxetine was active at the highest dose tested (20 mg/kg) only. In contrast, pregabalin (2.5-20 mg/kg) had no significant effect.
Conclusions: These results show that milnacipran and duloxetine possess an analgesic activity in the formalin pain model superior to that of pregabalin (both in terms of efficacy and potency). In the stress-induced USV model, milnacipran was more potent than duloxetine, whilst pregabalin was inactive. In conclusion, milnacipran, and to a lesser extent duloxetine, showed favourable activity in two animal models relevant to pain pathologies with a strong stress component, such as fibromyalgia.

P-20-009
Immunological efficacy of preparation cytoflavin in therapy of borderline mental disorders

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Objectives: to assess influence of cytoflavin on parameters of system of immunity in therapy of patients with borderline neuro-mental disorders.
Methods: cytoflavin has been included in therapy of 13 patients with BNMD. The given patients received cytoflavin (intravenously for 10 days), and traditional basic therapy. Group of comparison of patients (13 persons) received only basic therapy. Total number of leukocytes, lymphocytes, subpopulations of immune competent cells with receptors CD3 (Δlymphocytes) was identified, HLA-Dr (B-lymphocytes and activated (T-lymphocytes), CD16 (natural killers), CD4 (Δhelpers/inductors), CD8 (Δsuppressors/effectors), level of CIC, concentration of serum IgΔ IgG, IgΔ
Results: in all examined patients, we have revealed severe asthenic symptoms, headaches, sleep disturbances. Obligate were mnestic disorders and disturbances of other cognitive functions. On the background of treatment with cytoflavin on the part of cellular link of immunity in patients reliable reduction of total number of lymphocytes ($p < 0,05$) has been noticed, trend to increase of number of mature T-lymphocytes (ΔD3+) and T-helpers-inductors (ΔD4+), reliable increase of T-lymphocytes-suppressors (CD8+) ($p < 0,05$) and reliable reduction of amount of natural killers (CD16+). On the side of humoral link of immunity reduction of level of circulating immune complexes, increase in concentration of IgΔand IgΔ reduction of concentration IgG has been noticed. In group of comparison, on the background of traditional therapy, reliable increase of relative number of T-lymphocytes-suppressors (CD8+) ($p < 0,05$), tendency toward increase of amount of B-lymphocytes and active T-lymphocytes (ΔHLA-Dr +) have been noticed.
Conclusions: the greatest efficiency of inclusion of cytoflavin in the complex of therapy has been noticed in patients with severe asthenic conditions caused by combination of borderline neuro-mental disorders and somatic pathology. Clinical dynamic was accompanied by positive dynamic of indices of immunity.

P-20-010
The use of atypical antipsychotic in Saudi Arabia

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Objectives: to study the prescribing practices of atypical antipsychotic drugs in Saudi Arabia psychiatric hospitals and to investigate to what extent atypical antipsychotic, conventional antipsychotic and anticholinergics are prescribed simultaneously in dally clinical practice in Saudi Arabia.
Methods: A pharmaco-epidemoilogical study carried out in 18 psychiatric hospital in Saudi Arabia, 1 day cross sectional observational survey performed, prescription date of five atypical antipsychotic included in MOH formulary ,all prescriptions collected from inpatient, patients who had been using an atypical antipsychotic for more than 6 week will be include to the study.
Results: The study included 865 adult inpatients prescriptions with an antipsychotic drug. 212 prescription included an atypical antipsychotics with rispridone, olanzapine, clozapine, aripiprazole and qutapine. atypical antipsychotics prescribed mainly to the patients diagnosis as psychotic disease(67.9%)while bipolar disorder(32.1%). Male patients(73%) receiving an atypical antipsychotics more than female patients(26.2%) The more accounting prescribing for olanzapine 43% cases,followed by rispridone 33.3%,cases (4.8% 2mg, 21.4% 4mg, 4.1% 6mg) Then clozapine 21.4%cases(150mg1.5%,200mg 7.1%,300mg7.1%,400mg 2.4%,500mg 2.4%), aripiprazole 1.4% cases and qutapine1% cases. One third of patiants prescribed typical antipsychotics 40%. Patients receiving concomitant drug such as mood stabilizer around 70%, while half of patients 50% used anticholenergics. the typical antipsychotic 14%were associated with an atypical antipsychotics.
Conclusions: High percentage of Patients receiving concomitant antipsychotic with atypical antipsychotic and other drugs such as mood stabilizer, antidepressants and anticholinergic, illustrates the gap between clinical trials and utilization in naturalistic settings. The high association of co prescription with a typical antipsychotic has been insufficiently studied for efficacy or safety, and have to be explored further from both a pharmacological and clinical.,

P-20-011
Sexual dysfunction during risperidone and haloperidol treatment in schizophrenia

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Objectives: The aim of this study was to measure rates, frequency and course of sexual dysfunction in patients with schizophrenia during risperidone and haloperidol treatment compared with the general population.
Methods: Sexual dysfunction was assessed by a self-completed gender-specific questionnaire. The authors prospectively investigated 60 female patients who met ICD X criteria for schizophrenia and who received risperidone (N = 30) or haloperidol (N = 30) in a drug monitoring program, and 30 female persons recruited as controls.
Results: At least one sexual dysfunction was reported by 98% of female schizophrenics. Female schizophrenics patients reported less enjoyment, less sexual desire, high problems in having an orgasm and lubrication and also menstrual irregularities than the control group. Sexual dysfunction in female patients was statistically significant associated with negative schizophrenic symptoms. There was no statistically significant difference between the patients taking risperidone and those taking haloperidol in the frequency of these disturbances.
Conclusions: There was statistically significant difference between female patients with schizophrenia and female general population in regard to their sexual dysfunction. Female schizophrenics report much higher rates of sexual dysfunction than the female persons from general population. There was no statistically significant difference between sexual dysfunction and type of antipsychotic medication. Our results show that sexual dysfunction is widespread among female patients with schizophrenia on antipsychotic medications.

P-20-012
Clozapine withdrawal catatonia and neuroleptic malignant syndrome: A case report and literature review

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Objectives: This is a case of clozapine withdrawal in a patient treated with haloperidol. The patient had symptoms of catatonia and neuroleptic malignant syndrome. The symptoms may be explained by the effect of rapid withdrawal, rebound or supersensitivity of the known receptors affected by clozapine. Based upon these information and literature review recommendation regarding clozapine withdrawal are proposed.
Methods: Case Report and literature review
Results: Diagnosis: our case report The patient met criteria for both catatonia and Neuroleptic malignant Syndrome. It may be because patient had two separate disorders or due to their overlapping symptoms. The symptoms overlapping in both disorders and present in this case were: Rigidity; Dysphagia; Mutism; Autonomic abnormality.
Conclusions: 1) Clozapine Withdrawal: the possible mechanisms involved Cholinergic overdrive (Verghese et al 1996) Gamma-aminobutiric acid (GABA) suppersensitivity occurs after withdrawal (Verghese et al 1996) D2 supersensitivity (Yeh et al 2004) Serotonergic hyperactivity (Yeh et al 2004) 2) Treatment: literature vs. the treatment in our case report Lorazepam* (catatonia II) ECT*(catatonia II) Restarting Clozapine* Anticholinergics (10) 3) Safe Clozapine Discontinuation Slow taper down, probably at the same rate at which it was tapered up; Adding an Anticholinergic, especially if side effects necessitate rapid withdrawal because their use will help to ameliorate at least some of the symptoms; Cautious switch to an other antipsychotic since the newer generation of atypical neuroleptics has a receptor profile that differs from that of typical neuroleptics and clozapine. Many of these agents have combined dopamine and serotonin blocking action, with minimal anticholinergic activity.

P-20-013
Anticonvulsant activity and neurotoxicity of 3-(z)-[1-(aniline) ethylidene]-4,5-dihydrofuran-2(3h) – one derivatives in mice

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Objectives: Pharmacotherapy of epilepsy has two main concerns: 1) medication toxicity, 2) uncontrolled seizures (drug resistance) in a noticeable number of patients (up to 30%). In the search for new drugs to treat epilepsy, a series of 3-(Z)-[1-(aniline)ethylidene]-4,5-dihydrofuran-2(3H)-one derivatives were synthesized in order to evaluate their anticonvulsant activity
Methods: Compounds differed in their aromatic ring substitutions on anilinic group as follows: GL-274 (CF3- substitution at position 3), GL-280 (CH3O- at 4), GL-281 (CH3- at 3), GL-283 (CH3O- at 2), GL-287 (Cl- at 3), GL-288 (Cl- at 3 and CH3O- at 4), GL-300 (non substituted), GL-304 (CH3O- at 3) and GL-305 (Cl- both at 4 and 6 positions). Anticonvulsant activity was evaluated using Maximal Electroshock (MES) and subcutaneous Penthylenetetrazol (scPTZ) models in albino mice NMRI strain. Activity at a particular dose was ascribed when at least 50% of mice tested were protected (NINDS/NIH ADD Program). Neurotoxicity of each compound was also evaluated (Rotorod test)
Results: In MES model, active compounds were: GL-304 (30 mg/Kg), GL-300 (30 mg/Kg - 100 mg/Kg), GL-281 and GL-305 (>100 mg/Kg); remainder compounds did not exhibit activity at doses below 300 mg/Kg. GL-288 showed activity (30 mg/Kg) only in scPTZ model. For all of active compounds (in both models), time to peak effect (TPE) was found further 4 hours since drug administration. None of them resulted neurotoxic at doses up to 200 mg/Kg
Conclusions: There is no apparent association between anticonvulsant activity and electronic or lipofilia substituent parameters. Possibly, previous biotransformation reactions are being needed to render active compounds explaining prolonged latency onset observed. Particular substitutions in non active compounds could act by preventing these putative biotransformation reactions. Such proposal needs to be confirmed by additional assays

P-20-014

Monotherapy versus antipsychotic combination in maintenance treatment of schizophrenia: Expirience from two wards in specialized psychiatric hospital "Gornja Toponica"

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Objectives: Although, contemporary aproach to farmacotheraphy of schizophrenia promotes monotherapy as a standard, antipsychotic combination is common in schizophrenia. We followed-up two groups of patients with schizophrenia in Specialized Psychiatric Hospital in order to evaluate therapeutic and adverse effects of antipsychotic monotherapy versus cotreatment with a second antipsychotic.
Methods: Groups with 15 patients were formed on two male psychiatric wards for long-term treatment of schizophrenic patients: first on ward where leading principe was monotherapy (41 of 51 patients recieved only one antipsychotic) and second on ward where almost all of 40 patients recieved antipsychotic combination. Inclusion criteria was: long-term hospitalised patients with schizophrenia on maintenance treatment, duration of desease more than ten years. Follow-up period was three months. There were three visits. We evaluated severity of desease, quality of life, sleep quality, daily activities and participation of patients in different psychosocial therapeutic programs and adverse effects. We used: Positive and Negative Symptoms Scale (PANSS), Clinical Global Impression (CGI), Quality of Life Scale (QOL), Simpson-Angus Scale and Sleep Viusual Analog Scale (VAS).
Results: Results did not show significant differences between two groups on PANSS ang CGI scales. Group on monotherapy showed better results on QOL, Simpson-Angus and VAS scales. Patients on monotherapy were more active in psychosocial activities and social relationships.
Conclusions: Besides obvious advantage of monotherapy regarding clinical outcome in maintenance tratment of schizophrenia, it is clear that compliance is also better due to simplier daily dosage.

P-20-015

Agonism and inverse agonism at the benzodiazepine site of GABAA receptors: The influence on spontaneous locomotor activity and spatial memory

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Objectives: In the present study, we compared the modulation of behavioral responses in two unconditioned experimental methods: spontaneous locomotor activity and water maze, elicited by diazepam, a non-selective agonist, and DMCM, a non-selective inverse agonist at the benzodiazepine site of GABAA receptors.
Methods: Spontaneous locomotor activity in test cage during 30 min was recorded automatically, beginning 15 min after i.p. injections (diazepam, DMCM) without any habituation. The water maze apparatus consisted of a circular 2 m diameter pool with water, containing the escape platform. Male Wistar rats (6-8 animals per group) received apropriate dosis of diazepam, DMCM or vehicle, 20 min before a swimming block, each day for 5 consecutive days. Each block consisted of 4 trials, lasting a maximum time of 120 s. For assessment of reference memory at the end of learning, a probe trial was given 24 h after the last acquisition day. For statistical analysis we used two-way ANOVA.
Results: Diazepam dose-dependently decreased spontaneous locomotor activity. DMCM-treated animals emitted a long plateau phase of activity, characteristic of bimodal influence on locomotion. Diazepam dose-dependently affected water maze acquisition, with path efficiency and latency to reach the platform being significantly impaired by two higher doses. In respect to these two parameters, DMCM-treated animals were close to control during days 2 and 3; however, on the days 4 and 5 there was a significant decrease of path efficiency relative to control. In the probe trial, neither of two actives significantly decreased number of entries to platform zone relative to control.
Conclusions: These results show that amnesic effects of diazepam in the water maze are accompanied by distinct hypolocomotor influences of the agonist in the same dose range. On the other hand, the effects of inverse agonism at the BZ site of GABAA receptors in tests used are not straightforward, and suggest a kind of bimodal influence.

P-20-016

Drop-outs of patients in psychotherapy v/s patients in psychotherapy and pharmacotherapy

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Objectives: The scope of this study was to compare two groups of patients, those who were in a psychotherapeutic program and those in a combined program of psychotherapy and medication, in relation to the number of drop outs that occurred during their period of therapy.
Methods: There were 43 patients: 25 in psychotherapy and 18 in psychotherapy and medication several variables were examined such as sex, age, marital status, education, diagnosis, outcome of therapy and the time when the drop-out happened. (early phase 1-15, delayed phase >15)
Results: There were no differences in relation to the demographic variables.Women outnumbered men as did unmarried and high school educated patients.The dominating age group was (18-28). As for the clnical variables those with diagnosis in the AXIS II of the D.S.M system, outnumbered in both groups. Finally in relation to when the drop-outs occurred, for both groups most patients discontinned during the early phase but with a significant predominance for the patients in psychotherary only (76%) versus those in psychotherapy and medication (61%). The improvement of patients for both groups and for two phases of drop-outs was similar and specifically the absence of slight improvement of those in the early phase in contrast to those in the delayed phase where a greater improvement occurred.
Conclusions: In relation to the results, we could conclude that drop-outs in an early phase for both groups of patients could be attriputed to the essential absence of improvement up to that time in contrast to a substantial improvement in a delayed phase. The predominance during the early phase, of drop-outs of the patients in psychotherapy without medication could be due to the better effectiveness of a mixture of psychotherapy and medications as opposed to psychotherapy alone.

P-20-017

Task related adjustment of motorcortical excitability measured by transcranial magnetic stimulation (TMS) in normal adults pre and post methylphenidate (MPH) administration

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Objectives: Previous investigations using TMS have shown that neural inhibitory motor circuits are disturbed in ADHD and can be restored by MPH. We examined motorcortical excitability in normal adults on task conditions (continuous performance test, CPT), furthermore the influence of MPH on inhibitory and facilitatory motor circuits, with TMS paired pulse protocols using surplus long interval inter-stimulus intervals (ISI).
Methods: Motorcortical modulation was tested with TMS paired pulse protocols employing inhibitory ISI's (3 ms, 100 ms) and facilitory ISI's (13 ms, 50 ms) in 30 normal adults before and on taking MPH. TMS protocols were applied under three CPT conditions: attention, go and nogo. Test persons received 1 mg per kg body weight MPH. Furthermore, MPH serum concentration and clearance were measured. Fifteen of the thirty volunteers were tested neurophysiologically (TMS on task conditions (CPT)) intermediate under medication with 0.5 mg / kg body weight MPH (50% of the final dose). The approval by the national authorities (BfArM, Eudra CT) and the local ethics committee was given.

Results: A 3 X 6 X 2 three factorial MANOVA (n=30, MEP amplitudes as dependent variable) revealed a significant interaction between CPT condition, ISI, and MPH dosage (p=0.032). Subsequent two-factorial ANOVAs and t-Tests showed mainly differences for the go-condition and for facilitatory ISIs. MPH serum concentration and clearance was not correlated with MEP amplitude modulation (Pearson). The intermediate measuring (3 X 6 X 3 factorial MANOVA, n=15) failed to show a significant three-way interaction.
Conclusions: In normal volunteers, task condition, ISI and MPH modulate facilitatory and inhibitory motor circuits. For task conditions and ISIs we found specific effects, MPH seems to act in an unspecific but dosage dependent manner. The design is appropriate for the investigation of task related motorcortical modulation in ADHD, what could be of importance to understand symptoms like "hyperactivity" or "restlessness".

P-20-018
Therapeutic Effects of Alpha-Lipoic Acid in Treatment of Diabetic Neuropathy

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Objectives: Diabetic neuropathy is neurological complication of diabetic disease, which is characterised by peripheral nervous dysfunction, not due to another medical condition. Main clinical signs are feeling of numbness, pins and needles, as well as burning in distal parts of limbs, and neurologically, distal hypoaesthesia.
Methods: This study was conducted at Neuropsychiatric Ward of Military Hospital, Nis, in order to establish correlation between subjective difficulty, objective neurological signs and results of electromyoneurographic test (EMNG). Also, we tended to verify therapeutic effects of Alpha-Lipoic Acid in diagnosed neuropathy. Study included 82 patients diagnosed with diabetes mellitus type II.
Results: Results showed that nearly 60% of patients had subjective difficulties, followed by first signs of sensorial neuropathy in 20% of those patients. Unfortunately, 40% of patients had moderate or severe neuropathy, showed in EMNG results. All the patients with EMNG dysfunction were treated by Alpha-Lipoid Acid, 600 mg pro die (intravenous application), followed by peroral therapy (6 months, 600 mg pro die).
Conclusions: In conclusion, best improvement showed patients with initial stage of neuropathy, and two other groups showed improvement in subjective feeling, but without objective improvement of EMNG parameters.

P-20-019
Psychoneuroimmunomodulating effect of atypical neuroleptics

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Objectives: We have investigated dynamic of psychopathologic symptoms, indices of the immunity in groups of schizophrenic patients in the process of 6-week therapy with atypical neuroleptics Zyprexa (olanzapine) and Rispolept (risperidone).
Methods: Both groups have included 16 patients with paranoid schizophrenia each. We identified formula of blood, number of lymphocytes CD3+, CD4+, CD8+, CD16+, CD20+, CD95+, HLADR+ – phenotypes, concentration of IgM, IgG, IgA, level of circulating immune complexes (CIC). Dynamic of psychopathologic symptoms (sum estimation, subscales of positive, negative and general pathologic symptoms) was assessed in scores with psychometric scale PANSS. Investigation was conducted before treatment with atypical neuroleptics (point 1) and in 6 weeks of the therapy (point 2).
Results: Statistically significant positive dynamic of severity of sum estimation, negative, positive and general pathologic symptoms was noticed by week 6 of the therapy in all patients of both groups. Clinical effect was accompanied by certain positive dynamic of some indices of the immunity: olanzapine exerted normalizing action on number of CD16+-lymphocytes, concentration of IgM; Rispolept – on number of CD20+, CD16+ – lymphocytes and phagocytic activity of neutrophils. Correlation analysis has revealed single reliable interrelationships in point 1 of the investigation between scores of subscales PANSS and biological indices. In point 2 in both groups of patients we detect significant interrelationships in various variants between severity of negative, positive, general psychopathological symptoms and IgM, CIC, CD95+– lymphocytes, polymorphic-nuclear neutrophils.
Conclusions: Alteration of system of the immunity with positive dynamic of its components against the background of favorable clinical dynamic, increase of connection between investigated clinical and biological characteristics in the process of 6-week therapy is to be assessed as optimization of mechanisms of psychoneuroimmunomodulation under influence of atypical antipsychotics.

P-20-020
Effects of Piracetam on brain BDNF, NMDA- and nicotinic receptor content in mice

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Objectives: Neurotrophines, as well as cholinergic and glutamatergic systems are involved in processes of cognition. This work was aimed to study the in vitro and ex vivo effects of well-known cognitive enhancing drug Piracetam on brain NMDA- and nicotinic receptor binding, and BDNF content in mice.
Methods: Radioligand assay was provided using [3H-G]-MK-801 (210 Ci/mmol) and [3H-G]-Nicotine (140) in hippocampal and cortical membrane preparations, respectively. The detection BDNF in both brain structures was measured with sandwich format of ELISA method. Behavioral pattern of animals was evaluated in plus-maze test (Salimov et al., 1995).
Results: Piracetam directly affected the nicotinic cholinergic receptors (nAChRs) in vitro with IC50=8,13 uM and failed against NMDARs. After sub-chronic i.p. administration (300 mg per kilo, once daily for 7 days) the clear effects of Piracetam were observed only in subpopulation of mice with initially low exploratory (EL) activity in maze. In these mice the drug ameliorated the maze exploration by 60%, increased the number of NMDARs by 70%, decreased the number of nAChRs by 40% in comparison with mice demonstrating high activity (EH). Moreover, Piracetam increased both the hippocampal and cortical levels of BDNF in EL mice.
Conclusions: (1) The nicotinic cholinoreceptors can be considered as primary molecular targets for Piracetam and its structural derivatives. (2) The positive modulatory effect of Piracetam on "cognitive deficit" in cross-maze test is accompanied by lowering of nAChRs, growth of NMDARs, and increase of BDNF content.

P-28
Psychopharmacology / Antipsychotics

P-28-001
Trend in antipsychotic polypharmacy: A review of emergency prescriptions in a psychiatric hospital in Romania

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Objectives: To assess the incidence and trends of antipsychotic usage in emergency care in a psychiatric hospital in Romania. To examine the prevalence of antipsychotic polypharmacy in psychiatric patients admitted in emergency.
Methods: Retrospective longitudinall study of the psychiatric charts already archived, of acute psychotic patients with ICD diagnoses of schizophrenia, schizoaffective disorder and bipolar disorder, admitted in ward no# of Hospital "Al Obregia" through the emergency room, during 2006 and 2007. Frequencies, chi-square test, $p<0.05$ statistically significant were used into the analysis.
Results: 42% out of 235 charts received 2 antipsychotics (AP) in the emergency room in the year 2006. The most frequent combination of AP was with two FGA: Halperidol i.m. and Chlorpromazinum i.m. Those patients who received 2 AP in the emergency room were at risk to receive 2 AP in the inpatient period at +7days ($p<0.001$). Patients treated with 2 AP received benzodiazepines with a higher frequency compared with those who received only 1 AP ($p<0.05$). Results showed a decrease in the incidence of use of polypharmacy in the 2007 group of emergency treated patients (12,63% out of 190 charts). The most frequent AP (6 patients) combination was still between Haloperidol and Chlorpromazine in sedative doses. Isolated patients (2 out of 190) received combinations of 2 SGA. Benzodiazepines were added in 93% patients, regardless of AP used. Polipharmacy in our review was not associated significantly with male sex, or with use of anticholinergics.
Conclusions: Psychiatrists still find it necessary to use 2AP in management of acute patients, one of them being most frequently chlorpromazine, and also to add a benzodiazepine to the AP of first choice. Efforts should be made for the use of a "rational polypharmacy", until research results will prove polypharmacy is beneficial.

P-28-002
High dose of escitalopram in the treatment of obsessive compulsive disorder in a teaching hospital in Malaysia

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Objectives: To report a unique experience on the use of high doses of escitalopram in the treatment of obsessive-compulsive disorder with no ill effects.
Methods: A case report study
Results: This is the case of a 22 years old student in the university who presented to our center with symptoms of depressive disorder. Further history revealed long-standing symptoms of obsessive-compulsive disorder with mainly obsessions on religiosity and cleanliness. He took 8 years to present to us having suffered these symptoms since he was 14 years old. He was treated with escitalopram (lexapro™) but had maximum benefit at doses of 50mg per day. There were no ill effects at this dose and his depressive symptoms had resolved. His obsessive-compulsive symptoms were much improved and he was able to continue with his university course and related better quality of life.
Conclusions: This is the highest dose of escitalopram use for the treatment of obsessive-compulsive disorder in our center that we are aware of. Often times, patients with this condition need higher doses of serotonin selective reuptake inhibitor compared to other anxiety disorders. This case highlights that the use of escitalopram in patients with this condition who needs doses higher than 20mg per day appears to be efficacious but more importantly is safe with minimal to nil side effects.

P-28-003
A method to reduce polypharmacy and maximize effectiveness in chronically mentally Ill patients

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Objectives: Clients with severe or chronic psychiatric disorders are often prescribed multiple psychiatric medications. Unfortunately, unnecessary polypharmacy increases the risk of adverse side effects for these clients. The Optimization Program (OP) was developed as a clinical initiative to maximize effectiveness of pharmacological treatment in clients with severe mental illness in an urban Veteran's hospital within the United States. The objectives of the OP were to: 1) identify the most efficacious agents for the treatment of specific target symptoms; 2) minimize risks to safety associated with the use of psychiatric medications; and 3) reduce the utilization of redundant and/or questionably beneficial medications.
Methods: The OP enrolled patients with a psychiatric disorder who were prescribed polypharmacy (at least four psychotropic medications). The patients were evaluated using an instrument which included a five Axis diagnosis, review of current symptoms/problems, relevant mental status findings, and overall assessment of the patient. Each psychotropic medication was then evaluated on a rating scale for target symptoms, tolerance, safety, compliance, and efficacy. Based on the medication ratings, a plan was developed to optimize the pharmacological treatment of the client by systematically eliminating unnecessary medications and optimizing medications that were deemed to be clinically beneficial.
Results: Analysis of 18 patients who consented to have their records reviewed and participated in a follow-up OP visit, found that at the follow-up visit, the number of psychiatric medications was significantly reduced ($p<.000$) from an average of 5.3 to 4.2. During this same time, ratings of the Global Assessment of Functioning had no significant change.
Conclusions: Following a systematic approach to evaluating psychiatric medications, the total number of medications was able to be reduced without apparent increase of symptoms or decompensation of the client. Eliminating unnecessary medications may decrease the risk of harm to clients and reduce overall costs to the medical center.

P-28-004
Antidepressant effect of antipsychotics in Schizophrenia: Comparison of typical and atypical antipsychotic drugs

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Objectives: We conducted a cohort study to compare the effects of atypical and typical antipsychotics on depressive symptoms in patients with schizophrenia.
Methods: The data were drawn from a retrospective, naturalistic, observational study with 96 subjects diagnosed as being affected by schizophrenia during a re-exacerbation phase. The patients were taking typical or atypical antipsychotics. All subjects completed the Calgary Depression Scale for Schizophrenia (CDSS) to rate the severity of the depressive symptoms. The severity of schizophrenic symptoms was rated by the Positive and Negative Syndrome Scale (PANSS) and the Clinical Global Impression (CGI) severity and improvement scales. Assessments of scales above were undertaken at baseline, 8 weeks, 16 weeks and 24 weeks.
Results: Improvement of depressive symptoms was associated with use of antipsychotics, but the improvement was statistically significant just with atypical antipsychotics. The PANSS total score higher than 70 and female gender were significantly associated with the presence of depressive symptoms.
Conclusions: Our findings suggest that atypical antipsychotics seem to be more effective on the depressive symptoms during the course of schizophrenia than typical antipsychotics according with assessment by CDSS and PANSS depressive items.

P-28-005

Obsessive-compulsive symptoms and disorder in patients with schizophrenia treated with clozapine or haloperidol

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Objectives: We conducted a cross-sectional study to compare the prevalence and severity of obsessive-compulsive symptoms (OCSs) and obsessive-compulsive disorder (OCD) in patients with schizophrenia treated with clozapine or haloperidol.

Methods: Structured Clinical Interview for Diagnostic and Statistical Manual of Mental Disorders, Fourth Edition, Axis I disorders-patient edition was used to diagnose schizophrenia and OCD. Sixty subjects, 40 of them using clozapine and 20 using haloperidol, completed the Yale-Brown Obsessive-Compulsive Scale, the Positive and Negative Syndrome Scale (PANSS), and the Clinical Global Impression.

Results: The prevalence of OCD in patients taking clozapine was 20%, whereas the prevalence of patients taking haloperidol was 10%, although this difference was not statistically significant (P = .540). However, patients using clozapine showed higher severity of OCSs than patients using haloperidol (P = .027) did. When schizophrenia patients were divided according to the presence or absence of OCD or OCSs, patients with schizophrenia and OCD or OCSs showed higher severity of schizophrenia symptoms when compared to those with schizophrenia without OCD and OCSs (P = .002). A PANSS total score higher than 70 and the use of antidepressants were predictors of the presence of OCSs or OCD. Schizophrenia patients taking clozapine had higher severity scores both in obsessive-compulsive and schizophrenia rating scales.

Conclusions: These results may support an association between the exacerbation of obsessive-compulsive phenomena and the use of Clozapine.

P-28-006

Translation from the dopamine-glutamate interaction to antipsychotic pharmacotherapy: Role of Homer

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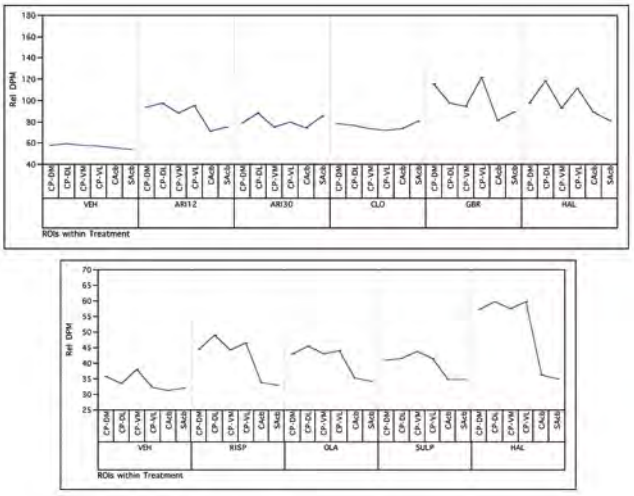
Objectives: A dysfunction in dopamine-glutamate interaction has been suggested as relevant in the pathophysiology of several neuropsychiatric disorders, above all in schizophrenia. Homer1 gene encodes for scaffold proteins which are essential constituent of the postsynaptic density and that have been demonstrated to be linked to both glutamatergic and dopaminergic neurotransmission. Moreover, Homer genes have been putatively implicated in the pathophysiology of behavioral disorders, such as schizophrenia, and in the mechanisms of action of psychoactive drugs. Homer1a, the inducible form of Homer1 gene, is induced in an immediate-early gene-like fashion and its expression is differentially modulated by typical and atypical antipsychotics, likely depending upon their specific impact on the dopaminergic neurotransmission.

Methods: Here we propose a group of studies in which we evaluated Homer1a gene expression following acute and chronic administration of antipsychotics with different antagonist profile at dopaminergic D2 receptors: Haloperidol, Olanzapine, Quetiapine, Sulpiride, Risperidone, Clozapine, Aripiprazole. We investigated gene expression by means of In Situ Hybridization Histochemistry, selecting specific regions of the rat forebrain considered dysfunctional in schizophrenia and that could likely represent the site of action of psychoactive compounds: cortex, caudate-putamen, nucleus accumbens.

Results: The topographical and statistical analysis of data demonstrated that Homer1a is dynamically induced in a region-specific fashion, and that its induction could be directly correlated to the degree of dopamine D2 receptors blockade exerted by each antipsychotic administered. Furthermore, in chronic paradigms, Homer1a induction exhibited a lack of sensitization to the persistent dopaminergic stimulation exerted by antipsychotics.

Conclusions: Therefore, our results suggest that: 1) Homer1a may be implicated in the mechanisms of action of antipsychotics and its pattern of expression may be tightly related to the D2 receptorial profile of each compound; 2) Homer1a may play a key role in the dopamine-glutamate trans-synaptic interaction, whose dysfunction may be at the basis of psychosis.



P-28-007

Acute efficacy of Olanzapine long-acting injection, oral Olanzapine, and haloperidol in patients with schizophrenia: A cross-study comparison

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Objectives: To compare the acute efficacy of olanzapine long-acting injection (OLZ LAI) with that of oral olanzapine (OLZ) and oral haloperidol (HAL) in acutely ill patients with schizophrenia.

Methods: Six-week results from an acute, fixed-dose, randomized, placebo-controlled OLZ LAI study (N=404) were compared with 3 fixed-dose oral olanzapine studies (Oral Study 1: OLZ vs HAL vs placebo [N=335]; Oral Study 2: OLZ vs HAL vs low-dose OLZ [N=431]; Oral Study 3: OLZ vs placebo vs low-dose OLZ [N=152]). All patients had a BPRS score ≥24 (0-6 scale) at study entry. Efficacy endpoints were compared and effect sizes (ES) were calculated for BPRS and/or PANSS.

Results: PANSS Total score decreased by 22.5-24.8 points for OLZ LAI, by 12.3-26.7 for oral, and by 20.0 for HAL. BPRS scores decreased by 14.2-15.4 for OLZ LAI, by 6.7-16.4 for oral, and by 12.4-12.9 for HAL. ES vs placebo for PANSS were 0.7-0.9 for OLZ LAI, 0.3-0.7 for oral, and 0.2 for HAL. ES vs placebo for BPRS were 0.4-0.5 for OLZ LAI, 0.2-0.7 for oral,and 0.1-0.6 for HAL. At study endpoint, weight increased by 2.8-3.9kg for OLZ LAI and 1.7-3.6kg for oral. ≥7% weight gain ranged from 19.1-35.3% for oral and 23.6-35.4% for OLZ LAI.

Conclusions: This analysis indicates that patients treated with OLZ LAI dosages of 210 mg/2 weeks, 405 mg/4 weeks, and 300 mg/2 weeks had a similar magnitude of symptom reduction as patients treated with 5±2.5 mg/day, 10±2.5 mg/day and 15±2.5 mg/day oral OLZ and 15±5mg/day oral HAL during 6 weeks of acute treatment.

P-28-008

Weight gain and changes in metabolic parameters during treatment with antipsychotics and Metformin: A systematic review of clinical studies

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Objectives: Weight gain and changes in metabolic parameters have been commonly reported in patients with schizophrenia and bipolar disorder. Metformin has been evaluated in clinical studies to prevent or reduce weight gain and changes in metabolic parameters in non-diabetic subjects. We undertook a systematic review of the efficacy and safety of metformin in reducing weight gain and changes in metabolic parameters in non-diabetic subjects with schizophrenia or bipolar disorder taking antipsychotic medication.
Methods: Medical databases were searched using terms including 'antipsychotic', 'atypical antipsychotic agent', 'antipsychotic agents', 'antipsychotic-drug' and 'metformin' and 'weight'. Studies reporting weight and/or metabolic outcomes in non-diabetic subjects with schizophrenia and bipolar disorder were included.
Results: 8 randomised, double-blind and 2 open cohort studies (n= 434 subjects), evaluating metformin effects on weight over trials up to 16 weeks were identified. Most participants received olanzapine and 3 studies were in subjects aged <18 years. The adult studies predominantly utilised non-Caucasian subjects with chronic schizophrenia. Weight and lifestyle programmes were provided to all subjects in 7 studies confounding interpretation of the data. In 9 studies metformin addition to antipsychotics either significantly attenuated weight gain compared with control groups or was associated with weight loss. 8 studies measured various glucose parameters. In 3 studies subjects prescribed metformin significantly improved glucose parameters relative to controls. The two studies in first-episode schizophrenia subjects demonstrated the largest effects of metformin on weight and glucose parameters. The most commonly reported adverse effect of metformin was nausea.
Conclusions: Metformin may have some value in reducing or preventing weight gain during treatment with antipsychotic medication particularly in first-episode psychosis, however it has been predominantly studied short term, in non-Caucasian populations. Interpretation of data in chronic schizophrenia is complex but clinical research in longer term studies is warranted using comparisons with lifestyle interventions.

P-28-009

Striatal and Extrastriatal D2/3-receptor binding properties of Quetiapine

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Objectives: The second generation antipsychotic (SGA) quetiapine is of low affinity at D2/3-receptors. Earlier PET-studies reported striatal D2/3-receptor occupancies of about 40%, which is below the proposed efficacy-threshold of 60%. PET-investigations on extrastriatal D2/3-receptor binding of other SGAs uncovered a preferential extrastriatal binding that is possibly caused by low receptor affinities. Thus, we determined the extrastriatal D2/3-receptor binding of quetiapine by PET and the high-affinity ligand [18F]fallypride (FP).
Methods: We examined 16 patients suffering from schizophrenia treated with quetiapine under steady-state conditions (753±317mg/d). One subgroup underwent an FP-scan (180min;221±24.3MBq,bolus injection) approximately at tmax of quetiapine kinetics, another group after a delay of approximately 19h after last drug ingestion. For calculation of receptor occupancies a control group consisting of 8 medication-free patients was scanned under analogous conditions. After movement-correction, normalization and VOI-definition (putamen,NC,thalamus and inferior temporal lobe,GTi), corresponding TACs were measured. BPND-values were calculated using the SRTM with the cerebellum as reference region.
Results: Mean quetiapine-induced D2/3-receptor occupancies ranged from 28±19% (mean±SD) in the putamen to 48±19% in the GTi. (NC:31±18%,thalamus 38±19%). Extrastriatal regions showed significantly higher D2/3-receptor binding than striatal regions (up to +21%). After correction for age-effects, D2/3-receptor occupancy values correlated significantly with intra-scan quetiapine plasma-levels in the NC and on a trend-level in the putamen. There were no significant correlations in extrastriatal regions. The interval between last drug ingestion and PET scan had no significant effect on the occupancy-values.
Conclusions: Our results show a pronounced preferential extrastriatal binding effect under stable quetiapine-treatment. Integrating these data with previous results of other SGAs, low drug affinities at D2/3-receptor appear to be an important mechanism for this effect. Furthermore, extrastriatal regions might be a highly important locus of antipsychotic drug action.

P-28-010

Glutamate and adenosine receptors mediate transcriptional activity induced by dopamine D2 antagonists in the striatum

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Objectives: Antipsychotic drugs are used to alleviate schizophrenia symptoms. Interaction with dopamine D2 receptors is a common characteristic shared by all compounds showing significant antipsychotic activity. However, the exact mechanism that explains this activity still remains elusive. Here we explored the relationship between glutamate, adenosine and dopamine receptors in the modulation of the transcription factor Nur77 in the striatal complex, an important brain structure involved in antipsychotic drug activity.
Methods: Groups of mice received acute injections of vehicle, MPEP (mGluR5 antagonist), SCH58261 (A2A antagonist), eticlopride (ETI; D2 antagonist), a combination of ETI and MPEP or SCH58261 and finally a combination of the ETI, MPEP and SCH58261. On a different set of experiment mice received acute injections of vehicle, MK-801 (NMDA antagonist), raclopride (RAC; D2 antagonist) and a combination of RAC and MK-801. Nur77 mRNA levels were detected by in situ hybridization.
Results: The results show that basal Nur77 mRNA levels are under a NMDA receptor dependent tonic activity. However, it is the activation of metabotropic glutamate type 5 (mGluR5) and adenosine A2A receptor subtypes that mediate eticlopride-induced Nur77 mRNA levels in lateral striatum. The role of glutamate is reinforced by the fact that eticlopride is still able to strongly induced Nur77 mRNA levels in the striatum of mice bearing a genetic deletion of the dopamine D2L receptor isoform.
Conclusions: These data suggest that modulation of the transcriptional status of striatal cells following dopamine D2 antagonist administration mainly results from interaction of the drug at presynaptic D2 heteroreceptors located on glutamatergic terminals. This reduces the inhibitory activity of D2 heteroreceptors over glutamate release, which in turn, increases the activity of postsynaptic glutamate receptors. Thus, modulation of striatal cell activity following D2 antagonist administration does not involve a direct interaction with postsynaptic D2 receptors, but instead rely on presynaptic modulation of glutamate neurotransmission.

P-28-011

Efficacy and tolerability among patients with recent onset schizophrenia treated with long - acting injectable risperidone – PROPEL study

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Objectives: To assess if risperidone long acting injectable (RLAI) could be effective and tolerated in treating recent onset psychosis.
Methods: In a 6-month, open label, flexible dose, multicentre, phase IV trial, 302 subjects with early-onset (2 years or less) schizophrenia were treated with RLAI (25 to 50 mg injection every 14 days). Assessments included PANSS, CGI-S, CGI-C, GAF, ESRS, SF-36 and adverse event (AE) reports.

Results: 86% of subjects completed the study. End dose was 25 mg for 49.5% of subjects, 37.5 mg for 31.0% and 50 mg for 19.5%. There were statistically significant improvements at LOCF endpoint on PANSS total -13 (SD 14, p<.0001); CGI-S -0.8 (SD 1.0, p<.0001); GAF 10.0 (SD 12.5, p<.0001) SF-36; -Physical component summary 3.7 (SD 8.7, p<.001); -Mental component summary 7.7 (SD 11.8, p<.001). CGI-C endpoint ratings: Very much improved 12.6%, Much improved 26.5%, Minimally improved 37.4%, Unchanged 17.3%, Minimally worse 2.7% and Much worse 3.4%. The most common AEs were akathisia (4.6%), extrapyramidal disorder (3.0%), and increased weight (3.0%). 18 subjects experienced 23 serious adverse events; 20 were psychiatric. There was one suicide and one death due to metastatic gastric cancer. Potentially prolactin related AEs were: amenorrhea (n=1); dysmenorrhea (n=1); galactorrhea (n=4); loss of libido (n=1); hyperprolactinemia (n=3); menses delayed (n=2); menorrhagia (n=1). ESRS total score decreased significantly from a baseline mean of 2.0 (SD 5.5) to LOCF endpoint by 1.0 (SD 3.5, p<.0001). BMI increased significantly from baseline mean of 25.3 (SD 4.10) to LOCF endpoint by 0.43 (SD 1.35, p<.0001).
Conclusions: In this open label study of early episode schizophrenia patients treated with RLAI, favorable efficacy and tolerability outcomes were obtained.

P-28-012
Premorbid functioning and treatment response among patients with recent onset schizophrenia: Prospective study with risperidone long-acting injectable – PROPEL study

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Objectives: Some studies suggest a relationship between premorbid functioning and antipsychotic treatment response. Yet these studies were not designed to test this relationship and did not assure drug adherence. We tested the association of premorbid functioning and antipsychotic treatment response after controlling for drug adherence by using a long acting injectable antipsychotic.
Methods: This was a prospective 6-month, open label, multicentre, phase IV trial in subjects with early-onset (<= 2 years) schizophrenia treated with flexible doses of Risperidone Long-Acting Injectable (RLAI) (25 to 50 mg every 14 days). Premorbid functioning was assessed at baseline with Premorbid Adjustment Scale-Structured Interview; efficacy was evaluated with clinician rated PANSS, CGI-S, CGI-C, GAF and subject completed SF 36, and tolerability with ESRS and adverse event (AE) reports. Analyses controlled for baseline scores and demographics.
Results: Using published PAS scoring criteria subjects were grouped into stable-good (n=142), stable-poor (n=116) and deteriorating (n=36) premorbid functioning. All groups showed significant improvement. The stable-good group had the most improvement and also best functioning at baseline on most efficacy measures. The PAS Global Assessment of highest level of functioning item (excellent n=75; good n=117; fair n=78 and poor n=31) also showed a strong association with baseline functioning and improvement and had a significant linear association with meeting Remission in Schizophrenia Working Groups PANSS symptom remission criteria at baseline (40.5%; 35.4%; 28.0%; 10.0%, p=.003) and also attaining and sustaining remission for 3 months during study (47.7%; 49.3%; 29.6%; 22.2%, p=.006). Treatment was equally well tolerated with no major differences associated with premorbid functioning.
Conclusions: In this open label study of early episode psychotic patients treated with RLAI, good premorbid functioning corresponds with greater improvement on both clinician and patient-reported measures.

P-28-013
Psychosis and Hiperprolactinemia in male patient: Contributions to pathophysiology and treatment

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Objectives: The prolactinoma is the most frequent pituitary tumor. The clinical presentation is characterized sterility, neurological and psychiatics symptoms.
Methods: Case Report: We studied one subject with first episode of psychosis. A 34 years old male patient with hallucinations, delusions, high levels of anxiety, obesity and gynecomastia.
Results: During the investigation, magnetic resonance imaging (MRI) showed a sellar mass associated with high prolactin level (935 microg/L) that initially was considered a macroprolactinoma, and treated with Cabergoline and Quetiapine.
Conclusions: The dopamine agonists constitute the prolactinoma treatment. Patients with psychosis have activation of hypothalamic – pituitary – adrenal axis during the acute phase of psychosis. Whether this has any morphological consequences for pituitary gland is currently unknown.

P-28-014
Repeated occurrence of clozapine-induced myocarditis in a patient with schizoaffective disorder and comorbid Parkinson´s disease

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Objectives: Myocarditis is a rare but life threatening adverse effect of clozapine. Some symptoms of myocarditis – elevated temperature, tachycardia and fatigue – appear commonly during the onset of treatment with clozapine and during the dose titration.
Methods: We present a case of a patient with concurrent schizoaffective disorder and Parkinson's disease, who twice developed clozapine-induced myocarditis.
Results: All symptoms disappeared after the discontinuation of the drug.
Conclusions: Early diagnosis, discontinuation of clozapine and supportive therapy of myocarditis lower the risk of a fatal outcome.

P-28-015
Asenapine: An overview of phase I pharmacokinetic studies

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Objectives: Asenapine is a novel psychopharmacologic agent being developed in a sublingual formulation for schizophrenia and bipolar disorder. We describe the results of a series of Phase I trials of asenapine, performed mainly in healthy volunteers.
Methods: In separate trials, we assessed the pharmacokinetic (PK) interactions between asenapine and several cytochrome P450 (CYP) modulators and the glucuronyl transferase (UGT) inhibitor valproate; asenapine PK in patients with varying degrees of renal or hepatic impairment; and the effects of water intake and concomitant smoking on sublingual asenapine absorption.
Results: Following single dosing, maximum plasma concentrations occurred at 0.5–1.5 hours and elimination half-life was approximately 24 hours. Asenapine exposure was increased by coadministration with fluvoxamine, but was otherwise minimally affected by standard CYP modulators and valproate. There were no significant correlations between creatinine clearance and asenapine exposure in patients with renal impairment of varying severity. Mild or moderate hepatic impairment did not affect asenapine exposure, but severe impairment increased exposure 7-fold. Mean asenapine exposure with water taken at 10 versus 30 minutes postdose differed by ≤2%; with water taken at 5 or 2 minutes postdose, asenapine exposure was decreased approximately 10% and 20%, respectively; concomitant smoking did not affect exposure.

Conclusions: These Phase I studies demonstrate that sublingual asenapine PK parameters are largely unaffected by interactions with most standard CYP modulators or a UGT inhibitor, or by renal impairment, mild or moderate hepatic impairment, water taken ≥10 minutes postdose, or concomitant smoking.

P-28-016
Amelioration of MK-801-induced cognitive impairment by lurasidone in mouse contextual fear conditioning test

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Objectives: Lurasidone is a novel atypical antipsychotic drug under clinical development. Previously we have reported that lurasidone markedly reversed MK-801-induced memory impairment in the passive avoidance test, the Morris water maze test, and radial-arm maze test. These findings suggest that lurasidone show not only a less cognitive impairing activity, but also more pro-cognitive effects comparing with the other atypical antipsychotics in these test.
Methods: We investigated the effect of lurasidone and other antipsychotics on cognitive impairment induced by MK-801 in the mouse contextual fear conditioning (CFC) test. Mice were conditioned in a conditioning chamber with electrical foot shock (0.5 mA, 2 sec). One week after the conditioning, the mice were placed in the same chamber, and the freezing behavior was observed with freezing analyzer for 5 min (ImageJ FZ2, O'hara Instrumental, Japan). Antipsychotics and MK-801 were administered 1 hr and 0.5 hr before the conditioning session, respectively.
Results: MK-801 (0.1 mg/kg, s.c.) shortened duration of the freezing behavior, suggesting MK-801 impaired learning and memory in the CFC test. Lurasidone (1-10 mg/kg p.o.) dose-dependently and potently reversed MK-801-induced impairment of learning and memory. Risperidone also showed a cognition-improving effect in this test, but compared to the effects of lurasidone, it was a mild effect and there was no dose-dependency. Olanzapine (0.3-3 mg/kg p.o.) did not improve amnesia induced by MK-801.
Conclusions: In accordance with the previous findings, the present results demonstrate that lurasidone has more potent cognition-improving effects than the other atypical antipsychotics such as risperidone. It is suggested that lurasidone would be more effective in treating cognitive impairments in clinic.

P-28-017
Quetiapine Alleviates the Cuprizone-induced Demyelination and promotes the Remyelination Following Withdrawal of Cuprizone

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Objectives: Schizophrenia is a brain disease featured with alterations in oligodendrocytes (OLs) indicated by recent human studies employing new magnetic resonance imaging techniques and micro-array analysis. However, there is little information available regarding effects of antipsychotic drugs on OLs. The present study reported effects of quetiapine (QTP, a new atypical antipsychotic) on demyelination, demyelination-related cellular responses, and remyelination in the brain of C57BL/6 mouse.
Methods: C57BL/6 mice were fed a 0.2% cuprizone-containing or control diet for 5 weeks and then removed to allow for remyelination. QTP (10mg/kg/day, P.O) or saline was administrated to the mice in demyelination for 5 weeks or in remyelination for 2 weeks. We used a combination of Luxol fast blue (LFB) myelin staining and immunohistochemistry for myelin basic protein (MBP) to detect the demyelination and remyelination; Glutathione Transferase-Pi (GST-pi) protein and NG2 protein as mature OL and OL progenitor cell marker; CD11b and Glial fibrillary acidic protein (GFAP) as markers of microglia and astrocyte, respectively.
Results: As in previous studies, this treatment induced a consistent and evident demyelination and dramatic decreases in myelin producing OLs in brain white matter. In response to demyelination, microglias and astrocytes were activated in the demyelinated sites where adult OL precursor cells dramatically increased. However, all these pathological changes were prevented or alleviated in the mice co-administered with CPZ and QTP. Recovery occurred automatically in demyelinated sites during a two-week period following the withdrawal of CPZ. This recovery was promoted by QTP treatment, indicated by more completed remyelination and a higher ratio of myelin producing OLs over OL precursor cells in demyelinated sites, as compared to vehicle-treated mice.
Conclusions: these findings suggest a new neural mechanism of antipsychotic action of QTP, and help to establish a role for oligodendrocytes in the etiopathology and treatment of schizophrenia.

P-28-018
Risperidone long-acting injectable and Olanzapine pamoate: Review of short- and long-term safety data

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Objectives: To review safety and tolerability of Risperidone Long Acting Injectable (RLAI) and olanzapine pamoate (OP) in the treatment of schizophrenia.
Methods: Systematic review of published data of RLAI and OP in patients with schizophrenia.
Results: For RLAI there is an estimated exposure of 678,000 patient-years since 2001, currently less knowledge is available for OP. In the majority of RLAI studies the severity of movement disorders was unchanged compared to baseline or further reduced during treatment. RLAI was associated with a weight gain of 0.5 to 2kg in short-term studies and up to 3kg after one year with no further weight gain apparent in patients receiving RLAI for up to 4 years. In addition, RLAI did not negatively affect lipid and glucose metabolism. Hyperprolactinemia associated with RLAI (2-7%) on average decreased over time and was not necessarily related with symptomatic side effects (1.3-2.5% over 12 weeks). OP's safety profile includes low potential for extrapyramidal side effects, but an unfavorable metabolic profile. In short and longer-term studies, significant changes in fasting glucose, total cholesterol, LDL and triglycerides were observed versus placebo. Mean baseline-to-endpoint changes in body weight were between 2.8±4.1 and 3.9±4.9kg in an 8-week study. In addition, for OP a Post-injection Delirium Sedation Syndrome (PDSS) has been reported in 1.4% of patients. Potential risk of PDSS exists for each injection regardless of duration of treatment. No cases of PDSS have been described with RLAI.
Conclusions: RLAI safety and tolerability profile is similar to that associated with oral risperidone. Overall tolerability profile for olanzapine pamoate seems to be similar to that for the oral formulation; however, with olanzapine pamoate there is an additional risk of PDSS.

P-28-019
Descriptive analyses of the aripiprazole arm in the Risperidone long-acting injectable versus quetiapine relapse prevention trial (ConstaTRE)

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Objectives: A recent randomized, open-label, relapse prevention trial (ConstaTRE) of risperidone long-acting injectable (RLAI) versus quetiapine and the oral atypical antipsychotic aripiprazole was carried out. Here we report the descriptive analysis of the aripiprazole arm.

Methods: Clinically stable adults with schizophrenia or schizoaffective disorder previously treated with oral risperidone, olanzapine, or oral conventional antipsychotic, in whom a switch in treatment was indicated, were randomized to treatment with RLAI (25, 37.5, or 50 mg/two weeks), quetiapine (initiated at 300–400 mg/day), or aripiprazole (in countries where available, initiated at 10–30 mg/day). Efficacy, safety and tolerability were monitored for up to 24 months of treatment. Due to the small group of patients treated with aripiprazole only descriptive analyses were performed between treatment groups.
Results: 45 patients were treated with aripiprazole and 329 patients with RLAI. Relapse occurred in 27.3% aripiprazole and 16.5% RLAI-treated patients. Kaplan-Meier estimates of mean relapse-free period were 314 versus 607 days for aripiprazole and RLAI patients, respectively. Full-remission was achieved by 34% aripiprazole and 51% RLAI patients and was maintained until the end of the trial by 30% aripiprazole and 44% RLAI patients. According to CGI-S, there were 61% aripiprazole and 62% RLAI patients moderately ill or worse at baseline, and 59% aripiprazole and 45% RLAI at endpoint, respectively. Tolerability was generally similar between treatment groups. Gastrointestinal disorders were more common in aripiprazole-treated patients (6% RLAI vs. 22% aripiprazole). Weight gain (7% RLAI vs. 4% aripiprazole), extrapyramidal AEs (10% RLAI vs. 4% aripiprazole), and possibly prolactin-related AEs (5% RLAI vs. 0 aripiprazole) were more common with RLAI treatment.
Conclusions: Time-to-relapse in stable patients with schizophrenia or schizoaffective disorder tended to be longer in RLAI-treated patients when compared with aripiprazole-treated patients. Both treatments were generally well tolerated.

P-28-020
Functional improvement in Schizophrenia and schizoaffective disorder: Results from the Risperidone long-acting injectable versus quetiapine relapse prevention trial (ConstaTRE)

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Objectives: To report the functional improvement results from an open-label, randomized-controlled, relapse prevention trial (ConstaTRE) in stable patients with schizophrenia or schizoaffective disorder treated with risperidone long-acting injectable (RLAI) or the oral atypical antipsychotic quetiapine.
Methods: Clinically stable adults with schizophrenia or schizoaffective disorder previously treated with oral risperidone, olanzapine, or oral conventional antipsychotics, in whom a switch in treatment was indicated, were randomized to treatment with either RLAI (25, 37.5, or 50 mg every two weeks) or quetiapine (initiated at 300–400 mg/day) for 24 months. Functional improvement was assessed using the Social and Occupational Functioning Assessment Scale (SOFAS) and two quality-of-life (QoL) measures (Short-Form 12 [SF-12] and Schizophrenia Quality-of-Life Scale Revision 4 [SQLS-R4]).
Results: 710 subjects were randomized to treatment with RLAI or quetiapine (n=355 patients/group). 327 patients randomized to RLAI and 326 patients randomized to quetiapine were included in the efficacy analyses. Baseline demographics were similar between treatment groups. Relapse occurred in 16.5% RLAI and 31.3% quetiapine patients. A total of 105 RLAI and 107 quetiapine patients dropped out of the study for other reasons than relapse, most commonly due to withdrawal of consent. A significant improvement in SOFAS, SF-12, and SQLS-R4 scores was observed from baseline to month 24 with both RLAI and quetiapine. At months 6, 12, and endpoint, SOFAS had significantly increased more for RLAI than quetiapine ($p<0.05$).
Conclusions: Improvement in functional status and QoL from baseline was observed with both RLAI and quetiapine. Among stable patients with schizophrenia or schizoaffective disorder, the likelihood of functional improvement appears to be higher in those switching to RLAI.

P-29
Psychopharmacology / Antidepressants

P-29-001
Tandospirone augmentation therapy is useful in depressed patients with inadequate response to SSRIs or SNRIs (Subsequent report)

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P-29-002
Frequency of treatment-emergent sexual dysfunction in outpatients with major depressive disorder treated with either duloxetine or a selective serotonin reuptake inhibitor antidepressant: 8-week observational data

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Objectives: To compare the frequency of treatment-emergent sexual dysfunction (TESD) in outpatients receiving 8 weeks of treatment with duloxetine hydrochloride or selective serotonin reuptake inhibitor (SSRI) monotherapy for major depressive disorder (MDD).
Methods: Male and female sexually active outpatients (≥18 years of age) with a primary diagnosis of MDD (ICD-10 or DSM-IV-TR criteria) and without sexual dysfunction will be enrolled in this prospective, observational study (study code F1J-MC-B019). Initiation of, and changes to treatment are at the discretion of the physician and patient. These are moderately depressed (CGI-S≥4) non treatment-resistant patients presenting with a current, new or first episode of MDD within the normal course of care. Assessment tools include the Arizona Sexual Experience Scale (ASEX), the Clinical Global Impressions of Severity (CGI-S) scale and the EuroQol questionnaire (EQ-5D). Patients will be assessed at study entry, and weeks 8, 16 and 24, with ongoing records of ASEX and medication data throughout the study.
Results: At the time of writing, approximately 1500 patients have been enrolled from Austria, mainland China, Hong Kong, Israel, Malaysia, Mexico, Philippines, Saudi Arabia, Singapore, Taiwan, Thailand and the United Arab Emirates. Patient enrolment will cease November 28, 2008. We will report comparative data on the frequency of TESD in this study population, and the changes from baseline in efficacy and health outcomes measures.
Conclusions: These observational data supplement those from randomized, controlled clinical trials, and facilitate insight into TESD with antidepressant use in actual clinical practice settings from a diverse range of countries.

P-29-003
Anxiolytic - and antidepressant-like effects in multiple preclinical assays shown by Lu AA21004, a novel drug

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Objectives: The aim was to characterize Lu AA21004 in a number of preclinical models with predictive validity of anxiolytic and antidepressant activity. Lu AA21004 is a novel antidepressant with a unique pharmacological profile. Lu AA21004 is a 5-HT3 receptor antagonist (human (h)5-HT3 receptors Ki=4.5 nM), a 5-HT1A receptor agonist (h5-HT1A receptors: Ki=15 nM), and a 5-HT transport inhibitor (h5-HTT IC50=5.4 nM) that increases extracellular serotonin (5-HT), norepinephrine, dopamine, and acetylcholine levels in vivo in rat brain regions relevant to mood disorders.
Methods: Antidepressant potential was assessed in the mouse forced swim and tail suspension tests, and anxiolytic potential was assessed using the mouse marble burying, rat conditioned fear, and rat social interaction tests. The behavioral responses in the rat were related to 5-HTT occupancy levels measured by ex vivo binding techniques using 3H-DASB as the radioligand.

Results: Lu AA21004 produced dose-dependent antidepressant- and anxiolytic-like effects in mice (minimal effective dose [MED] 16, 17, and 3.9 mg/kg s.c. in the forced swim, tail suspension, and marble burying tests, respectively). Lu AA21004 showed significant and dose-dependent anxiolytic-like effects (MED 10 and 1.0 mg/kg p.o. in the conditioned fear and social interaction tests, respectively) at very low 5-HTT occupancy levels (approximately 45% and <5%, respectively). The selective serotonin reuptake inhibitor paroxetine was inactive in the conditioned fear test and the dual 5-HT and norepinephrine reuptake inhibitor duloxetine and the 5-HT3 receptor antagonist ondansetron were inactive in all tests of anxiolytic activity.
Conclusions: Lu AA21004 showed a robust antidepressant- and anxiolytic-like profile in multiple preclinical assays. The profile was different from other antidepressants, which suggests that Lu AA21004 may be a unique therapeutic agent.

P-29-004
Lu AA21004, a novel drug for the treatment of mood disorders: In vitro profile

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Objectives: Lu AA21004 emerged from a research program designed to identify a drug with a unique pharmacological profile that would significantly benefit patients with mood disorders. The aim of the present study was to determine the in vitro profile of Lu AA21004 using cloned and native serotonin (5-HT) receptors and 5-HT transporters, and a series of other receptors, enzymes, ion channels and transporters.
Methods: Binding affinities for human and rat 5-HT receptors and transporters were determined by displacement binding of appropriate [3H] ligands at cloned and native receptors and transporters. Functional antagonism at 5-HT3-receptors was determined by electrophysiological recordings in Xenopus oocytes expressing the receptor.
Results: Lu AA21004 showed high affinity binding for the cloned human 5-HT3A receptor (Ki=4.5nM) and potent functional antagonism at cloned rat and human 5-HT3A receptors (IC50=0.2nM and IC50=20nM, respectively). Lu AA21004 showed affinity for the cloned human 5-HT1Areceptor (Ki=15nM) but was considerably less potent at native rat 5-HT1A receptors (Ki=230nM). In a functional [35S]GTPgammaS binding assay, Lu AA21004 demonstrated agonism (intrinsic activity=96%) at the cloned human 5-HT1A receptor. Lu AA21004 showed high affinity binding for the cloned human 5-HT transporter (Ki=1.6nM) and similar potent activity when uptake inhibitory potency was measured in rat brain synaptosomes (IC50=5.3 nM). At 1microM, Lu AA21004 showed no significant activity when tested against 70 other receptors, enzymes, ion channels and transporters.
Conclusions: Lu AA21004 is a 5-HT3-receptor antagonist, a 5-HT1A receptor agonist, and a 5-HT transporter inhibitor. This in vitro profile may result in a unique antidepressant and anxiolytic agent.

P-29-005
Lu AA21004, a novel potential treatment for mood disorders: In vivo effects

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Objectives: There are unmet needs in the treatment of depression and anxiety, despite the availability of selective serotonin reuptake inhibitors (SSRIs) and serotonin and norepinephrine reuptake inhibitors (SNRIs). Lu AA21004 emerged from a research program designed to identify a drug with a unique pharmacological profile that would significantly benefit patients with mood disorders. The aim of the present study was to determine the in vivo pharmacological profile of Lu AA21004 in preclinical animal models.
Methods: In vivo studies were conducted using male Sprague Dawley rats. Acute effects of Lu AA21004 on neurotransmitter [serotonin (5-HT), norepinephrine (NE), dopamine (DA), acetylcholine (ACh)] levels were measured by microdialysis in the prefrontal cortex and the ventral hippocampus of freely-moving rats. Subchronic effects of Lu AA21004 (3-day s.c. administration via osmotic minipumps) on 5-HT levels in the ventral hippocampus and 5-HT transporter (5-HTT) occupancy of Lu AA21004 were assessed using microdialysis and radioligand 3H-MADAM binding, respectively. Effects of Lu AA21004 on the 5-HT3 receptor were studied by measuring inhibition of the Bezold-Jarisch-like reflex in rats.
Results: Lu AA21004 (2.5-10 mg/kg, sc) significantly increased extracellular 5-HT, NE, DA and ACh levels. After 3 days of treatment, Lu AA21004 (5 mg/kg/day, sc) increased 5-HT levels significantly at only 40% 5-HTT occupancy. Lu AA21004 dose-dependently inhibited the Bezold-Jarisch-like reflex.
Conclusions: The microdialysis results support a profile of Lu AA21004 that differs fundamentally from SSRIs. Enhanced neurotransmitter levels produced by Lu AA21004 may be related to its 5-HT3 receptor antagonist and 5HT1A agonist properties, since these receptors are involved in the regulation of neurotransmitter release in multiple brain regions. The preclinical in vivo pharmacological profile of Lu AA21004 suggests a unique antidepressant agent that may benefit patients with depressive disorders.

P-29-006
The effects of Antidepressants on BDNF productions in PBMC culture of healthy subjects

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Objectives: We explored the effects of antidepressant agents on brain-derived neurotrophic factor (BDNF) production in peripheral mononuclear cells (PBMC) of healthy subjects.
Methods: Four different antidepressant with 3 different drug levels (amitrylptyline: 10 ng/ml, 100 ng/ml, and 1 μg/ml, paroxetine: 5 ng/ml, 50 ng/ml, and 500 ng/ml, mirtazapine: 5 ng/ml, 50 ng/ml, and 500 ng/ml, and venlafaxine: 15 ng/ml, 150 ng/ml, and 1.5 μg/ml) were administered into culture grounds, and then the unstimulated and LPS+PHA stimulated whole blood was cultured for 48 hours at 37° C. BDNF production was examined in culture supernatants of unstimulated and stimulated whole blood.
Results: The BDNF productions were not significantly altered in unstimulated cultures with increasing concentrations of 4 antidepressant agents. There were not significant changes of stimulated BDNF productions by 4 antidepressant agents. However, mirtazapine slightly increased BDNF productions in stimulated culture, which was not statistically significant. There were no significant differences between amitrylptyline, paroxetine, mirtazapine, and venlafaxine.
Conclusions: Our findings suggest that some antidepressant agents, including amitryptiline, paroxetine, mirtazapine, and venlafaxine, cannot significantly alter BDNF productions of peripheral blood cells. Increased BDNF after antidepressant treatment could not be due to its productions of peripheral blood cells.

P-29-007
Imipramine reverses oxidative damage in rat hippocampus in the absence and presence of chronic inhaled ozone: Support for a role of oxidative stress in depression

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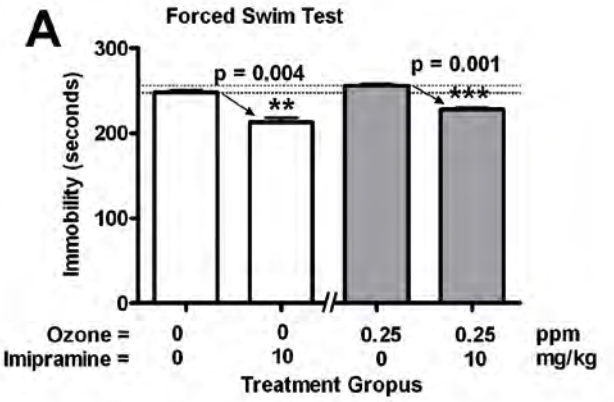
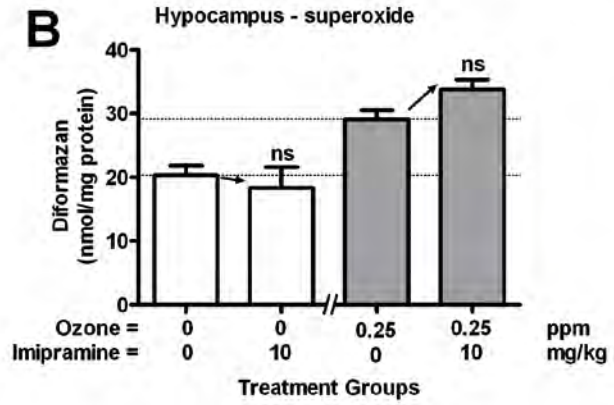
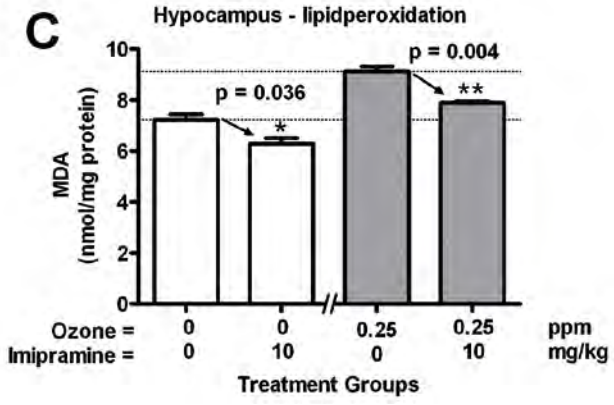
Objectives: Oxidative stress may play a role in depression. Antidepressants are believed to be neuroprotective and to modulate neuroplasticity. This study investigated whether chronic ozone exposure evokes depressogenic and pro-oxidant effects in the rat hippocampus, and whether the antidepressant imipramine modulates these cellular and behavioural changes.

Methods: Sprague Dawley rats were exposed daily for 4 hours to 0 or 0.25 ppm ozone, continuing for 30 days. On the penultimate day, rats were exposed to 15 min forced swim in the forced swim test (FST) 24 hours before final FST testing and given 0 or 10 mg/kg imipramine intraperitoneal (IP). Rats then received their last ozone exposure, followed by the corresponding 2nd and 3rd IP imipramine doses 5 and 1 hours prior to the FST, followed by a final 5 min FST session. Thereafter rats were decapitated, the hippocampi dissected, snap frozen and stored at -70°C until use. Subsequently, hippocampal superoxide (diformazan) and lipidperoxide (MDA) were determined.
Results: Imipramine significantly reduced immobility in the absence and presence of ozone. Ozone increased hippocampal superoxide, with imipramine having no effect. However, while ozone increased lipid peroxidation, imipramine significantly reduced lipid peroxidation in the absence and presence of ozone exposure.
Conclusions: As expected, the results of the current study confirm the antidepressant-like activity of imipramine in Sprague Dawley rats and that ozone increases oxidative stress by increasing superoxide in the hippocampus. Importantly, imipramine reduced both ozone-induced lipid peroxidation and oxidative damage. The study provides further support for a role of oxidative stress in depression and for a protective action by antidepressants on cellular oxidative stress.







P-29-008
Duloxetine versus escitalopram in the treatment of major depressive disorder and generalized anxiety disorder dual diagnosis

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Objectives: We focused upon the evaluation of duloxetine efficacy in treating MDD and GAD dual diagnosis patients, using an selective serotoninergic reuptake inhibitor comparator, escitalopram.
Methods: A 15 patients group, 10 male and 5 female, mean age 32.7, admitted in our clinic, that met the DSM IV TR criteria for both MDD and GAD, were distributed in two groups, receiving either duloxetine 60 mg daily dose (n=7) or escitalopram 20 mg daily (n=8). We assessed patients evolution under treatment every two weeks for 6 months using Hamilton Depression Rating Scale 17 items (HAMD-17), Hamilton Anxiety Scale for Anxiety (HAMA), Global Assessment of Functioning Scale (GAF) and Clinical Global Impressions (CGI). Inclusion criteria: patients aged between 18 and 65, no prior contact with either duloxetine or escitalopram, HAMD over 20, HAMA over 25, GAF under 70, CGI at least 4. Exclusion criteria: severe general medical conditions, axis II dual diagnosis, suicidal behaviors at the baseline.
Results: In the intent-to-treat (ITT) and last-observation-carried-forward (LOCF) analysis, differences between groups became statistically significant at week 4, duloxetine treated patients improved better as HAMD-17 (-10.8 points, $p<0.05$) and HAMA (-11.9 points, $p<0.05$) scores reflected. The end-point HAMD-17 and HAMA scores were smaller in the duloxetine treated group (7.7 versus 9.1, $p<0.05$). Endpoint CGI (1.5) and GAF (92) scores were also better in duloxetine treated group ($p<0.01$). There was recorded one dropout in the escitalopram treated group, due to persistent sexual dysfunction.
Conclusions: The 6 months clinical trial proved duloxetine superior to the active comparator, escitalopram, in the treatment of MDD and GAD dual diagnosis. Duloxetine improved both depressive core symptoms and generalised anxiety after 4 weeks of treatment.

P-29-009
Milnacipran efficacy in major depressive disorder and alcohol dependence dual diagnosis

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Objectives: To validate the effect of milnacipran in improving depressive symptoms, daily alcohol intake and quality of global functioning.
Methods: A group of 14 inpatients, 10 male and 4 female, medium age 38.5, diagnosed with Major Depressive Episode (DSM IV TR) and alcohol dependence (also according to DSM IV TR criteria) were evaluated for 24 weeks using HAMD- 17 items, CGI-I, CAGE Questionnaire, Inventory for Drug Taking Situations (IDTS)- alcohol focused version and GAF. Milnacipran was administered in 100 mg daily in combination with B complex vitamin therapy and carbamazepine (flexible dose 200-600 mg daily). Inclusion criteria were: documented history of alcohol dependence; actual depressive major episode has a medium or severe intensity, without psychotic features. Exclusion criteria: seizures or psychotic disorders in personal history, milnacipran use before this admission, severe hepatic impairment.
Results: A significant decrease in HAMD score appeared after 4 weeks (-8.4 points to baseline) and a continuous decline was recorded throughout the length of study until -18.2 points after 6 months. This evolution was paralleled by CGI-I improvements (-2 to baseline in the third week and -3.5 at the end of the study). CAGE score also decreased (-2.5 points at three weeks) but didn't maintain during all the lenght of the study, having a more variable evolution and the final level was 1.5. IDTS scores declined from 144 to 82 after 6 months. Global Assessment of Functioning reflected the improvement in clinical symptomatology (+ 28 points). There were 2 dropouts recorded, due to noncompliance issues.
Conclusions: Depressive symptomatology and alcohol dependence both tend to improve under milnacipran treatment, although there is not a paralleled evolution, since depressive phenomenology severity decrease was more stable throughout the study and alcohol dependence improved equally fast but less stable.

P-29-010
Tianeptine efficacy in the treatment of multiple sclerosis associated anxiety disorder

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Objectives: To evaluate the impact of tianeptine over the anxious cluster symptoms in patients diagnosed with anxiety disorder due to multiple sclerosis.
Methods: A group of 12 patients, 7 male and 5 female, mean age 42.2, diagnosed with multiple sclerosis, were referred to our hospital and a diagnosis of anxiety disorder due to a general medical condition was established (according to DSM IV TR criteria). Our patients presented generalised anxiety subtype (n=6), panic attacks (n=5) and obsessive-compulsive symptoms (n=1). We initiated treatment with tianeptine in doses of 37.5 mg daily and patients were receiving specific treatment for their etiologic condition. We evaluated these patients every 4 weeks during 6 months for symptoms of anxiety using Hamilton Rating Scale for Anxiety (HAM-A), Beck Anxiety Inventory (BAI) and for their global symptoms improvement using Clinical Global Impressions (CGI-I). Inclusion criteria: age over 18 and under 65, HAMA scores at least 25, BAI scores over 35. Exclusion criteria: severe organic or psychiatric comorbidity, previous treatment using tianeptine.
Results: Patients receiving tianeptine recorded a significant improvement in their mood status after 4 weeks, as both HAM-A (-14.2 points) and BAI (-10.8 points) reflected. The CGI decreased to a mean value of 3.2 after 4 weeks. The decreasing trend was also observed at week 8 and 12 and reaches a stable value after that (7.6 on HAMA, 6.2 on BDI and 1.5 on CGI). No drop-outs were recorded throughout the study as the overall tolerability of tianeptine treatment was good.
Conclusions: Tianeptine is efficient inthe treatment of anxiety disorder due to multiple sclerosis and is well tolerated by these patients.

P-29-011
Comparison of Sertralines efficacy and tolerance with those of Clomipramine during the treatment of patients with obssessive compulsive disorder

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Objectives: In Albania there are absent studies about psychiatric treatments and their efficacy. This is the first study done in our country on efficacy treatment. Aim: The study's aim was the comparison of efficacy and tolerance of the OCD patients treated with Sertraline toward those treated with Clomipramine.
Methods: The study was focused on the inpatients and outpatients presented at psychiatric Clinic, diagnosed with OCD during September 2005-March 2006. The criteria of being selected were randomization of those with > 20 points according to Yale-Brown Obsessive Compulsive Scale and > 4 points according to Clinical Global Impression Scale. There were two groups: first group was treated with Clomipramine and the second with Sertraline. Sertraline doses were 50 and 200 mg/day and Clomipramine 100, 125 and 150 mg/day. The study was conducted during a period of 12 weeks including three evaluations through YBOC scale and CGI.
Results: 91.8% of the patients completed the study. 18 were treated with Sertraline and 16 with Clomipramine. both treatments resulted with the same efficacy in treating the OCD symptoms. The patients treated with Sertraline reported less side effects frequency and intensity and more tolerance than the patients treated with Clomipramine.
Conclusions: Both treatments showed therapeutic efficacy in treating the OCD symptoms. Clomipramine caused more side effects and the number of patients dismissed from the study was higher in the group of clomipramine. Sertraline is as effective as Clomipramine for treating the OCD but has more compliance and less side effects.

P-29-012
A unifying theory of antidepressant action

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Objectives: The hypothesis states that clinical depression is a state of synaptic Long Term Depression that can be reversed by antidepressant treatments.
Methods: The review shows that: 1) All antidepressants (chemical antidepressants, ECT, rTMS, sleep deprivation) increase dopamine or dopamine turn-over in the prefrontal cortex (PFC). 2) Dopamine, in the PFC, facilitates, with an inverse U shape curve, Long Term Potentiation (LTP) and neuroplasticity. 3) LTP has an antidepressant effect.
Results: 1) Antidepressants increase dopamine in the PFC: We found in a literature search that all antidepressants increase dopamine in the PFC. The dopamine, measured by microdialysis in rodents or monkeys, is increased in the PFC by the following antidepressants: amineptine, bupropion, reboxetine, fluoxetine, citalopram, paroxetine, fluvoxamine, venlafaxine, clomipramine, desipramine, amoxapine, amitriptyline, nortryptiline, maproptyline, mianserine, mirtazapine agomelatine, deprenyl, IMAO, tianeptine. The dopamine enhancement is also evident with lithium, pindolol, amantadine, idazoxan, buspirone, yohimbine, thyroid hormone, oestrogen, glucocorticoid. Other antidepressant treatments such as ECT, rTMS, sleep and paradoxical sleep deprivation also increase dopamine in the PFC. 2) Dopamine modulates LTP and neuroplasticity in the PFC: Dopamine D-1 receptors activation is necessary for the induction of medial PFC glutamate-based LTP (Cappa-Hopman 2008) and reverses the deficit induced by chronic stress (Mizoguchi 2002). Too little or too much dopamine-D-1 receptor interaction impairs working memory performance (Arnsten 1998), the cellular basis for memory formation (Gurden 1999, Gurden 2000, Jay 2003), the growth of new dendritic spines and the increased number of spine synapses (Matsuzaki 2004, Yuste 2001). 3) LTP-like synaptic potentiation reverses the effects of chronic stress, a model of animal depression. Exposure to chronic mild stress, an animal model of depression, blocks LTP, facilitates LTD and impairs neurogenesis (Cerqueira et al, 2007; Holderbach 2007). Exposure to chronic stress decreases the extracellular concentration of dopamine in the PFC (Mizoguchi 2008).
Conclusions: Antidepressants could reverse synaptic Long Term Depression

P-29-013
Cyclooxygenase (COX)-2 inhibition in depression: Evidence from animal studies

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Objectives: A functional hyperactivity of the COX-2 pathway has been suggested to contribute to the pathogenesis of affective disorders and beneficial effects of COX-2 inhibitor co-treatment have been demonstrated in human studies. In order to gain more insight into the role of COX-2 inhibition in behavioural changes related to depression or antidepressant effects, the influence of treatment with selective COX-2 inhibitors was investigated in mice.
Methods: Male DBA/2 mice were behaviourally tested in various test paradigms after acute or chronic oral treatment with the selective and potent COX-2 inhibitor Cimicoxib. Different biochemical parameters, including brain derived neurotrophic factor (BDNF) expression and hypothalamus-pituitary-adrenal (HPA)-axis related factors, were investigated in brains of animals treated with either Cimicoxib or vehicle to disclose a possible pathway of its antidepressant effects.

Results: Cimicoxib treatment for 28 days led to behavioural changes in the forced swim test resembling those of classical antidepressants. The effects were dose-dependent and persistent as an antidepressant-like behavioural profile was observed also in a second exposure to the FST, 24 hours after the last Cimicoxib application. No influence on locomotor behaviour was observed when compared to untreated animals, a normalization of reduced locomotion was observed when compared to vehicle treated animals. In the hippocampus of Cimicoxib treated animals, we observed a decrease of COX-2 protein and an increase of BDNF protein expression.
Conclusions: The results of the present study demonstrate that Cimicoxib exerts antidepressant-like behavioural effects as well as a positive effect on BDNF.
In line with the increasing evidence that patients suffering from depressive disorders might benefit from treatment with Cox-2 inhibitors we currently perform a Phase IIa study to investigate the safety and efficacy of Cimcoxib in combination with sertraline for the treatment of major depression.

P-29-014
Sexually dimorphic effects of antidepressant imipramine on glucocorticoid receptor hormone binding properties and association with heat shock proteins in the rat liver and kidney

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Jelena Brkljacic, Gordana Matic

Objectives: Females, in comparison to males, exert more pronounced response to stress (Young EA, Crit Rev Neurobiol 1995, 19: 371 381; Seale JV et al., J Neuroendocrinol 2004, 16: 516 524), higher risk for stress related disorders, particularly depression (Kuehner C, Acta Psychiatr Scand 2003, 108: 163 174), and different response to antidepressant treatment (Kornstein SG, Am J Psychiatry 2000, 157: 1445 1452). Taking the role of glucocorticoid hormones in the systemic reaction against stress and in pathogenesis of depression, the aim of the present work was to study gender related differences in glucocorticoid signaling and potential contribution of these differences to sexually dimorphic response to a typical antidepressant drug, imipramine.
Methods: Gender related differences in glucocorticoid receptor (GR) functional properties were assessed using hepatic and renal whole cell extracts of female and male rats before and after long-term imipramine treatment. The receptor's hormone binding parameters, Bmax and KD, were determined by radioligand binding assay, the GR and heat shock proteins (Hsp70 and Hsp90) levels by quantitative immunoblotting, and the interaction of these proteins within GR heterocomplex by co immunoprecipitation.
Results: GR binding potency (Bmax/KD ratio) was several fold higher in males than females in both examined tissues, before as well as after treatment with imipramine. In addition, long term imipramine treatment led to gender specific changes in the GR binding parameters which were found to be associated with alterations in the receptor interaction with Hsp70 and Hsp90. Although GR protein level did not vary between untreated female and male rats, it was affected by imipramine treatment only in females.
Conclusions: The results of the study point to sexual dimorphism in the glucocorticoid signaling and imply that GR functional alterations might contribute to gender related differences in vulnerability to stress and stress related disorders, and in response to antidepressant drugs.

P-29-015
Preperential prevention of apoptosis by citalopram in mouse cortical cell cultures

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Objectives: Several line of evidence showed that neuronal injury may be a possible pathway to mood disorder. Also we have reported that R(–)- and S(+)- of citalopram, the apoptotic neuronal injury in mouse cortical neuronal cell culture. The present study was performed to examine the possibility that the neuroprotective effects of effects of R(–)- and S(+)-citalopram would depend upon types of neuronal cell death.
Methods: Free radical neurotoxicity was induced in mixed cortical cell cultures by continuous exposure to 30 uM Fe++ 24 hr, which produces hydroxyl radicals via a Fenton reaction. Cortical cell cultures (DIV 12) were exposed for 24 h to 50 uM NMDA to induce excitotoxicity Neuronal apoptosis was induced in mixed cortical cell cultures by 100 nM stausporine exposure for 24 hr. Neuronal death was analyzed 24 h later by measuring the efflux of lactate dehydrogenase (LDH) into the bathing medium in mixed cultures or by counting viable neurons after staining with trypan blue.
Results: Co-treatment with R(–)- or S(+)- citalopram prevented staurosporin induced apoptosis of cultured cortical cells along with prevention of activation of caspase 3. In contrast to the differences between enantiomers in serotonin uptake inhibition and in the in vivo behavioral depression model, both enantiomers showed protective effects on staurosporin induced apotosis by similar potency. Mixed cortical cell cultures (DIV 12–14) exhibited marked neuronal cell body swelling accompanied by widespread neuronal death over 24 h following exposure to 30 μM Fe or 50μM NMDA which was not sensitive to either the R(–)- or S(+)-enantiomers of citalopram.
Conclusions: These features suggest that neuroprotective effective of citalopram depends on type of neuronal injury.

P-29-016
Body weight and antidepressants: A comprehensive review and meta analysis

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Alessandro Serretti

Objectives: Weight gain is a frequently adverse event observed with antidepressant drugs but findings are not consistent across studies and comprehensive studies allowing to compare the effect of different drugs on body weight are lacking. In the present work we reviewed studies reporting body weight changes during treatment with different antidepressants, and performed meta-analysis testing the individual drugs vs. placebo both during acute treatment and over the medium-long period.
Methods: Methodological quality of studies, heterogeneity and publication bias were systematically controlled. Analysis were perfomed by RevMan5 comparing weight changes in treated patients with placebo.
Results: Results of analyses substantially confirmed previous sparse observations: mirtazapine and the TCAs amitriptyline and nortriptyline were associated with a greater risk for weight gain, while SSRIs, SNRIs and the NRI reboxetine were overall associated with a variable weight loss during acute treatment, but restoration seems to occur over longer periods. Paroxetine induce the largest weight gain among SSRIs in the medium and long-term period. Finally, moclobemide was most potent weight loss promoter, though no information was available over the long term.
Conclusions: Despite some analyses were done only on few studies, due to the difficulty to find accurate information about weight changes associated with some antidepressants in literature, in the present study we reported antidepressants differing markedly in weight changes induction.

P-29-017
Effect of monoaminergic antidepressant drugs on the hippocampal neurogenesis in a model of depression

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Objectives: Depression and anxiety disorders have been linked to dysfunction of the hypothalamo-pituitary-adrenal (HPA) axis and structural changes within the hippocampus. Unpredictable chronic mild stress (UCMS) may induce downregulation of hippocampal neurogenesis which can be reversed by antidepressant (AD) treatment. The present study was designed to investigate causality between changes in hippocampal neurogenesis and the effects of both chronic stress and chronic ADs.
Methods: Mice were treated with either a sham procedure or focal hippocampal irradiation to disrupt cell proliferation before being confronted with 5 weeks of UCMS. From the third week onward, monoaminergic ADs (imipramine, fluoxetine), the corticotropin-releasing factor 1 (CRF1) antagonist SSR125543, or the vasopressin 1b (V1b) antagonist SSR149415 daily.

The effects of UCMS regimen, AD treatments, and irradiation were assessed by physical measures (coat state, weight), behavioral testing (Splash test, Novelty-Suppressed feeding test, locomotor activity), and hippocampal BrdU labeling.
Results: Elimination of hippocampal neurogenesis had no effect on animals' sensitivity to UCMS in several behavioral assays. Both neurogenesis-dependent and -independent mechanisms were involved in the reversal of stress-induced behaviors by AD drugs. Loss of neurogenesis completely blocked the effects of imipramine or fluoxetine, but did not prevent most effects of the CRF1 and the V1b antagonists.
Conclusions: Hippocampal neurogenesis accompanied by the monoaminergic ADs may counteract the effects of stress, whereas similar effects could be achieved by directly targeting the HPA axis and related neuropeptides.

P-29-018
Region and subtype specific effects of SSRI and TCA drugs on 1-adrenoceptor sub types in rat brain

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Objectives: The present study was undertaken to examine the differential effect of these types of specific antidepressants on the density of alpha 1-adrenoceptor sub types in rat brain.
Methods: The density of alpha 1A and alpha 1B was measured in cortex and cerebellum of rat brain by differential radioligand binding of [3H] prazosin, in presence of specific antagonist having high affinity to alpha 1B-adrenoceptors (WB-4101). Rats were treated with Amitriptyline (AMI), a tricyclic antidepressant (TCAs) and Floxetine (FLX) a SSRI, for 30 days.
Results: In cortex the density of alpha 1A -and alpha 1B-adrenoceptors, measured by using [3H]prazosin, was significantly decreased in AMI (84% and 35%; p<0.001) treated rats, when compared to control rats. However, in FLX treated rats only alpha 1A-adrenoceptors were significantly decreased (25%; p<0.001). In cerebellum the density of both alpha 1A and alpha 1B-adrenoceptors was significantly decreased in AMI (45% and 9%; p<0.001) and Floxetine (98% and 42%; p<0.001) treated rats.
Conclusions: The results suggest that chronic AD treatment down regulates alpha 1-adrenoceptor subtypes differentially in rat brain and the effect is region specific. TCAs like AMI down regulate both cortical and cerebellar alpha 1-adrenoceptor subtypes, whereas, SSRIs like Floxetine down regulate predominantly cerebellar alpha 1B -adrenoceptors. This could be one of the mechanisms of action of AD and the efficacy of certain ADs.

P-29-019
Paroxetine specificity profile in major depression

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Objectives: Define the most suitable clinical profile for the use of paroxetine as antidepressant treatment.
Methods: 63 randomized controlled trials including paroxetine for the treatment of Major Depression were analysed. We sorted out the clinical profile that better reacted to paroxetine with respects the other antidepressants (TCAs and other SSRIs mainly) by the use of the effect sizes (Cohens' d) measured by the HDRS deltas in a set of different time-points during antidepressant treatment. Normal distribution was tested. Parametric or non parametric tests were run for the analysis between groups while covariating for clinical and sociodemographic variants. When needed, multiple regression was used in order to sort out the relative impact of continuous variants. Due to the asymmetry of literature's results, calculations were weighted with the number of patients enrolled in each study.
Results: Paroxetine was more efficacious than TCAs at week 3 and than the other SSRIs and TCAs at week 6 (p<0.001); it was associated with a better improvement in older patients from week 2 with respect to the other SSRIs. Females better responded to paroxetine or TCAs when compared to SSRIs. Males were found to better respond to SSRIs other than paroxetine (p <0.001). Patients with a shorter episode responded better to the antidepressant treatment, even though paroxetine was found to be able to modulate this: starting from the 4th week of treatment, medium long episode treated with paroxetine showed similar responses compared to short episodes.
Conclusions: These findings placed paroxetine into an intermediate level between TCAs and the other SSRIs for some specific issues as relevant as the time of response, the impact of the duration of the episode, the age of patients. This could be depending on its specific molecular properties. Further analyses are necessary in order to confirm these results.

P-29-020
The role of fluoxetine in treatment of obsessive-compulsive disorder and co-substance abuse-a case report

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Objectives: Fluoxetine hydrochloride is an antidepressant of the selective serotonin reuptake inhibitor (SSRI) class and is approved for the treatment of obsessive – compulsive disorder (OCD) (in both adult and pediatric populations). Some of OCD patients group are substance abuser or have some experience with drugs,particulary with MDMA
Methods: we exposed the 30-old male patient who treated outpatient in the Special Hospital on Addiciton,Belgrade,Serbia for a 12 week.We used the medical protocol,data collected from the history of illness,psychiatry interview,BIS/BAS scales,Hamilton Depression Rating Scale with 21 - item (HDRS),Clinical global impression scale (CGI) and blood sample analyses. The patient has a diagnosis of OCD ,substance abuse and severe depressive episode without psychotic symptoms according the ICD-X.Other disorders are excludes
Results: The patient has diagnosis of OCD 15 years ago (the main symptoms are hand washing and fear of contamination).The last 6 years he used abuse the MDMA and alcohol,rarely cocaine and marijuana.It was appear the depressive symptoms at the one year ago.There were no prescribing medications of that time.We took the fluoxetine in doses of 60 mg per day for a 12 weeks and there were significant improvement in reduced depressive symptoms (HDRS decreased from 19 to 16), stabile abstinence from MDMA and alcohol (checking by specific urine test and blood alcohol measuring for several times),also it provide the partial reduction OCD symptoms.The medication was combine with behavioral - cognitive therapy
Conclusions: patients with OCD may be diagnosed with other disorders or conditions.Many papers show the link between substance abuse and OCD and demonstrating there is a higher risk among those with any anxiety disorder (including the depression).Also, we find out drug abuser among OCD patient may serve as a type of compulsive behavior.

P-29-021
The most severe somatic disorders treated with excitalopram – more than just survival

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P-29-022
The most severe somatic disorders treated with excitalopram

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P-38
Psychopharmacology II

P-38-001
Comparison of Olanzapine long-acting injection switching methods: An 8-month analysis of patients with schizophrenia at risk of relapse

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Objectives: To compare the safety and efficacy of direct switch versus taper of previous antipsychotic medication when changing to olanzapine long-acting injection (LAI). Analyses were based on 8-month data from an ongoing 2-year open-label study of olanzapine LAI in adults with schizophrenia.
Methods: Outpatients considered at risk for relapse (N=264) received olanzapine LAI every 4 weeks with a starting dose of 405 mg and flexible dosing thereafter. Investigators could either directly switch patients or taper their previous antipsychotic medication during the first 2 weeks of treatment.
Results: At time of study entry, 63 patients were receiving typical antipsychotics, 188 were receiving atypical antipsychotics (76 receiving oral olanzapine), and 34 were not receiving any antipsychotic; a total of 16 were on injectable antipsychotic medication. Of 264 total patients, 150 (56.8%) were switched directly and the rest were tapered. The 2 groups did not significantly differ in discontinuation rate (direct: 32.0%, taper: 30.7%, p =.894) and there was no significant difference between the groups on PANSS total score mean change at any time up to 8 months (direct: -1.9, taper: -3.1, p= .834, from a mean baseline of 56.7 [SD=9.8]). Treatment-emergent adverse events in >=5% of patients were: increased weight (12.5%), insomnia (8.3%), anxiety (6.8%), somnolence (7.2%), and increased appetite (5.7%). The switch groups did not significantly differ in mean weight change (p= .862), with an average weight gain of 2.0 kg, nor did they significantly differ in terms of laboratory analytes or other safety parameters.
Conclusions: Based on this 8-month analysis of efficacy and tolerability/safety data, there did not appear to be clinically significant differences for those who were directly switched to olanzapine LAI versus those who were tapered.

P-38-002
Long-term open-label safety of olanzapine long-acting injection: 190-week interim results

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Objectives: The primary objective of this ongoing open-label study is to examine the long-term safety and tolerability of olanzapine long-acting injection (LAI). Current results are from an interim analysis, with a maximum treatment duration of 190 weeks.
Methods: Patients were 18-75 years of age with schizophrenia or schizoaffective disorder (N=931), enrolled in an open-label extension study following 1 of 3 randomized, controlled studies of olanzapine LAI, in which patients had been randomly assigned to oral olanzapine, olanzapine LAI, or placebo. During the open-label extension, all patients received flexibly-dosed olanzapine LAI at injection intervals of approximately 2-4 weeks.
Results: At time of analysis, rate of study discontinuation was 46.3%. Discontinuation rate at 18 months was 34.3%. The most common reasons for discontinuation were: subject decision (23.4%), adverse event (6.7%), and lost to follow-up (5.7%). Adverse events in >=5% of patients were increased weight, insomnia, anxiety, somnolence, headache, and nasopharyngitis. There were 26 occurrences of temporary post-injection syndrome, characterized by sedation- and/or delirium-related symptoms following possible accidental intravascular injection of a portion of the dose; all of these patients fully recovered within 72 hours. Mean weight change was +1.88 kg, with 32.1% of patients experiencing >=7% weight gain. Percentages of patients who increased from normal to high on fasting glucose, random total cholesterol, or random triglycerides were 5.5%, 5.2%, and 14.3%, respectively. Mean Clinical Global Impressions-Severity scores remained stable throughout (2.9 at baseline to 2.8 at endpoint).
Conclusions: Olanzapine LAI discontinuation rates have been low compared with studies of other depot antipsychotics. Safety findings were consistent with those observed with oral olanzapine treatment, with the exception of those specific to intramuscular injection.

P-38-003
Different art therapies applied with the antipsychotics

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Simon Szilagyi

P-38-004
Eating disorders: Bibliotherapeutics to increase the pharmacotherapeutic compliance

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Objectives: Hypothesis: Bibliotherapeutically treated patients have increased pharmacotherapeutic compliance consequently more chance to be recovering. The large and ascendant number of eating disorder problems necessitates to apply more treatment forms.
Methods: The problem of compliance is not a specific problem of eating disorders, it is well-known e.g. in the field of depression but the bibliotherapy as a problem solving method shows a prominent efficiency especially by these diseases. The method of this research is a classical data analysis in different patients' groups.
Results: Result in numbers - later.
Conclusions: 1. clinical 2. educational (specify - later)

P-38-005
Effect of alcoholic extract of hypericum perforatum on fear behavior in adult male rats

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Objectives: Fear is biologic response that protects animal from acute danger. Fear and anxiety is important matter in psychological science. Different mechanism and drug were introduced for their control and therapy. Herbal drugs have mild effects on fear and more sedative than chemical drugs.
Methods: In this research the effect of intra-cerebro-ventricular (I.C.V) microinjection of Hypericum perforatum on fear were studied. Animals were divided into 5 groups: saline, pentylenetetrazole (PTZ) 20 mg/kg as Positive control (I.P) and three groups that received 5, 10, 20 µg/rat alcoholic extraction of H. perforatum (ICV) respectively. A cannul was placed into lateral ventricle by Stereotaxic apparatus. After recovery period, Elevate plus-maze were used for evaluation of the fear. Percent open arm entries (% OAE) and percent of open arm time (%OAT) was evaluated.
Results: Our result showed that 10 µg/art and 20 µg/rat doses increased %OAE and %OAT significantly (p<0001).
Conclusions: We concluded that alcoholic extraction of H. perforatum is an effective drug in fear reduction. It probably acts on serotonergic and GABAergic system and decreases their reuptakes. By this michanism decreased fear.

P-38-006

Effect of inhalation alcoholic extract of Peganum harmala, on induction of anxiety like behavior in elevated plus-maze

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Objectives: Based on the extensive application of peganum harmala (P.h) seed in the Asian traditional medicine, we tried to investigate its possible anxiety effect. So, the effect of P.h extract inhalation was evaluated in adult male rats using elevated plus-maze apparatus.
Methods: The humidity of prepared ethanol extract was 37%. Animals in different groups (n=6) received 2, 4, 6, 12 or 18 gr/ml doses of the extract using Nebulizer. Harmaling drug (0.13gr/ml) was used as positive control drug.
Results: Results shown that compared with saline treated group, harmaline as the positive control significantly caused fear in rats as it was shown by increased time spent in closed arm of plus-maze ($p<0.05$). Also, ethanol extract of P.h was able to show anxiety effect at doses 6, 12 and 18 mg/ml ($p<0.05$).
Conclusions: Our data showed effective anxiety effect ethanol extract of Peganum harmala. Its effect should be considered in the context of its extensive usage in the human daily life. More studies are required to elucidate its mechanism and site of action.

P-38-007

What pharmacological agents are most efficacious for the treatment of cognitive and behavioural problems following traumatic brain injury?

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P. Wheaton, R. Vink

Objectives: Pharmacological treatments may reduce persistent cognitive and behavioural problems following traumatic brain injury (TBI). While a variety of treatments have been examined, the research findings are inconsistent and unclear with respect to their relative efficacy. This study provided an evidence-based evaluation of existing pharmacological treatments for patients who have sustained a TBI.
Methods: The current study undertook a meta-analysis of all research, published between 1980 and 2008, that examined the effects of pharmacological treatments (administered ≥ 1 week post-injury) on cognitive and behavioural outcome following TBI. A comprehensive search of the PubMed and PsycInfo databases was undertaken using 35 search terms. Detailed inclusion criteria were used to screen all studies. Weighted Cohen's d effect sizes, percent overlap statistics and Fail safe N statistics were calculated for each treatment. Studies that used different experimental designs were examined separately (independent groups repeated measures, independent groups, repeated measures, cross-over designs).
Results: Nineteen treatments were investigated by 30 studies, comprising 441 TBI patients in the treatment groups and 225 TBI controls. The majority of studies examined moderate to severely injured males. 75 measures of cognitive and behavioural outcome (cognition, mood, combativeness, general outcome, psychosocial function) were used to assess treatment efficacy. Two dopamine agonists (methylphenidate, amantadine) and one cholinergic agent (donepezil) showed significant treatment benefits for cognition and behaviour using rigorously designed studies. In contrast, one serotonergic agent (sertraline) markedly impaired cognition and psychomotor speed. Notably, the study design and measure of outcome influenced the likelihood of finding a treatment benefit.
Conclusions: Current treatment guidelines for the cognitive and behavioural effects of TBI are limited and are largely based on non-quantitative reviews of the research literature. Treatments leading to positive and negative effects have been identified by this meta-analysis, providing an evidence-based approach to treatment selection.

P-38-008

A randomized, placebo-controlled, double-blind, crossover study to investigate the residual effects of ramelteon (8 mg) and zopiclone (7.5 mg) on actual driving, memory, psychomotor performance and body balance in healthy volunteers

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Monique Mets, Juna de Vries, Lieke de Senerpont Domis, Edmund Volkerts, Berend Olivier

Objectives: Ramelteon is a sleep medication with a unique mechanism of action different from hypnotics that act on GABAA receptors. Ramelteon is an MT1/MT2 melatonin receptor agonist. This study evaluated the effect of ramelteon on middle-of-the-night balance and next-day driving.
Methods: Thirty healthy volunteers participated in a double-blind, placebo-controlled crossover trial. Subjects received ramelteon (8 mg), zopiclone (7.5 mg), or placebo at bedtime. Subjects were wakened after 2 hours for a balance test (AccuSway plus platform) and returned to bed. Real traffic driving, memory, and psychomotor tests were performed 9 to 11 hours after treatment administration. Standard deviation of lateral position (SDLP) was the primary variable. Statistical analyses were performed using analysis of variance for a crossover model.
Results: Ramelteon (+2.2 cm) and zopiclone (+2.9 cm) significantly increased SDLP compared with placebo ($P<0.001$). Ramelteon and zopiclone produced significant impairments on reaction time in the Sternberg Memory Scanning Test, slow and fast tracking, reaction speed, and tracking in the Divided Attention Test, and delayed recall in the Word Learning Test compared with placebo ($P<0.05$ for all). No significant differences between ramelteon or zopiclone versus placebo were observed for percentage of errors on the Sternberg Memory Scanning Test and Divided Attention Test, and immediate recall of the word learning test. In contrast to ramelteon, zopiclone impaired performance on the DSST and the middle-of-the-night balance test ($P<0.001$ for both).
Conclusions: Compared with placebo, ramelteon (8 mg) and zopiclone (7.5 mg) significantly impaired driving, memory, and psychomotor performance 9 to 11 hours after bedtime administration. The magnitude of impairment was comparable to that observed after a blood alcohol concentration of 0.05%. Zopiclone significantly impaired performance on the DSST and middle-of-the-night balance, while ramelteon and placebo had no adverse effect on these measures.

P-38-009

Methylphenidate significantly improves declarative memory functioning in adult patients with Attention-Deficit Hyperactivity Disorder (ADHD)

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Objectives: Declarative memory deficits are common in untreated adults with Attention-Deficit Hyperactivity Disorder (ADHD), but limited evidence exists to support improvement after treatment with methylphenidate. The objective of this study was to examine the effects of methylphenidate on memory functioning of adults with ADHD.
Methods: Eighteen adults with ADHD who were good responders to methylphenidate participated in this randomized crossover trial. After 3 days of no treatment, patients received in random order either their usual methylphenidate dose (mean: 14.7 mg; range: 10–30 mg) or placebo, separated by a 6-7 day washout period. Patients performed an immediate word recall test 1 hour after treatment administration. Three hours after intake, patients performed the second part of the memory test (delayed word recall and a recognition test). Data was analyzed with ANOVA.
Results: Delayed recognition and immediate recall was similar on treatment and on placebo. Delayed word recall was significantly better in the methylphenidate than in the placebo condition ($F1, 17= 7.0$, $p<0.017$).
Conclusions: Methylphenidate significantly improves declarative memory functioning in patients with ADHD.

P-38-010
Can MDR 1 Polymorphism predict the side effect of oros-methylphenid in children and adolescents with Attention Deficit/ Hyperactivity Disorder?

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Objectives: Multidrug resistant protein 1 (MDR1, ABCB1) transports many psychotropic agents including methylphenidate. We examined whether MDR1 polymorphisms were associated with the side effects of OROS-methylphenidate(MPH) in children and adolescents with attention deficit/hyperactive disorder(ADHD)
Methods: 133 children and adolescents with ADHD were treated with OROS-MPH during 8 weeks. The side effects of OROS-MPH were measured with Barkley's side effect rating scale. 133 patients were analyzed with 5 single nucleotide polymorphisms(SNPs) in the MDR1 gene which were found in Korean population. They were divided into two groups, those who experiencing side effects and those who did not.
Results: The c.2677G>A/T was associated with total score of Barkley's side effect rating scale at week 1, 2, 4 and 8. Especially, TT genotype of the SNP are more likely to experience side effects of OROS-MPH. Methylphenidate-MDR1 ATPase assay supported that T allele did not transfer almost methylphenidate out of cell.There was linkage disequilibrium between G2677A/T and C3435T(r2=0.71). TT haplotype was associated with side effects(p=0.03).
Conclusions: These results stronly support that the c.2677G>T polymorphism in human MDR1 gene is associated with adverse reactions to methylphenidate.

P-38-011
Prevalence of Metabolic Syndrome in chronic female patients

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Objectives: To determine the prevalence of metabolic syndrome in patients at the Psychiatric Hospital, medicated with antipsychotics.
Methods: a sample of 18 female chronic inpatients was studied (age ranging from 23 to 65 years) All meet the DSM IV criteria for schizophrenia or schizoaffective disorders. 88 % of the sample takes Haloperidol at range doses of 5 – 15 mg daily and 11.1% take Olanzapine 10mg daily. Two third of the sample takes the antipsychotics drug for periods greater than 3 years (up to 12 years) Metabolic syndrome was identified by the the Institute Diabetes Federation criterion. The investigated variables were: anthropometrics and biochemical analysis and arterial blood pressure measure
Results: the finding rates were 66.6% for metabolic syndrome, its most prevalent components were: 100% for abdominal obesity, 55.6% for hypertriglyceridemia, 38.9% for hypertension, 72.2% for HDL cholesterol and 5.5% for fasting glycemia.
Conclusions: chronic female patients at the Asuncion Psychiatric hospital had a high and distressing prevalence of overweight and metabolic syndrome. The high rate of metabolic syndrome, stresses the importance of the physical care together to mental health care, rising the need to be awareness on the detection and appropriate treatment of these conditions.

P-38-012
Clinical interest of measuring out serical valproic acid rate in psychiatry

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Objectives: In neurology, measuring out serical valproic acid rate is systematically used to make sure the patient is really in the therapeutic anticonvulsion zone (50 to 100 mg/L). The upper norm is used to avoid toxicity risk. As valproic acid is now frequently used in psychiatry to treat bipolar disorders, how do psychiatrists respect its rate ? Is there a link between the plasmatic concentration of valproic acid and its clinical efficiency ?
Methods: The various studies aiming to prove the efficiency of the molecule using the monitoring of plasmatic rate are inventoried. The works on the pharmacokinetic and about the pharmacodynamic data of the molecule are used as a theoretical basis for an explicative analysis.
Results: The plasmatic concentration ranges considered to be useful vary with indication, but also with the author. Data concerning the free plasmatic part underline, because of interindividual and intra-individual variation, the difficulty to interpret a dosage. The free part, being the only one to have the pharmacological properties on the central nervous system, is an important parameter and has to be taken into account for clinical efficiency and pharmacological tolerance.
Conclusions: To take care of manic phase, the 45 mg/L point seems pertinent as a minimal efficient dose, the 125 mg/L one for side-effects and toxicity. More recent data refer to a more noticeable efficiency from 71 mg/L and even more noticeable from 96 mg/L. Finally, it is still useful to look at this rate, for it helps limiting toxicity risks, to optimize observing and to adapt the dosage in case of co-prescription.

P-38-013
Depressive syndromes and suicides of subjects treated with varenicline: Psychiatric and neurobiolological aspects

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Jean-Michel Pinoit

Objectives: US and French Health Departments published in the end of 2007 an emergency bulletin after noticing major depression, suicidal ideas and actual suicide attempts of subjects treated with varenicline, a recently discovered molecule used to help smoking withdrawal. The aim of this work is to assess whether these effects are real and to study the neurobiological mechanisms this molecule may be involved in.
Methods: The various tolerance (controlled, randomised and double-blind) studies of varenicline, during smoking withdrawal care, are inventoried. The current works about depression physiopathology and suicidal behaviour are used as a theoretical basis for an explicative analysis.
Results: Clinical tolerance studies did not significantly reveal any mood disturbances, nor suicidal behaviour. This molecule is very selective for cholinergic nicotinic alpha4-beta2 receptors and an important number of neurotransmission system seem to be regulated by the cholinergic system: the main systems are the dopaminergic, serotoninergic, and noradrenergic ones.
Conclusions: The loss of activity of the dopaminergic system may have caused the depressions. On the other hand, varenicline is theoretically able to stimulate 5-HT1A serotoninergic receptors which inhibit releasing serotonin. Neurotrophic factors expressing and neuronal plasticity could also be regulated by the cholinergic system. Concerning suicidal behaviour, serotoninergic and dopaminergic systems (of which mesolimbic way can be activated) seem to be the main possible actors in impulsivity and observed suicide attempts. These clinical phenomena, if following alerts keep confirming it, would confirm the fragility of the cholinergic system of smoking subjects and maybe more precisely of smoking subjects who have had major depression episodes.

P-38-014
Atypical antipsychotics and social functioning in schizophrenic patients

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Objectives: To study the influence of antipsychotic therapy: typical versus atypical medications in relation to social functioning. The study was designed to examine connection between social functioning and type of antipsychotics in a group of schizophrenic patients, also according to the gender, education and duration of illness.
Methods: Patients (N=123), living in supportive accommodation, with diagnosed shizophrenia according to ICD 10 criteria were included in the investigation. 31.7% of patients, 26 females and 13 males, were on atypicals (olanzapine, risperidone, clozapine). The Social Functioning Scale according to Bellack has been used for the assessment of social functioning in the study. We used the descriptive analysis, regression analysis, discriminatively analysis and group of centroids for statistical evaluation of data.

Results: There is no difference in social functioning between patients on atypicals and patients treated by typical antipsychotics. Results have shown the better social functioning of women in compare to males. Also, the education and duration of illness were not in relation to social function.
Conclusions: Although there were not difference in social functioning in two groups of patients treated by different type of antipsychotics, we observed a positive trend of better social functioning in group of patients who takes atypicals. The importance of that positive trend has to be checked in larger sample of patients to make further conclusions. The better social functioning of women was in concordance with the results of other investigators.

P-38-015
Maintaining of long-term effect of wellness program in psychiatric patients

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Objectives: The wellness program is manual-based step by step program developed to reduce the risk factors of cardiovascular disease and metabolic syndrome in the psychiatric patients. The aim of the study was to evaluate the long-term effects of wellness program through the comparison of results obtained at the end of the program and at least a one year later.
Methods: Patients (n=23) diagnosed with different mental disorders were included in study to assess the benefit of 12-week wellness program after 12 to 39 months (mean 27±7.8). The patients were treated by antipsychotics and/or antidepressants and six of them by a mood stabilizator. The groups met once a week during 12 weeks for 90 minutes. Data were obtained through the comparison of body mass index (BMI) and waist circumference (WC) at the beginning, and end of program as well as after long period of time. Wilcoxon signed-rank test was used for statistics.
Results: The decline in waist circumference was recorded in significant number of patients (17/23) at the end of program with average decline of 4.2 cm. The further decline - after at least a year, was recorded in six of them (6/17). After the long period of time waist circumference increased in the eleven patients (11/17) but WCs didn't reach the values they have had before the wellness program. The decline in BMI was recorded in 11 patients at the end of program and ten of them maintain the decline after the long period of time.
Conclusions: The wellness program can be effective in reducing the risk of metabolic syndrome in psychiatric patients through decline of waist circumference and body mass index.

P-38-016
Reward sensitivity and response to the augmentation with topiramate in treatment-resistant anxiety

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Objectives: The use of topiramate in neuropsychiatry includes adjunctive treatment of the treatment-refractory anxiety. The purpose of our study was to test the hypothesis that sensitivity to reward would positively predict the response.
Methods: We had used the Sensitivity to Punishment and Sensitivity to Reward Questionnaire, developed by Torrubia. The response to treatment was assessed with Hamilton Anxiety Rating Scale (HAM-A) and we considered as responders to the augmentation treatment the patients with scores less that 14 or a fifty percent reduction on the HAM-A. Differences between the groups (responders versus the non-responders) were analysed using the SPSS v.10.0, and statistical signification was established at $p < 0.05$.
Results: The susceptibility to reward was significantly higher in the group of the patients who responded at the augmentation with topiramate of their anxiety treatment ($p<0.037$).
Conclusions: These results support the hypothesis that the reward responsiveness might predict the response to augmentation with topiramate of the anxiety resistant to treatment.

P-38-017
Topiramate in psychiatry as illustrated by an inpatient data base

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Objectives: The use of topiramate in psychiatry includes adjunctive treatment of bipolar disorder, treatment-resistant anxiety, alcohol dependence, impulse control disorder and for management of atypical antipsychotic-induced weight gain. This study examines the utilization of topiramate with respect to diagnosis, symptom clusters and associated combinations.
Methods: The charts of all the patients admitted to an inpatient psychiatric setting between 01 January 2008 – 01 January 2009 were reviewed and were selected those whom received topiramate in their psychiatric treatment. Data on diagnosis, symptom profiles, psychotropic medications, and severity of illness were extracted and analyzed.
Results: Bipolar patients were prescribed topiramate more frequently than patients with other diagnoses. Polytherapy (combination of the topiramate with antidepressants, antipsychotics or sedative-hypnotics) seems to be the rule.
Conclusions: As the use of topiramate expands, studies to refine its specific indications, safety, and efficiency in combination strategies will be necessary.

P-38-018
The beneficial effect of Milnacipran on Fibromyalgia is not related to its antidepressant effects: A European, Multicenter, Controlled Trial

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Objectives: To investigate the efficacy and safety of milnacipran compared to placebo in treating fibromyalgia syndrome in a European population, and to determine whether its effects on fibromyalgia are predicated on its antidepressant effects.
Methods: This was a phase III, placebo-controlled, double-blind, multicenter study enrolling 884 fibromyalgia patients randomized to placebo (n=449) or milnacipran 200 mg/day (n=435) for 12 weeks of fixed-dose exposure. The planned primary analysis used a sequential testing procedure involving a composite response criterion, and then the change in Fibromyalgia Impact Questionnaire (FIQ) total score. Fibromyalgia composite responders were defined as patients concurrently reporting ≥30% improvement from baseline in 24-hour recall pain and a rating of "very much improved" or "much improved" on the Patient Global Impression of Change (PGIC) scale. Beck Depression Inventory (BDI) was used as one of the secondary efficacy criteria.
Results: After 12-weeks of fixed dose, significantly more patients on milnacipran met criteria as fibromyalgia composite responders compared to subjects on placebo (P=.0003; odds ratio, 1.9). Mean improvements on FIQ total score were significantly greater for milnacipran versus placebo (P=.015). Pre-specified secondary analyses revealed that milnacipran treatment led to statistically significant improvements on multiple domains at the 3-month endpoint compared to placebo. In contrast to what might be expected if a drug functioned primarily as an antidepressant, differential response rates between placebo and drug were greater for patients with lower baseline BDI scores. Overall improvements in patients' condition and functioning were confirmed by significant improvements in weekly pain measured on daily electronic diaries, Brief Pain Inventory (BPI), SF-36 (Mental and Physical components), Multidimensional Fatigue Inventory (MFI) total score, FIQ Physical function subscale score, and Multiple Ability Self-Report Questionnaire cognition total score (MASQ). Milnacipran was well tolerated.
Conclusions: These findings confirm that milnacipran is an effective treatment for the multiple symptoms of fibromyalgia syndrome independent of baseline mood.

P-38-019
The effect of Milnacipran on pain modulatory systems in Fibromyalgia: An FMRI analysis

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Objectives: The present study used functional MRI (fMRI) analysis to evaluate the impact of milnacipran, a noradrenalin-serotonin re-uptake inhibitor, on the experience of pain in fibromyalgia.
Methods: 92 FM female patients participated in a 13-week, multicenter, placebo controlled trial assessing the effect of 100 mg b.i.d. milnacipran or placebo on brain activity measured by fMRI before and after treatment. Before inclusion, patients washed off medications that could influence pain perceptions. Brain activity was assessed during repeated application of subjectively equal pain stimuli (scored as 50mm on a VAS) evoked by 2.5s of blunt pressure. The resulting brain images provided a comprehensive representation of regions previously identified in fMRI studies as having important roles in pain processing, including S1, S2, insula, cingulum, cerebellum, thalamus and amygdala. The effects of milnacipran or placebo were quantified by a second, post-treatment assessment of subjective ratings of pressure pain and fMRI analysis.
Results: Treatment with milnacipran reduced pressure pain sensitivity in comparison to placebo, an effect that approached significance for all patients ($p = 0.11$). fMRI analyses revealed significantly increased brain activity following milnacipran treatment in multiple brain regions including the caudatus nucleus, anterior insula, anterior cingulum and amygdala. In contrast, placebo treatment increased activity only in the parietal region and mid insula. A statistical comparison between the effects of milnacipran and placebo showed increased activity in a large region of posterior cingulate/precuneus ($p<0.05$).
Conclusions: Milnacipran reduces tenderness and alters activity evoked by painful pressure stimulus in brain regions known to be involved with pain modulation. The specific effects of milnacipran provide important information for further development of pharmacological treatment in patients with fibromyalgia and related disorders.

P-38-020
Control of Tourette's syndrome with Paliperidone and Topiramate: A case report

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Objectives: Tourette's syndrome (TS) is characterized by multiple involuntary motor and phonic tics associated with psychiatric conditions. Pharmacotherapy, either for functional impairment from the tics or for comorbid psychiatric illness, is often unsatisfactory. Dopamine receptor antagonists are drugs of first choice. Risperidone, and in some countries sulpiride, have become first line drugs, owing to a favorable efficacy and tolerability profile. Some encouraging data for olanzapine, aripiprazole and ziprasidone are also reported.
Methods: Case report: a 24 year-old female had taken antipsychotics since the age of eight due to TS. At first she was treated with haloperidol. From the age of 12 she was switched to risperidone. She had also received different antidepressants and anticonvulsants. Her first admission to an inpatient service was at the age of 20 after the death of her father and this was her 7th hospitalization. For the last year her tics were severe. Two months ago she was switched to aripiprazole, escitalopram and oxcarbamazepine. During these two months she had agitation, insomnia, persecutory ideas, was suicidal and lost 15kg. After two unsatisfactory trials she was switched to paliperidone 6mg, sertraline 100mg and topiramate 100mg.
Results: There was a marked reduction of tics and this regimen had a good effect on her psychiatric symptoms and was also well tolerated. She was discharged four weeks later and was referred to our Day Center where she works and is almost free of tics and psychiatric symptoms -with paliperidone being raised to 9 mg two months after its intitiation- for more than 6 months.
Conclusions: Paliperidone seems effective and safe and could become a drug of choice in the treatment of TS. Only few controlled trials have been performed on antipsychotics in TS and longer-term studies are needed to evaluate the durability of efficacy and safety of atypical antipsychotics over time.

P-39
Pschopharmacology/ Antipsychotics II

P-39-001
Gabapentin is an important adjuvant in the treatment of resistant schizophrenia

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Objectives: Gabapentin is an antiepileptic drug which modulates aggressiveness and mood. To our knowledge there is no pharmacological study about the potential influence of gabapentin for the treatment of schizophrenia with resistant symptoms. The effectiveness of gabapentin as an adjuvant treatment in resistant schizophrenia with aggressive behaviors seems asserted by a preliminary case-report. The observation was made that violent behaviors end when gabapentin is administered and resume when it is removed (Demily & Franck, Schizophr Res, 2008).
Methods: So, we made the hypothesis that the indication of gabapentin can be generalized for resistant symptoms. We conduct a retrospective open pharmacological study to evaluate the efficiency and the tolerability of gabapentin.
Results: Patients with schizophrenia (DSM-IV criteria, n=20) with resistant symptoms (> 3 months with an antipsychotic monotherapy) were recruited. CGS (Clinical Global Score) was evaluated before and after a three-month treatment by gapapentin (doses range 200 mg to 2700 mg), as an adjuvant treatment to antipsychotics. The results remain very conclusive with an excellent tolerance and a significant efficacy. Results will be presented.
Conclusions: Gabapentin has several different pharmacological actions: it increases GABA synthesis and decreases glutamatergic excitability. The good level of tolerability of gabapentin suggests that this antiepileptic drug may be useful, in association with antipsychotics, for treating resistant paranoid schizophrenia with resistant symptoms.

P-39-002
Next-generation GRII antagonist prevents and reverses antipsychotic-induced weight gain

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Objectives: Previous animal studies demonstrated that mifepristone, a glucocotricoid antagonist and progesterone receptor, can reverse and prevent olanzapine-induced weight gain (Beebe, 2006). Rats administered mifepristone also had less abdominal fat compared with rats taking only olanzapine. The goal of the current pair of animal studies was to investigate the ability of CORT 108297, a newly-identified selective glucocorticoid antagonist (no progesterone activity), to both reduce and prevent olanzapine-associated weight gain.

Methods: Reduction of Olanzapine-Induced Weight Gain. In this 56 day experiment, rats (n=72) were allowed to eat a normal diet. For the first 35 days, 12 rats received vehicle and 60 rats received olanzapine. Then, these 60 animals were randomized to receive additionally, for 21 days, one of the following: vehicle, olanzapine, CORT-108297 (20mg/k), CORT-108297 (60mg/k), CORT-108297 (120mg/k), or mifepistone (60mg/k). Prevention of Olanzapine-Induced Weight Gain. In this 21 day experiment, a group of naive rats (n=72) were randomized to one of the six conditions: vehicle, olanzapine only, olanzapine plus CORT-108297 (20mg/k), olanzapine plus CORT-108297 (60mg/k), olanzapine plus CORT-108297 (120mg/k), or olanzapine plus mifepistone (60mg/k). In both experiments, weight and food consumption were measured every two days, and abdominal fat was measured at study end.
Results: In experiment 1, rats assigned to olanzapine only gained significant weight throughout the study. Rats who received adjunctive 108297 after day 35 subsequently lost significant weight; and, the amount of weight loss was linearly related to dose of 108297. Rats administered 108297 plus olanzapine had significantly less abdominal fat than rats assigned to only olanzapine. In experiment 2, rats who took olanzapine plus 108297 gained significantly less weight than rats receiving only olanzapine.
Conclusions: CORT 108297, a pure glucocorticoid antagonist appears to have the potential to block the weight gain caused by atypical antipsychotics. Eventually, this novel compound may be tested in clinical trials with humans.

P-39-003
Mifepristone reduces weight gain associated with Risperidone use

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Objectives: The purpose of this study was to evaluate the efficacy of mifepristone, a glucocorticoid antagonist, for the prevention of antipsychotic-induced weight gain. Our previous randomized controlled trials demonstrated that mifepristone significantly mitigated the weight gain associated with olanzapine, an antipsychotic known for deleterious side effects including weight and metabolic changes. The current study tested the role of mifepristone in the mitigation of weight gain due to another antipsychotic: risperidone. Like olanzapine, risperidone use has also been associated with weight changes, although to a lesser extent.
Methods: Healthy, Indian males (BMI>18 and <23 kg/m2) were enrolled in a three-arm randomized clinical trial conducted in an institutional setting. Participants were randomized to receive either risperidone plus placebo, risperidone plus mifepristone, or mifepristone plus placebo. Participants were dosed daily for 28 days. The primary endpoint was the change in weight from baseline to day 28. Secondary endpoints included changes in food intake, abdominal fat, and waist circumference.
Results: Analyses of covariance indicated that the group receiving risperidone plus placebo gained significantly more weight compared with the group receiving risperidone plus mifepristone ($p<.01$). Group differences were also observed on several secondary endpoints.
Conclusions: Preliminary results indicate that participants taking risperidone gained significant weight in a short period of time. However, participants taking mifepristone in conjunction with risperidone gained significantly less weight and had less abdominal fat. The potential for mifepristone to reduce the substantial health risks associated with antipsychotic use is discussed.

P-39-004
Use of nicotine as augmentation agent in schizophrenia treatment

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Objectives: Nicotiana tabacum is a plant chewed or smoked for many years from American natives, believed to have therapeutic qualities in its early days of use, and has been the main delivery system of Nicotine to human brain. Although this decade the attitude towards smoking, the main provider of nicotine, is negative, we shouldn't overlook the fact that nicotine is acting in the acetylcholine receptors in the brain. In this review we are trying to explore the possibilities of nicotine use as an augmentation therapeutic agent at the treatment of mental disorders.
Methods: Thorough research of the main medical databases, and web search engines for relevant studies. We scrutinize them independently, before reaching consensus about appropriateness.
Results: Although antipsychotic drugs are therapeutically effective in attenuating the hallmark symptoms of schizophrenia, these improvements do not return most patients to normative standards of cognitive function and thus complementary drug treatment may be needed. Nicotine has positive effect in extra pyramidal symptoms, attention, concentration, cognitive function and acoustic prepulse inhibition. Research is not conclusive in the positive affects in schizophrenia as other researchers report troubling results.
Conclusions: Nicotine is a novel and promising therapeutic agent with complex interactions with other neurotransmitters in the brain. Before condemning nicotine along with smoking we should acknowledge the potential use of nicotine as a therapeutic compound since research shows that some of these positive effects appear not only to smokers after abstinence but also to non smokers. Contemporary research focus on neuronal nicotinic acetylcholine receptors (nAChRs) and particularly subtypes 7 nAChRs, and alpha 4/beta 2 nAChRs, may play a significant role in mental health symptoms and disorders.The implications of nicotine receptor modulation is currently under investigation, utilizing techniques that include psychopharmacological, cognitive, electrophysiological and neuroimaging analysis.

P-39-005
Atypical antipsychotics combination at medical discharge from psychiatry hospitalization unit

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Objectives: To describe the pattern of combination of atipycal antipsychotics (AA) in a sample of patients recently discharged from psychiatry hospitalization service. To analyse reasons for prescribing more than one AA in this sample.
Methods: All patients discharged during 2008 from psychiatry hospitalization unit of Parc Tauli Hospital, treated with AA, were recruited. Sociodemographical data and clinical data (including evaluation with several psychopatological scales) were compiled. A comparison between sample treated with single AA and sample treated with two or more AA was carried out.
Results: 20% of discharged patients treated with AA were treated in combination. The main DSM-IV diagnostic were paranoid schizophrenia followed by other types of schizophrenia, and by schizoaffective disorder. Looking at study variables, some statistically significant differences between two samples were found, being the combination AA group older, mainly men, with higher rates in psychopathological scales. They have spent longer period in unit, and they have longer illness. Just one of them have been treated whit single clozapine, and it was changed for adverse effects (sedation). The most frequent combination was risperidone with olanzapine, followed by olanzapine with ziprasidone and depot risperidone with quetiapine. The combination of depot and oral risperidone was also surprisingly frequent (5% of the sample).
Conclusions: Treatment with AA combination at discharge from hospitalization unit is a frequent practice in our environment, though there does not exist robust scientific evidence that supports it. It is possible to find clinical specific characteristics for those treated with multiple AA.

P-39-006

Treatment of severe hospitalized bipolar affective and schyzoaffective disorders in naturalistic conditions: Gender differencies

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Objectives: Determine the treatments patterns in a clinical sample of severe BD inpatients.
Methods: Population: Older than 18 years inpatients with DSM-IV diagnostic of Affective or Schizoaffective BD. Design: Analysis of consecutive admission of BD (both Affective and Schyzoaffective) between 11/2003 and 09/2007. We describe the gender-related prevalence in different psychopharmacological subgroups and different individual drugs. Descriptive stadistical analysis.
Results: We detected 283 consecutive episodies, corresponding to 205 inpatients, 146 males. Mean age 42.4y, predominantly BD Type I (145 episodies, 51.2%) and in phase maniac (143 episodies, 50.5%). Schizoaffective BD received lower frequently lithium (both actual and lifetime) or other eutimizants patterns and similar frequency of antipsychotic treatments than Affective BD Type I. Rapid-cycling have higher prevalence of lifetime treatment with lithium. Men received more eutimizants and more eutimizant monotherapy than women. Men also received more frequently lithium, valproate, oxcarbacepine and lamotrigine than women. Only carbamacepine and topiramat were more frequents in women. All the dosages (except for topiramate) are higher in men. Men received more frequently antipsychotic monotherapy and more olanzapine, oral risperidone, amisulpride, long-acting risperidone and depot zuclopentixol than women, but women received more frequently quetiapine, ziprasidone, haloperidol and clotiapine. All neuroleptic dosages (except quetiapine, ziprasidone and, more significantly, long-acting risperidone) are lower in women. The clinically relevant secondary side effect are higher in women (28%) than in men (23.8%), specially parkinsonism (11.25 vs 8.9%).
Conclusions: In our sample, there are relevant gender differences in naturalistic treatment patterns and dosages.

P-39-007

Prepulse inhibition of the startle response in amisulpride-treated patients: Comparison with typical antipsychotics

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Objectives: Individuals with schizophrenia are known to show deficits in prepulse inhibition (PPI) of the startle response (1). PPI refers to a response suppression in reaction to a strong startling stimulus, if preceded briefly by a weak non-startling stimulus and represents a well-established animal model to investigate information processing deficits in schizophrenia. It has been reported that prepulse inhibition deficits may be responsive to and at least partially reversed by treatment with atypical antipsychotics but not with typical antipsychotics (2). Despite clear evidence of gating and habituation mechanisms in animal models, it is still unknown which neurotransmitter systems are involved in schizophrenic patients. Thus, we compared the effects of a combined 5-HT2A/D2 and a pure D2/D3 antagonist on PPI in patients with schizophrenia.
Methods: The the acoustic startle response (ASR) was measured in 10 acute schizophrenic patients who were randomized and treated with amisulpride (atypical antipsychotic) or zuclopenthixol (typical antipsychotic). Patients were assessed during the first week and after eight weeks of treatment. Twenty healthy matched control subjects were examined likewise. Primary dependent measures were startle responsivity and prepulse inhibition (response inhibition with the prepulse preceding the pulse by 30, 60 and 120 ms).
Results: Patients when treated with typical antipsychotic showed significantly less PPI than healthy subjects and than when they were receiving Amisulpride. Subjects treated with Amisulpride did not differ from control subjects for PPI measures.
Conclusions: Our preliminary findings suggest that the PPI-restoring effect of antipsychotics is probably attributed to a dopamine D2 receptor blockade (3). References 1. Braff et al., (2001).Schizophr Res 49:171 –178 2. Kumari V et al., (2002). Schizophr Res 55: 139-146. 3. Quednow et al., (2006). Biol Psychiatry. ;59:536-45

P-39-008

Expirience with zuclopenthixol on female forensic ward in specializad psychiatric hospital "gornja toponica"

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Objectives: Clopixol, with generic name zuclopenthixol, is thioxanthene derivate with strong antipsychotic and sedative effect. It is used for the firs time in our Hospital.
Methods: Five female patients are included on this agent. All of them are long-term hospitalised schizophrenic patients and they had poor outcome on previously used antipsychotics. Washout period lasted three days. After inclusion on Clopixol, from September 2008, they recived medicament as a monotherapy. We applied Brief Psychiatric Rating Scale (BPRS), Clinical Global Impression Scale (CGI), Positive and Negative Symptoms Scale (PANSS) and Simpson-Angus Scale. We started therapy with Clopixol by applying Clopixol Acuphase 50 mg, every third day and continued with Clopixol Depot 200 mg every two weeks combined with Clopixol Tablets in daily dose from 25-75 mg.
Results: All five patients are still on Clopixol therapy and have good outcome. Comparing to baseline all of them showed improvement on used scales. As a side effects, we registrated hipotension, which required simptomatic therapy in low doses. The patients did not show symptoms of extrapiramidal syndrom. There were no reasons for discontinuation.

P-39-009

Influence of clopixol monotherapy on improvement of quality of life in inpatient conditions on female forensic ward in specialized Psychiatric Hospital "gornja toponica"

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Objectives: We are using in our Hospital Clopixol, with generic name zuclopenthixol, during last four months. Five female patients from Forensic ward were included on this agent.
Methods: Besides clinical improvement and improved rates on used scales:Brief Psychiatric Rating Scale (BPRS), Clinical Global Impression Scale (CGI), Positive and Negative Symptoms Scale (PANSS) and Scale of extrapiramidal side effects, we noticed improved activities which reflect quality of life in inpatient conditions.
Results: All treated patients, during follow-up period, had opportunity to take walk out of ward twice a day without praesens of stuff, were included in different occupational and work activities, established contacts with their families through therapeutic weekends more than earlier. They participated in all organised activities on ward or hospital level: celebrations, shoping in the city, visiting theatre or concerts.

P-39-010

Psychological stress and body temperature: Effects of Alprazolam and Flupentixol

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Objectives: Acute stress induces hyperthermia by activating the autonomic nervous system. Since the autonomic response also contributes to manifestation of anxiety disorders we were interested if anxiolytic drugs can block the raise of temperature under acute stress.

Methods: In this study we explored in 69 healthy men (age 18-45 years) effects of psychological stress under laboratory conditions (Trier Social Stress Test) on body temperature, as verified by an infrared camera and ear thermometer. Skin and ear temperature were analyzed in three groups, which either received a single dose of placebo (n=23), 1mg Alprazolam (n=23) or 0.5mg Flupentixol (n=23). Medication was administered 1 or 3 hours prior to the stress protocol, respectively.
Results: ANOVAs revealed that under placebo conditions, ear temperature was highest in anticipation of the stressor, and this effect was significantly lower under Alprazolam. The average skin temperature of the probands' faces during the psychosocial stress test continuously increased under all 3 conditions, while this effect was significantly blunted by Alprazolam.
Conclusions: In sum, our data show dissociation in the progression of ear and skin temperature. Furthermore, Alprazolam reduced temperature measures independent of the locus of assessment.

P-39-011
Haloperidol and atypical antipsychotics in the long-term treatment of psychotic disorders: Preliminary data from a naturalistic study

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Objectives: The treatment of psychotic disorders consists not only in the remission of acute symptoms, but also in the prevention of relapses. The aim of this naturalistic study is to evaluate the prevention of relapses for patients treated with haloperidol vs atypical antipsychotics.
Methods: 93 outpatients, treated with a single antipsychotic for at least 3 months and with a DSM-IV diagnosis of Schizophrenia (n=57), Schizoaffective Disorder (n=16), Delusional Disorder (n=16), Substance-Induced Psychosis (n=4), were divided into two groups according to the prescribed pharmacological treatment: haloperidol (n=37) and atypical antipsychotics (n=56) (risperidone=28, olanzapine=23, quetiapine=3 and clozapine=2). The main demographic and clinical variables were compared between the 2 sub-groups using $\chi 2$ tests for dichotomous variables or t-tests for continuous ones. A survival analysis (Kaplan-Meier) of the follow-up period (4 years) was performed considering death events as the change of treatment due to hospitalization, side effects or relapses.
Results: The two groups were homogenous regarding gender ($\chi 2$=0.79, df=1, p=0.403), age (t=- 0.182, p=0.856), age at onset (t=-0.614 p=0.541), diagnosis ($\chi 2$=8.733, df=5, p=0.09) and comorbidity with substance abuse ($\chi 2$=4.429, df=3, p=0.231). Survival analysis did not show any differences in terms of survival between the two treatment groups (Log Rank: $\chi 2$=8,532, p=0.683; Breslow: $\chi 2$=8,532, p=0.852). Side effects, in particular extrapyramidal ones, were more frequent in the group treated with haloperidol respect the other group ($\chi 2$=17.342, df=8, p=0.005).
Conclusions: Results did not show any difference between haloperidol and atypical antipsychotics in terms of survival. The group treated with haloperidol showed more frequently side effects, in particular extrapyramidal ones (EPS), affecting disability and low quality of life. However the relatively small size of the sample do not allow to reach definitive conclusions that should be regarded as preliminary.

P-39-012
Quetiapine and hypothyroidism: A literature review

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Objectives: Recently, there is an interest in the possible association between quetiapine and hypothyroidism. The aim of this study is to critically review all the reported cases in the international literature.
Methods: A Medline search for all studies dealing with quetiapine induced hypothyroidism was carried out from January 1997 to December 2008.
Results: Published literature on quetiapine's impact on thyroid function consists of 2 double-blind studies, 2 open label studies, 3 case reports and data from the product monograph. A study in elderly psychotic patients revealed only small decreases in T4 levels, while another one in adolescents showed trends for decrease in T4 and a marked increase in TSH. An observational study of thyroid function in patients treated with quetiapine and other antipsychotics found a decrease in T4 with no changes in TSH and T3 and another one only slight increases in TSH. In the case reports all patients exhibited clinical hypothyroidism. In one case there was a positive history of hypothyroidism, while in another one the patient had experienced lithium induced hypothyroidism in the past. According to the quetiapine product monograph, 0.4% of patients experienced TSH increases and half of them required thyroid replacement treatment. In studies where quetiapine was adjunct to lithium or divalproate, 12% of patients had elevated TSH levels.
Conclusions: We suggest a careful thyroid monitoring for patients initiating quetiapine, since hypothyroidism may emerge and masquerade psychopathologic manifestations. However, there is an open question whether thyroid dysfunction could spontaneously resolve even without quetiapine discontinuation.

P-39-013
Spontaneous resolution of quetiapine induced hypothyroidism without quetiapine discontinuation

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Objectives: Quetiapine induced hypothyroidism is a rare side effect requiring either drug discontinuation or initiation of thyroid replacement therapy. We highlight the potential reversibility of quetiapine induced hypothyroidism in two cases.
Methods: Two case reports.
Results: Case 1. Quetiapine (200mg/day) was initiated to a psychotic female patient due to exaggeration of positive symptomatology. Although her thyroid function tests (TFTs) upon admission were normal, after a month significant decreases in T3 and T4 level and an elevation in TSH was observed. 45 days later the TFTs returned to normal, although she remained on quetiapine. Case 2. Quetiapine (300mg/day) was prescribed to a bipolar male patient due to a mixed affective episode with a very good response. Despite his normal admission TFTs, three weeks later a decrease in total T4 level and a marked increase in TSH were observed. 45 days later, despite remaining on quetiapine without thyroid replacement therapy, TFTs returned within reference range.
Conclusions: These are the first cases reporting reversibility of quetiapine induced hypothyroidism without quetiapine discontinuation. Published clinical trials support quetiapine related decreases in T4 and T3 levels and minimal effects on TSH secretion, which are dose-dependent and linked to a positive history of thyroid abnormality. These changes are maximal in the first two to four weeks of treatment and have been reported to persist during more chronic therapy. Both of our patients presented hypothyroidism with low doses of quetiapine, despite having a negative history of thyroid disease. Besides, hypothyroidism resolved although the antipsychotic therapy was continued and no thyroid replacement therapy was given. We suggest a careful thyroid monitoring for patients initiating quetiapine. However, physicians should wait in cases of thyroid dysfunction, since thyroid dysregulation may soon resolve.

P-39-014
Impact of haloperidol and Quetiapine on the expression of genes encoding antioxidant enzymes in human Neuroblastoma SH-SY5Y cells

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Objectives: Antipsychotics are known to alter antioxidant activities in vivo. Therefore, the aim of the present study was to examine in the human neuroblastoma SH-SY5Y cell line the impact of a typical (haloperidol) and an atypical (quetiapine) antipsychotic on the expression of genes encoding the key enzymes of the antioxidant metabolism (Cu, Zn superoxide dismutase; Mn superoxide dismutase; glutathione peroxidase; catalase) and enzymes of the glutathione metabolism (gamma-glutamyl cysteine synthetase, glutathione-S-transferase, gamma-glutamyltranspeptidase, glutathione reductase).
Methods: The cells were incubated for 24h with 0.3, 3, 30 and 300 µM haloperidol and quetiapine, respectively; mRNA levels were measured by polymerase chain reaction.
Results: In the present study, we observed mostly significant decreases of mRNA contents.With respect to the key pathways, we detected mainly effects on the mRNA levels of the hydrogen peroxide detoxifying enzymes. Among the enzymes of the glutathione metabolism, glutathione-S-transferase- and gamma-glutamyltranspeptidase-mRNA levels showed the most prominent effects.
Conclusions: Taken together, our results demonstrate a significantly reduced expression of genes encoding for antioxidant enzymes after treatment with the antipsychotics, haloperidol and quetiapine.

P-39-015
Effect of perospirone on sLORETA images of P300 and social cognition in schizophrenia

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Objectives: The purpose of this study was to determine if perospirone, a second generation antipsychotic drug and partial agonist at serotonin-5-HT1A receptors, enhances electrophysiological activity, such as event-related potentials (ERPs), in frontal brain regions, as well as cognitive function mediated by frontal lobes, e.g. social cognition, in subjects with schizophrenia.
Methods: Twenty right-handed patients with schizophrenia, who gave written informed consent, participated in the study. P300 current source images were obtained by means of standardized low resolution brain electromagnetic tomography (sLORETA) before and after treatment with perospirone for 6 months. Social cognition, as measured by the script tasks, and verbal learning memory, as measured by a word memory test, were also evaluated.
Results: Perospirone significantly increased P300 current source density in the left superior frontal gyrus, and improved positive symptoms and performance on the script tasks, while verbal learning memory tended to be improved. There was a significant correlation between the changes in P300 amplitudes on the left frontal lead and those in the scores of the script tasks.
Conclusions: These results suggest that changes in three-dimensional distribution of cortical activity, as demonstrated by sLORETA, may mediate some of the actions of antipsychotic drugs. The distinct cognition-enhancing profile of perospirone in the treatment of schizophrenia may be related to its actions on 5-HT1A receptors.

P-39-016
Cognitive remediation therapy in schizophrenia: Experience of a 12-month follow up group

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Objectives: Schizophrenia is associated with a poorer patient outcome and cognitive difficulties. These impairments have a direct impact on the quality of life. A year-long program of IPT was used to remediate cognitive deficits in outpatients with schizophrenia who were participating in this program.The integrated psychological treatment for schizophrenia is composed of six modules that can be implemented either separately or in an articulated way.
Methods: In this case, we used the first phase, with exercices specifically focused on selective attention,memory, logical-reasoning, perception and communication skills. We followed a group of five stable outpatients with predominant DSM 4 defined schizophrenia, during one year. Symptoms where assessed with: Trail Making Test, Wisconsin Card, Stroop Test, WAIS, verbal fluency test, and the self-esteem scale of Rosenberg. Measurments were taken at the beginning and the end of the program.
Results: Patients attended the workshop on a regular basis. We noticed positive interaction between participants. In our study, cognitive functions, social autonomy, self-esteem and symptoms, were improved by the IPT program.
Conclusions: These results confirm that the therapeutic impact of cognitive remediation therapy among schizophrenic patients were stabilized.

P-39-017
Use of aripiprazole and clozapine in the treatment of resistant schizophrenia: Two case reports

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Objectives: Treatment-resistant schizophrenia poses a real therapeutic problem. Clozapine is a very good standard treatment for resistant schizophrenia. But Clozapine monotherapy is not enough for 40 to 70 % of the patients in treating refractory schizophrenia.
Methods: Two patients with DSM4 schizophrenia who had refractory schizophrenia, with a poor or partial response to long-term Clozapine treatment were followed. We measured the BPRS, SANS and SAPS to evaluate their symptoms. These studies were conducted from August 2008 through January 2009.
Results: We noticed an improvement with Aripiprazole treatment with Clozapine for negative symptoms assessed by the BPRS negative symptoms sub-scale and the SANS total score but not for positive symptoms. The contact was better, the patients could speak, and their anxiety disappeared. They also had less cognitive disturbances. Because of this, they could begin to integrate into the psychosocial rehabilitation program.
Conclusions: Favorable clinical results were noticed in all two patients, with no noticeable adverse side effects. Aripiprazole associated with Clozapine can improve the negative symptoms of schizophrenia in treatment-resistant patients, who have failed to respond to Clozapine alone.

P-39-018
The A-effect of aripiprazole

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Objectives: The unique effectiveness of aripiprazole, the "A-Effect", as compared with that of other currently available antipsychotic drugs has not been well characterized or definitively established. If such an effect exists, identifying its mechanism of action and beneficiaries presents opportunity for clinical improvement in some patients who would otherwise endure a greater degree of illness, as well offer insight into the heterogeneity of schizophrenia. To evaluate the A-Effect, we compare aripiprazole with typical and atypical antipsychotics through the review of cases provided by primary treating psychiatrists.

Methods: This study drew on the expertise of psychiatrists experienced with aripiprazole and employed several methods to systematize and codify their clinical observations of its use. Twelve psychiatrists were recruited and were interviewed individually to report their various qualifying cases and to complete the Positive and Negative Symptoms Scales (PANSS), the Salience Scale and the Clinical Observation Scale.
Results: Twenty-eight cases manifesting the A-Effect were collected, consisting of 12 male and 16 female patients, ranging in age from 10 to 80 years old, diagnosed with schizophrenia (n=13, 46.4%), schizoaffective disorder (n=4, 14.3%), affective disorder (n=7, 28%), conduct disorder (n=3, 10.7%) and dementia (n=1, 3.6%). While 37.5% of patients received aripiprazole monotherapy, the rest of the group received a combination regimen that included other antipsychotic medications, mood stabilizers and antidepressants. The major difference between aripiprazole and seven other antipsychotic drugs was the perceived advantage of the former in active social avoidance, emotional withdrawal and difficulty with abstract thinking as measured by PANSS, and improvement in mood, energy, cognition and appropriate social interaction measured by the Clinical Observation Scale and the Salience Scale.
Conclusions: Study results suggest that aripiprazole has a unique beneficial effect on interpersonal function, emotional expression, mood and cognition distinctly different from and, in some patients, superior to that of other antipsychotic treatments.

P-39-019
Flexible doses of paliperidone ER in non-acute patients with schizophrenia switched due to lack of tolerability with their previous oral antipsychotic

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Objectives: To explore tolerability, safety and maintained efficacy of flexibly dosed paliperidone ER in adult non-acute patients with schizophrenia requiring a change in their medication due to lack of tolerability with their previous oral antipsychotic.
Methods: Interim analysis of a prospective 6-month, open-label, international study after 3 months of paliperidone ER treatment. Endpoints were the change in the Positive and Negative Syndrome Scale (PANSS) from baseline to endpoint, Clinical Global Impression-Severity Scale (CGI-S), Extrapyramidal Symptom Rating Scale (ESRS), weight change and adverse events (AEs).
Results: 124 patients were included (62.1% male, mean age 39.2±12.3 years, 87.9% paranoid schizophrenia). 85.5% of patients completed the first 13 weeks of the study. Main reasons for early discontinuation were AE (4.0%), subject choice (3.2%) and lack of efficacy (2.4%). The average dose of paliperidone ER was 6.1±2.2 mg/day. A ≥ 20% reduction in total PANSS at endpoint was observed in 57.7% of patients. Mean total PANSS decreased statistically significantly from 67.1±16.6 at baseline to 57.0±13.8 at endpoint (mean change -10.1±16.6; 95% confidence interval [CI] -13.1;-7.2, p<0.0001). TEAEs reported in ≥ 5% of patients were insomnia (12.1%) and anxiety (8.9%). Total ESRS decreased from 6.1±8.0 at baseline to 3.6±7.0 at endpoint (p<0.0001). Mean weight change from baseline to endpoint was 0.5 kg (95%CI -0.12;1.11, p=0.046).
Conclusions: These interim data support results from recent randomized controlled studies that flexibly dosed paliperidone ER is safe, well tolerated and effective in patients with schizophrenia requiring a change in medication due to lack of tolerability with their previous oral antipsychotic treatment.

P-39-020
A flexible-dose study of paliperidone ER in non-acute patients with schizophrenia previously unsuccessfully treated with oral risperidone

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Objectives: To explore tolerability, safety and treatment response of flexible doses of paliperidone ER in adult non-acute patients with schizophrenia transitioned due to lack of efficacy of previous oral risperidone treatment.
Methods: Interim analysis of an international prospective 6-month, open-label study. Endpoints were the Positive and Negative Syndrome Scale (PANSS), Clinical Global Impression-Severity Scale (CGI-S), patient satisfaction, adverse events (AEs), extrapyramidal symptoms (Extrapyramidal Symptom Rating Scale; ESRS) and weight change.
Results: 81 patients were included (52% female, mean age 39.8±12.9 years, 74% paranoid schizophrenia). 84% of the patients completed the 6-month study. Reasons for early discontinuation were lack of efficacy (8.6%), lack of efficacy plus AE (3.7%), loss to follow-up, patient choice and AE (1.2% each). The median mode dose of paliperidone ER was 6 mg/day. 64.2% of patients had a greater than or equal to 20% improvement in total PANSS at endpoint. Mean total PANSS decreased statistically significantly from 82.7±18.1 at baseline to 70.9±25.4 at endpoint (mean change -11.8±19.6; 95% confidence interval -16.1;-7.5, p<0.0001). The percentage of patients rated mildly ill or less in CGI-S increased from 23.4% to 48.2% at endpoint. Patient satisfaction rated "good" or "very good" at endpoint was 67.5%. The only TEAE reported in greater than or equal to 5% was insomnia (14.8%). Extrapyramidal symptoms in ESRS decreased statistically significantly from 2.9±4.3 to 1.5±3.1 (p<0.0001). Mean weight change from baseline to endpoint was 0.96±3.96 kg (p=0.066).
Conclusions: These data support results from recent randomized controlled studies that flexibly dosed paliperidone ER is safe, well tolerated and effective in patients previously unsuccessfully treated with oral risperidone.

P-39-021
Safety, tolerability and treatment response of flexible doses of Paliperidone ER in acutely exacerbated patients with schizophrenia

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Objectives: To explore tolerability, safety and treatment response of flexible doses of oral paliperidone ER in patients with schizophrenia suffering from an acute episode.
Methods: Six-week prospective, open-label, international study. Endpoints were the rate of responders defined as a ~30% improvement in the Positive and Negative Syndrome Scale (PANSS) from baseline to endpoint, the Clinical Global Impression-Severity Scale (CGI-S), weight change and adverse events (AEs).
Results: 294 patients were analyzed (53% male, mean age 40.3±12.4 years). 80% of patients completed the study. Most frequent reasons for early discontinuation were subject choice (9%) and lack of efficacy (6%). The mean dose of paliperidone ER was 7.5±2.1 mg/day. An improvement of ≥ 30% in total PANSS was observed in 66% of patients (95% confidence interval [CI] 61%;72%], with a decrease in mean total PANSS score from 100.2±17.2 at baseline to 72.7±20.3 at endpoint (mean change -27.5±20.1; 95%CI -29.8;25.2, p< 0.0001) and an onset of efficacy as of day 2. The percentage of patients rated as at least markedly ill in CGI-S decreased from 74.1% to 19.7%. AEs reported in at least 5 % were insomnia (23%, only 5% assessed as causally related to study medication), tachycardia (9%), headache (7%), extrapyramidal disorder (7%), and anxiety (5%). Mean weight gain was 0.6 kg (95% CI 0.29;0.98) from baseline to endpoint.
Conclusions: This flexible dose study supports data from recent controlled studies that flexibly dosed paliperidone ER is safe, well tolerated and associated with a clinically meaningful treatment response in patients suffering from an acute schizophrenic episode.

P-48
Psychopharmacology / Antipsychotics III

P-48-001
Reasons for olanzapine discontinuation in Japanese patients with schizophrenia. Comparison with the results of CATIE

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Objectives: Although there are many clinical researches that evaluate antipsychotic discontinuation, those are few in Japan. In this report, we focused on olanzapine which showed the lowest discontinuation rate in the CATIE. We uniquely and constructively investigated the discontinuation rate and the reasons for discontinuation.
Methods: Subjects were 20 Japanese outpatients with schizophrenia at the Teikyo University Hospital who began the olanzapine therapy. Discontinuation rate and the reasons for discontinuation were investigated for 12 months.
Results: Nine cases were able to continue the olanzapine treatment (45%). Others discontinued the treatment for the following reasons: one case of insufficient effect (5%), nine cases of side effects (45%), one case of data untraceable (5%). Difference in the discontinuation rates of olanzapine among the patients' age, sex, duration of the disorder, severity of the symptoms at the start of the study, presence of a former treatment, and usage of concomitant drug was not observed.
Conclusions: The discontinuation rate and the discontinuation reason for olanzapine in this report confirm the results of the CATIE although there is a big difference in the designs of the two studies.

P-48-002
Evaluating clozapine dose - response relationship using EEG monitoring

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Objectives: Clozapine is an atypical antipsychotic drug widely used in refractory Schizophrenia. However, drug toxicity, side effects, mortality and tolerability has been a matter of concern. Normally the dose adjustment of clozapine is bases upon clinical judgment and WBC count and appearance of other side effects. There is no clear therapeutic marker for precise decision regarding dose escalation. Serum level of clozapine has been found helpful. However this facility is neither available in developing countries nor it unequivocal in its merit. Studies suggest that's serum level and efficacy possibly has some correlation, however this complex area needs further studies.
Methods: A naturalistic cross sectional cohort study was undertaken to find out possible correlation between dose, efficacy and EEG pattern. Fifty patients completed the study out of 99 recruited. These patients were assessed by clinical parameters and by using PANSS for defining outcome. Electroencephalographist recorded a conventional 10-channel EEG. All assessment tools including EEG were applied at weeks 4,8 and 12.
Results: Findings suggest that clozapine is effective in chronic and resistant schizophrenia in about 50% patients at a mean dose of 450 mg/day, and significant EEG abnormalities are observed in 56% patients. There is statistically significant positive correlation with mean dose of 450 mg/day, and prevalence of EEG abnormalities. Variety of EEG abnormalities like slow waves, spikes, and sharp waves were observed. The study implies that dose escalation beyond 450 mg needs to be done with grate caution.
Conclusions: Preliminary findings suggest that it may be possible that EEG may serve as a marker of response & dosing in therapeutics of clozapine, However it required further well controlled study in a large sample, and that this needs to be further studied.

P-48-003
Does Neuroendocrine offer an outcome predictive indicator: Experience of Serum Prolactin in 5 year outcome in first episode drug naive patients

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Objectives: Serum prolactin is an indicator of tuberoinfundibular dopamine activity. It has been reported to be increased in wide variety of mental illness. It has close relationship with antipsychotic therapy. However its relationship with psychopathology and outcome is not clear.
Methods: Serum prolactin level was measured in 30 male and 30 female drug naive patients of schizophrenia. Subsequently, these patients were treated with antipsychotics. The severity of psychopathology at the baseline and subsequent improvement at the end of 3 weeks and 6 weeks was assessed on modifies brief psychiatric rating scale (BPRS). Available to follow up at five years 18 males & 22 females patients were reassessed and findings analyzed for predictive significance.
Results: Contrary to the expectations, a two-fold increase in serum prolactin level was observed in drug naive male and female patients of schizophrenia. The difference was found to be statistically significant in males. No correlation was observed between the baseline serum prolactin level and the severity of baseline psychopathology and subsequent improvement in psychopathology at the end of 3 weeks and 6 weeks. The difference was statistically significant in males but it was not found to be significant in females probably due to a relatively small sample size. However correlation at 5 years outcome in psychopathology and level of functioning in both males and females was found to have significant correlation. Though at base male and females both did not show any significant correlation as individual groups but at the 5 years follow up, male, females individually and total group, all three showed statistically significant correlation.
Conclusions: From the present study it seems that baseline serum prolactine level in drug naive patients of schizophrenia may not be a reliable indicator of psychopathology but it may be an indicator of good prognosis in long term. Further research is necessary to arrive at a definite conclusion.

P-48-004
Does Serum Prolactin elevation & Prolactin related side effects of atypical antipsychotics represent a Prolactin-Dopamine subgroup in schizophrenia

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Objectives: Prolactin related side effects often determine compliance in schizophrenia and atypical antipsychotics show a significant increase in serum prolactin level as well as Prolactine related side effects. It is not very clear that those subjects who develop prolactin related side effects possibly due to sustained levels of prolactin, are a distinct subgroup in heterogeneity of schizophrenia. The present study attempts some of these issues in a prospective hospitalized cohort in India, specifically to find out patterns of rise in serum prolactin in response to two atypical antipsychotic drugs, cocaine and risperidone at a fixed duration of 60 days in schizophrenics switched over to atypical antipsychotics.
Methods: Prolactin level was assessed in 120 patients: thirty patients each in four groups, male and female (premenopausal) treated with clozapine and risperidone, using radioimmuno assay technique (RIA).Serum prolactin was estimated at baseline after seven days washout in hospital and at the end of 60 days. The prolactine related side effects were studies and correlated with serum prolactin
Results: The treatment groups were demographically comparable. Maximum rise of prolactin was observed in risperidone treated female group ([X bar] = 110micrograms/L). The two groups differed significantly on dosage (clozapine [X bar] = 224mg and risperidone 4.1mg $P < 0.001$). There was significant rise of serum prolactin at 60 days compared with baseline in risperidone group ([X bar] = 76, $P < 0.001$) than clozapine group treated group. Fifteen percent of patients in clozapine treated group & 23% in respiridone treated group were significantly symptomatic, however there was no significant difference in the two groups.

Conclusions: High increase in prolactin in risperidone group was observed. However all patient do not develop raised prolactin. Few patients only develop prolactin related side effects without significant difference in risperidone or clozapine group. Findings and implications are discussed.

P-48-005

Study completion rates with Risperidone long-acting injectable and Olanzapine Pamoate: A review of published long-term studies

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Objectives: To compare 12-month study completion rates with risperidone long-acting injectable (RLAI) and olanzapine long-acting injectable (olanzapine pamoate; OP) in patients with schizophrenia as a proxy measure for treatment effectiveness.
Methods: Systematic review of published long-term studies with RLAI and OP meeting the following criteria: diagnosis of schizophrenia or schizoaffective disorder, prospective open-label design, study duration ≥ 12 months, dose range and dosing interval within the approved label, and no other exit criteria which influence completion rates, such as relapse. Demographics, baseline characteristics and differences in study designs and patient populations are summarized. Completion rates at 12 months were compared and a weighted completion rate for RLAI was calculated, accounting for significant differences in patient numbers.
Results: Seven published open-label, single arm, prospective 12-month studies were identified for RLAI, six of which met inclusion criteria for this analysis (total n=5,619), and one large published open-label, single arm, prospective 12-month study for OP (n=1,045). Reasons for exclusion of one RLAI study from the analysis was an injection interval outside the approved RLAI label. Completion rates at 12 months for RLAI were between 54.4% and 89.7% (mean 70.3%), and 72.2% for OP. The weighted mean completion rate for RLAI after accounting for differences in patient numbers was 74.0%.
Conclusions: In this analysis of published prospective long-term studies with risperidone long-acting injectable or olanzapine pamoate, 12-month treatment completion rates were comparable.

P-48-006

Tolerability, safety and treatment response of flexible doses of paliperidone ER in recently diagnosed patients with schizophrenia

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Objectives: Explore tolerability, safety and treatment response of flexibly dosed paliperidone ER in adult non-acute patients recently diagnosed with schizophrenia (less than or equal to 5 years) transitioned due to lack of efficacy with previous antipsychotic.
Methods: Interim analysis of an international prospective 6-month, open-label study. Endpoints were Positive and Negative Syndrome Scale (PANSS), Clinical Global Impression-Severity Scale (CGI-S), adverse events (AEs), extrapyramidal symptoms (Extrapyramidal Symptom Rating Scale; ESRS), weight change and patient satisfaction.
Results: 81 patients were included (60.5% male, mean age 33.4±11.1 years, mean duration of schizophrenia 2.3±1.8 years), and 75.3% completed the study. Most frequent reasons for early discontinuation were lack of efficacy (9.9%) and patient choice (6.2%). The median mode dose of paliperidone ER was 6 mg/day. 67.1% of patients had a ≥ 20% improvement in total PANSS. Mean total PANSS decreased from 80.7±14.2 at baseline to 65.1±19.4 at endpoint (mean change -15.6±19.7; 95% confidence interval [CI] -20.0;-11.2, p<0.0001). Percentage of patients rated mildly ill or less in CGI-S increased from 18.5% to 57.0%. Patient satisfaction rated "good" or "very good" was 13.5% with the previous antipsychotic and 63.6% with paliperidone ER. TEAEs reported in ≥ 5% were insomnia (14.8%), weight increase (7.4%), extrapyramidal disorder and somnolence (6.2% each). ESRS decreased from 2.3±3.8 to 1.3±2.9 (p=0.0039). Mean weight change from baseline to endpoint was 1.3 kg (95%CI 0.28;2.35, n.s.).
Conclusions: These data support results from previous randomized controlled studies that flexibly dosed paliperidone ER is safe, well tolerated and effective in recently diagnosed patients with schizophrenia previously unsuccessfully treated with other oral antipsychotics.

P-48-007

Long-term remission in schizophrenia and schizoaffective disorder: Results from the risperidone long-acting injectable versus quetiapine relapse prevention trial (ConstaTRE)

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Objectives: To report the long-term remission results from the relapse prevention trial (ConstaTRE) in stable patients treated either with risperidone long-acting injectable (RLAI) or the oral atypical antipsychotic quetiapine.
Methods: Clinically stable adults with schizophrenia or schizoaffective disorder treated with oral risperidone, olanzapine, or oral conventional antipsychotics, in whom a switch in treatment was indicated, were randomized to treatment with either RLAI (25, 37.5, or 50 mg every two weeks) or quetiapine (initiated at 300–400 mg/day) for 24 months. Efficacy and tolerability were recorded for up to 24 months of treatment. Remission was defined as achieving and maintaining mild or less symptoms of schizophrenia over a 6-month period as defined by Andreasen et al, 2005.
Results: 710 patients were randomized (n=355 per group) to either RLAI or quetiapine. 327 patients randomized to RLAI and 326 patients randomized to quetiapine were included in the efficacy analyses. Demographics were similar between treatment groups. Relapse occurred in 54 RLAI (16.5%) and 102 quetiapine (31.3%) patients (p<0.001). Full remission was achieved by 51% RLAI and 39% of quetiapine-treated patients (p=0.003) and was maintained until the end of the trial by 44% of RLAI and 31% of quetiapine patients. Mean duration of full remission was 540.8±181.4 and 508.1±188.0 days for RLAI and quetiapine groups, respectively (p=0.1325). Tolerability was similar between treatment groups. Most adverse events (AEs) were transient. Six RLAI and 10 quetiapine patients discontinued study treatment due to AEs.
Conclusions: Among stable patients with schizophrenia or schizoaffective disorder, remission was more likely to occur in patients switching to RLAI when compared with quetiapine. Both RLAI and quetiapine treatments were well tolerated.

P-48-008

Atypical neuroleptic risperidone modulates astroglial functions

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Objectives: Considering the putative involvement of astroglial cells in neuropsychiatric disorders, we investigated the effect of risperidone on parameters of astrocyte activity.
Methods: C6 glial cells were cultured in DMEM (pH 7.4) supplemented with 5% serum at 37oC/5% CO2. Experiments were performed in absence or presence of risperidone in a range from 10 to 40 μM. Glutamate uptake was measured by addition of L-[2,3-3H] glutamate. Glutamine synthetase (GS) activity was measured by colorimetric assay, glutathione (GSH) levels were measured by fluorimetric assay. Glial marker S100B was measured by ELISA. Cell death was performed by propidium iodide uptake assay. Data were analyzed statistically by ANOVA followed by Tukey´s test. $P < 0.05$ was considered significant.
Results: Risperidone was able to induce a significantly increase on glutamate uptake (32%); GS activity (15%); GSH levels (58%) and S100B secretion (80%). In the presence of high doses of risperidone, C6 cells become stellate, with process-bearing cells and partial retraction of the cell body followed by detachment from the adhesion surface with no cell death. Llysophosphatidic acid, a specific positive regulator of the GTPase RhoA, prevented the effects of risperidone on cell morphology.

Conclusions: These results indicate that risperidone is able to interfere with C6 cell activities without toxic effects. These data contribute to the proposal that glial cells are targets of risperidone, which could be involved in the therapeutic response of risperidone to improve autism and other psychiatric disorders.

P-48-009
Differential effects of olanzapine, risperidone and haloperidol on serum brain - derived neurotrophic factor levels and psychopathological variables in chronic schizophrenic patients

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Objectives: Studies suggest that second-generation antipsychotics (SGAs) compared to first-generation antipsychotics (FGAs) have neuroprotective effects through an alteration of expression of neurotrophic factors such as BDNF.
Methods: In the present study we investigate the effects of a 6 week treatment with olanzapine, risperidone and haloperidol on serum BDNF levels in 42 patients with schizophrenia in relapse and in 44 healthy controls.
Results: Healthy controls showed significantly higher serum BDNF levels compared to the group of patients with chronic schizophrenic disorder ($p<0.005$). Serum BDNF levels for healthy volunteers were 27.5 ± 8.2 ng/ml. In the drug-free state serum BDNF of relapsed patients with schizophrenia were 19.3 ± 8.6 ng/ml. Following a 6 week medication serum BDNF levels were 19.9 ± 10.7 ng/ml. Serum BDNF was increased significantly in the group of olanzapine after 6 weeks treatment (15.0 ± 4.8 vs 21.0 ± 4.3 ng/ml, $p=0.001$). In the olanzapine subgroup significant correlations were found between increased serum BDNF levels and decreased PANSS Positive and Negative subscale scores ($F=2.24$, $P<0.05$), whereas no such correlations were found in the haloperidol and risperidone groups.
Conclusions: Our results, in short term treatment, indicate possible differential effects of olanzapine, with regard to neuroprotection and improvement of positive and negative symptoms.

P-48-010
Skill proceduralization in schizophrenia – the differential effect of typical and atypical neuroleptics

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Objectives: Considering the different affinities of D2 receptors for typical and atypical neuroleptics (NLP), these drugs may differentially affect the functions of the striatum – a determinant brain structure involved in procedural learning. The question of skill proceduralization over time and under two different classes of NLP treatment was addressed in the present study.
Methods: Twenty six Schizophrenic (SZ) patients under atypical (risperidone; 2-6 mg) or typical (haloperidol; 2-40 mg) NLP medication and matched healthy participants were compared on a non-motor procedural task involving semantically-related inverted word pairs, at baseline, 3, 6 and 12 months later to determine the extent of skill consolidation.
Results: SZ patients were found to acquire new procedural skills necessary to read these inverted word pairs. However, relative to controls, all SZ participants showed generalized slowing of reading time performance, suggesting less efficient encoding. Furthermore, performance was poorer in the haloperidol-treated participants over the duration of the experiment, indicating that there is a differential impact of NLP medication on the acquisition and consolidation of a new skill.
Conclusions: Taking into account that the ability to perform activities of daily living may be governed by procedural learning, the present results have considerable implications for clinical management of SZ symptoms in regards to the choice of NLP treatment.

P-48-011
5-HT2A receptor occupancy in first episode schizophrenia patients treated with quetiapine

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Objectives: There is converging evidence that the serotonin 5-HT2A receptor is a unique therapeutic target in schizophrenia; it appears to be implicated in both the psychotic and the cognitive symptoms of the disorder. To date, there are no in vivo studies of the 5-HT2A receptor in first episode antipsychotic-naïve schizophrenic patients before and after sustained monotherapy with an atypical antipsychotic compound and therefore, the relationship between 5-HT2A receptor occupancy and treatment effect is unknown. The aim was tomeasure 5-HT2A receptor occupancy in antipsychotic-naïve first episode schizophrenic patients after 6 months of quetiapine monotherapy and to explore the relationship with quetiapine and nor-quetipine plasma levels and the treatment effect.
Methods: The participants were fifteen (10 males, mean age: 28.9 years, SD=5.4) first episode schizophrenic patients. The in vivo 5-HT2A binding before and after 6 months of quetiapine mono-therapy was measured with Positron Emission Tomography, and the 5-HT2A specific radioligand, [18F]altanserin in a bolus infusion approach. The 5-HT2A receptor occupancy was determined from an occupancy plot based on the regional distribution volumes in the unblocked, and in the partially blocked condition. The treatment effect was defined as the difference between the PANSS score at baseline and the PANSS score at the second scan.
Results: Significant nonlinear relationships were found between drug dose and 5-HT2A occupancy ($r2 =0.69$, $P<0.0001$) and between plasma quetiapine concentrations and 5-HT2A receptor occupancy ($r2=0.68$, $P<0.0001$). Furthermore, a significant nonlinear relationship was found between 5-HT2A occupancy and treatment effect on positive symptoms ($r2=0.75$, $P<0.001$), but not on negative symptoms.
Conclusions: This study supports that the 5-HT2A receptor has an important therapeutic role in the treatment of schizophrenia, and suggest that measurements of plasma drug concentrations can aid in the treatment of the individual patient.

P-48-012
The metabolism of chlorpromazine by human cytochrome P450 isoenzymes – a comparison with other phenothiazines

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Objectives: Our previous investigations indicated that differences in the structure of phenothiazine neuroleptics (mainly the structure of a side chain) influence their interaction with the catalytic site of cytochrome P450 (CYP). CYP1A2 and CYP3A4 are the main isoenzymes responsible for the 5-sulphoxidation of promazine, thioridazine and perazine. However, some inter-drug differences were observed in the catalysis of side chain N-demethylation (promazine - CYP1A2 and CYP2C19, thioridazine - CYP1A2 and CYP3A4, perazine - CYP2C19). The aim of the present study was to identify CYP isoforms (CYPs) involved in the 5-sulfoxidation, mono-N-demethylation and di-N-demethylation of the aliphatic-type phenothiazine neuroleptic chlorpromazine in human liver.
Methods: Chlorpromazine metabolism was examined in vitro using cDNA-expressed human CYPs (CYP1A2, CYP2A6, CYP2B6, CYP2C8, CYP2C9, CYP2C19, CYP2D6, CYP2E1, CYP3A4) at a therapeutic concentration of the neuroleptic (10 uM). The amount of chlorpromazine and its metabolites formed by CYPs was assayed using HPLC with UV detection.
Results: Mono- and di-N-desmethylchlorpromazine were formed only by CYP1A2, while the abilities of CYP isoforms to catalyze chlorpromazine 5-sulphoxidation was as follows: CYP1A2 > CYP2C19 > CYP3A4 > CYP2B6 > CYP2D6. Considering the obtained results and the relative expression of various CYPs in human liver, it has been estimated that CYP1A2 is the main isoform responsible for chlorpromazine 5-sulfoxidation (64%) and the only CYP isoform catalysing the mono- and di-N-demethylation of chlorpromazine (100%) at a therapeutic concentration of the drug. CYP3A4 contributes to a lesser degree to chlorpromazine 5-sulphoxidation (34%). The role of CYP2B6, CYP2C19 and CYP2D6 in the catalysis of the latter reaction seems negligible (0.1-2%).

Conclusions: The obtained results indicate that the catalysis of chlorpromazine 5-sulphoxidation and N-demethylation in humans exhibits a stricter CYP1A2 preference compared to the previously tested phenotiazines. These findings may have significant implications for the prediction of potential drug-drug interactions involving chlorpromazine and CYP1A2.

P-48-013

Asenapine improves a subchronic phencyclidine-induced deficit in object recognition memory in the rat

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Objectives: Asenapine is a novel psychopharmacologic agent being developed for schizophrenia and bipolar disorder. It has a unique human receptor signature characterized by high affinity for a range of serotonergic, dopaminergic, and α-adrenergic receptors, but no appreciable affinity for muscarinic cholinergic receptors. In previous experiments, asenapine improved phencyclidine (PCP)-induced reversal learning deficits in animal models. The novel object recognition (NOR) test provides a reliable method for assessing the ability of atypical antipsychotics to attenuate subchronic PCP-induced episodic memory deficits in rats. This study assessed the ability of asenapine to attenuate a subchronic PCP-induced deficit in episodic memory using the NOR paradigm in the rat.

Methods: Female Hooded-Lister rats received vehicle (intraperitoneally [IP] twice daily) or PCP (2 mg/kg IP twice daily) for 7 days followed by 7 drug-free days. Asenapine (0.01–0.075 mg/kg) or vehicle was administered subcutaneously 30 minutes before testing. In the acquisition phase, rats explored 2 identical objects for 3 minutes, followed by a 1-minute intertrial interval. In the retention trial, rats explored a familiar object and a novel object for 3 minutes. Exploration time of each object in each trial was recorded.

Results: In the retention trial, vehicle-treated animals spent significantly more time exploring the novel object than the familiar object ($P<0.001$); time spent exploring the familiar object increased in PCP-treated rats, abolishing this difference. Asenapine (0.01–0.075 mg/kg) attenuated the effects of PCP and significantly increased novel-vs-familiar object exploration time ($P<0.01$–<0.001 vs vehicle). Asenapine did not significantly reduce exploratory behavior at any dose tested.

Conclusions: Asenapine significantly attenuated the PCP-induced episodic memory deficit. The ability of asenapine to improve reversal learning and episodic memory deficits suggests potential use in the treatment of cognitive deficits in psychiatric disorders. This effect may be explained by enhanced release of cortical dopamine through antagonism at serotonin receptors.

P-48-014

The effects and characteristics of high-dose Quetiapine (equal/higher than 800mg/day) use

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Objectives: To assess the characteristics, efficacy and safety of high-dose quetiapine use

Methods: This was a retrospective, open label, naturalistic study. We reviewed the medical chart of whom had ever used quetiapine ≥800mg while they were admitted between January 1st, 2002 and December 31st, 2007 at Maryknoll General Hospital, Busan, South Korea. The subjects were selected among the In-patients who had ever used quetiapine 800mg/day. The study group was divided into three subgroups by dosage of ≤ 499mg. 500mg ~ 799mg and ≥ 800mg while they had been titrated. The primary outcome measure was the changes in PANSS As the second outcome measure, we compared the initial PANSS changes among the groups who were effective with quetiapine and who were not. We also assessed the dose at which side effects were occurred.

Results: For 6 years, there were 41 subjects who had ever used quetiapine ≥800mg a day. The PANSS changes were all statistically significant. Between the quetiapine-use group and quetiapine-discontinuation group due to ineffectiveness, the initial PANSS was 23.89±5.57 vs. 30.23±2.87 (positive score) and 15.63±4.33 vs. 22. 59±2.87(negative score) and there were no significant differences in general score (39.37±8.18 vs. 42.45±8.68) The most common adverse effects were dry mouth, sedation, constipation and dizziness while less common in dysuria, blurred vision, dysarthria and EPS. There were hardly observed the complications such as dysarthria, blurred vision and dysuria and only 1 EPS at≤499mg.

Conclusions: We observed that regardless of dose of quetiapine, there were statistically significant improvements in PANSS in subjects who had ever used quetiapine ≥800mg/day with favorable EPS Similarly, the initial PANSS was relatively assessed in high score in subjects who were ineffective to quetiapine.

P-48-015

Interaction of Aripiprazole with Citalopram and MDMA: Potential role of SEROTONIN 5-HT2B receptor antagonism

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Objectives: The atypical antipsychotic, aripiprazole has shown clinical efficacy as adjunct treatment with selective serotonin reuptake inhibitors (SSRI), for refractory depression (Hellerstein et al., Biol. Psychiatry 32, 2008) but the mechanism of this activity is unclear. Interestingly, whereas many atypical antipsychotics antagonise 5-HT2A/2C receptors, aripiprazole potently antagonises 5-HT2B receptors (Shapiro et al., Neuropsychopharmacology 28, 2003) a subtype that influences 5-HT transport in serotonergic neuronal cells (Launay et al., FASEB J. 20, 2006). Further, 5-HT2B receptors are implicated in the control of methylenedioxymethamphetamine (MDMA)-induced hyperactivity in mice (Doly et al. J. Neurosci. 28, 2008).

Methods: We therefore compared the influence of aripiprazole and of the selective 5-HT2B antagonist, LY266097, on (i) the increase in extracellular 5-HT levels induced by the selective 5-HT reuptake inhibitor, citalopram, in the prefrontal cortex of rats using in vivo microdialysis and (ii) MDMA-induced hyperactivity in mice.

Results: Citalopram (0.16-10 mg/kg, i.p.) dose-dependently increased extracellular 5-HT (320% of baseline values at 10 mg/kg) and the increase in 5-HT levels induced by citalopram (0.63 mg/kg; approx. 200%) was significantly decreased by pre-administration of aripiprazole (0.63 mg/kg, i.p.; 122%). The effect of aripiprazole was mimicked by the 5-HT2B antagonist, LY266097 (2.5 and 10 mg/kg, i.p.; 127 and 138%, respectively). MDMA (10 mg/kg i.p.) induced marked hyperactivity in mice (4-fold increase over vehicle-treated controls) which was significantly decreased by aripiprazole (0.04 to 0.63 mg/kg i.p.). The effect of aripiprazole was mimicked by LY266097 (0.01 to 0.16 mg/kg, i.p).

Conclusions: These data suggest that 5-HT2B receptor antagonism is involved in these neurochemical and behavioural effects of aripiprazole. Further, 5-HT2B antagonism may be of utility in the control of some aspects of neuropsychiatric disorders.

P-48-016
Neurotensinlike peptides with the properties peculiar to antipsychotics

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Objectives: Neurotensin is postulated to act as endogenous neuroleptic in CNS. The number of short neurotensin analog peptides were synthesized and tested for potential antipsychotic properties.
Methods: The total of 10 peptides was screened in both behavioral and receptor paradigms. The behavioral tests used were apomorphine induced «climbing» and stereotypy and 5-hydroxytriptophan induced «head twitch» performed in mice to estimate involvement of dopamine and serotonin systems respectively. Radioligand assays were carried out in rat frontal cortex and striatum using tritium labeled spiperone, olanzapine, ketanserin and mesulergine as probes for dopamine D2 and serotonin 5-HT2 receptors and olanzapine as reference standard. The atypical antipsychotic olanzapine was explored as a reference standard.
Results: Some of the peptides synthesized were shown to displace D2 and 5-HT2 receptor ligands from the sites of their specific binding. The ability of certain peptides (0.1-10 mg/kg) to block behavioral manifestation of dopamine and serotonin systems hyper function was demonstrated in animal experiments. The effects of the peptides in these tests were similar to that of olanzapine at therapeutic doses (0.1-1.0 mg/kg). The peptides studied did not exert any negative side effects at all acute doses used while olanzapine induced lethality at high doses. Olanzapine given both acute and chronically suppressed locomotion in mice, while the peptides stimulated the movement of the animals as well as their exploratory behavior in "open field" system. The latter may serve as indirectly evidence for stimulation of cognitive functions under peptide treatment.
Conclusions: The ability of peptides tested to interact with dopamine and serotonin systems which represent the main targets for atypical antipsychotics might be considered as the basis to create new antipsychotic medicines effective in the treatment of negative, positive and cognitive disorders in patients with schizophrenia and other psychoses with minimal undesirable side actions.

P-48-017
Effects of olanzapine on visual recognition memory in mice

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Objectives: One of the most important problems of the schizophrenic patients is the impairment of cognitive functions. It is known that typical antipsychotics don't have the ability to improve cognition dysfunction while atypical antipsychotics have beneficial effects on cognitive dysfunction (Meltzer and McGurk 1999, Woodward et al. 2005). Olanzapine is a widely used antipsychotic drug in schizophrenia, psychosis and depression. The aim of this study was to investigate the effects of olanzapine on memory functions in naive mice in the novel object recognition test. Besides the effects of olanzapine on locomotion and anxiety were also evaluated in open field test.
Methods: Olanzapine (0.2, 0.4, 0.6 mg/kg) was injected intraperitoneally 1h. before the tests. One way-ANOVA post hoc Tukey was used as a parametric test and Kruskal Wallis was used as a nonparametric test.
Results: Mice spent significantly less time ($p<0.01$) exploring the novel object compared to the familiar object in 0.4 and 0.6 mg/kg olanzapine treated groups. In the open field test, olanzapine (0.2-0.6 mg/kg) showed no significant effect on the total distance moved and on the velocity of the animals. Moreover it also exerted no significant effect on the time spent in the center zone and the distance to the center zone.
Conclusions: Our results confirm that olanzapine disturbs hippocampal dependent visual recognition memory in naive mice which can be explained by the anticholinergic effects of olanzapine. Furthermore it had no effect on locomotion or anxiety in the open field test in doses used.

P-48-018
The use of atypical antipsychotics in patients with substance-related disorders and posttraumatic stress disorder and their self-perception of quality of life

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Objectives: Nowadays some of atypical or second-generation antipsychotics (serotonin-dopamine antagonists) are started to be used more frequently for treatment of alcohol-related disorders (ARD), drugs-related disorders (DRD) and posttraumatic stress disorder (PTSD). Aim: The main aims of this research were to evaluate our experiences and results of using atypical antipsychotics in groups of patients suffering from ARD, DRD and PTSP, as well as to access the correlations between clinical results and self-perception of quality of life in mentioned patients.
Methods: 150 patients treated in Psychiatric Hospital Rab, Croatia, from ARD, DRD and PTSP included both gender, 18-45 years of age. In all of them, after few unsuccessfully attempts of treatment in our or in other hospitals, we started with treatment of patients with some of mentioned diseases using some of atypical antipsychotics such as quetiapine, risperidone, olanzapine, ziprasidone and sertindol. Basic methods of work were evaluation of medical documentation of patients, short interview with them as well as administration of questionnaire Short Form 36 (issues) Health Survey (SF-36) to access the patients' self-perception of quality of life.
Results: Preliminary results of this pilot study point on good answer of subjects with ARD, DRD and PTSP on treatment with atypical antipsychotics after several weeks of treatment. In 60-70% of all patients was noted clinicaly positive reaction on treatment, with no differencies related to gender or age. In the same time with clinical improvement, in those patients were also noted better self-perception of quality of life in relation to the others without clinical improvement.
Conclusions: Results of this research suggest a clinical improvement followed by improvement of subjective feeling of quality of life i.e. health in patients with ARD, DRD and PTSP treated with atypical antipsychotics.

P-48-019
CIPS: A naturalistic study of Consta in Polynesian subjects

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Objectives: To measure in a naturalistic setting the effects of use of Risperdal Consta on symptoms and function level and the tolerability of this treatment for Polynesian patients with established psychotic disorder.
Methods: Subjects were clients of ethnic specific (Pacific Island or Maori) services who were entered to the trial if the treating doctor believed they might benefit from Consta treatment. The primary exclusion was existence of any conditions which contra-indicated the prescribing of risperidone. Dose commencement and continuation decisions were made by the treating psychiatrist. The design was a before/ after type with baseline assessments made before commencement of treatment then at one and two year follow up after treatment. These assessments included PANSS, HoNOS, SSTICS, DAI, AIMS, Simpson Angus and Barnes scales. The function of the patient was evaluated and hospitalisations and crisis care needs were recorded.
Results: 56 subjects were enrolled. Of these 49 completed one year of treatment and 38 two. There were few reports of adverse treatment experiences. The overall 1 and 2 year analysis showed a decrease in the PANNS scores, total, positive and negative, between baseline and both follow up periods. There was evidence of improved personal and interpersonal function.
Conclusions: This client group where there has been past suggestion of a higher incidence of psychotic disorder and also an increased severity of illness with more involuntary treatment and incarceration showed high tolerability of Consta injection and encouraging signs of symptomatic and also functional improvement. The data available compares very favourably with outcome results in European and mixed-race studies internationally.

P-48-020

Risk factors of aripiprazole treatment discontinuation in japanese schizophrenia patients

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Objectives: Aripiprazole is second generation antipsychotics used widely all over the world. The aim of this study was to determine factors associated with aripiprazole treatment discontinuation in Japanese schizophrenia patients.

Methods: This was a retrospective cohort analysis of schizophrenia patients consecutively admitted to the Department of Neuropsychiatry at Kansai Medical University between August 1, 2006, and November 30, 2008, and treated with aripiprazole. Diagnoses were identified using DSM-IV codes. Kaplan-Meier survival curves were generated for the time-to-discontinuation data, and differences among treatment groups were compared using log-rank tests at an alpha level lower than 0.05 level of significance. All analyses were conducted using SPSS Version 15.0.

Results: 210 patients included in this study were divided into three groups by the aripiprazole dose (low dose group: < 6 mg/day, N = 65, moderate dose group: 7-17 mg/day, N = 52, high dose group: >18 mg/day, N = 65). Strong significance was detected between high dose group and low dose group with higher risk of discontinuation in low dose group ($p < 0.0001$). Significant difference could not be seen among following three strategies: (I) immediate aripiprazole initiation with simultaneous immediate discontinuation of other antipsychotics; (II) immediate aripiprazole initiation while tapering off other antipsychotics; (III) titrating aripiprazole upwards while tapering off other antipsychotics in 127 patients switched from other antipsychotics to aripiprazole.

Conclusions: In japanese patients, treatment with sufficient dose can avoid discontinuation compared to low dose. On the other hand, switching strategies were not related the development of discontinuation. The findings from this study should be interpreted conservatively because of its non-randomized observational design.

P-49
Psychopharmacology III

P-49-001

Prevalence of drug induce psychosis among amphetamine and methamphetamine dependence patients

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Objectives: Psychosis associated with stimulant use is an increasing problem, but there is little research evidence about the nature of the problem. The present study was aimed at exploring the prevalence of psychosis and factors associated with drug induce psychosis among amphetamine and methamphetamine dependence patients.

Methods: This was a cross-sectional study. The data were obtained from patients who were admitted to a drug rehabilitation centre in Malaysia. All patients who consented for the study were interviewed. A structured face-to-face interview was used to assess drug use, demographics, and symptoms of psychosis in the past year and other associated factors. The prevalence rates of lifetime and current psychotic symptoms and other psychiatric diagnosis were determined by using Mini-International Neuropsychiatric Interview. Data of 106 patients (all male) were obtained from those who fulfilled the DSM IV criteria for amphetamine and methamphetamine dependence. Buccal swab was also obtained from the patients to determine the genetic polymorphism.

Results: 36.8% had experienced clinically significant psychotic symptoms in the past year. Polysubstance abuse (OR 5.7, 95% CI: 2.1, 18.2) especially cannabis and alcohol, antisocial personality disorder (OR 6.6, 95% CI: 2.7, 16.4) and psychiatric co-morbidity (OR 22.2, 95% CI: 6.7, 99.6) especially schizophrenia and bipolar affective disorders were associated with more risk of developing psychotic symptoms. Other factors were duration of drug dependence ($p < 0.05$) and amount of money spend to buy the drugs ($p < 0.05$). Genetic polymorphism results will be reported in another study.

Conclusions: Dependent amphetamine and methamphetamine users are a particularly high-risk group for psychosis especially those with psychiatric co-morbidity, poly-substance abuse and antisocial personality disorder.

P-49-002

Safety and efficacy of aripiprazole in the treatment of amphetamine and methamphetamine induce psychosis: A preliminary results

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Objectives: To date there have been no reports on safety and efficacy of aripiprazole in amphetamine type stimulant (ATS) induce psychosis. The primary objective of the study is to determine the safety of Aripiprazole in treatment of ATS induce psychosis using the BARS, SAS, AIMS and adverse events (AE) monitoring as safety measures. The secondary objective is to determine the efficacy of Aripiprazole in the treatment of ATS induce psychosis using the PANSS and CGI scales as efficacy measures.

Methods: Open-label pilot study, approved by Ethics Committee involving 22 patients. Treatment duration was 14 days. Inclusion criteria were male or female, aged 18 – 60 year, current DSM-IV diagnosis of ATS dependence; urine must be positive for amphetamine and methamphetamine at time of screening; able to provide written informed consent and to comply with all study procedures; having psychotic symptoms with PANSS score of more than 60 and CGI score more than 3. Exclusion criteria were pregnant or breast-feeding women, any significant clinical disorders; individuals with any DSM-IV Axis I disorder not defined in the inclusion criteria. Patients were started on 10 mg of aripiprazole and dose can be titrated up or down depending on the patients' tolerability. No other antipsychotics were allowed. All patients were antipsychotic naïve.

Results: Akathasia was the most common AE, however the overall BARS, SAS and AIMS score was not significant (all $p>0.05$). No patients required dose adjustment or discontinued from the study due to AEs. Significant improvement was observed in PANSS and CGI Severity of Illness scores by day 7(all $p < 0.05$), and was maintained throughout the study at day 14 (all $p < 0.05$).

Conclusions: Most patients tolerated aripiprazole therapy, with statistically and clinically significant improvement in psychotic symptoms by day 7. Aripiprazole is safe and effective for the treatment of ATS induce psychosis.

P-49-003

Aripiprazole's intrinsic activity is not enhanced on striatal membranes of rat chronically pre-treated with haloperidol

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Objectives: Aripiprazole is known to be a partial agonist of the dopaminergic D2 receptor. The properties of a partial agonist are influenced by the density and sensitivity of target receptors in the tissue. On these considerations, we hypothesized that the switch from typical neuroleptics (haloperidol), responsible for an up-regulation and a hypersensitivity of the D2 receptors, to aripiprazole, would enhance its partial agonist profile, leading to clinical issues, as already observed.
Methods: Wistar rats have been treated daily with 4mg/kg of haloperidol for 21 days. In biochemical assays, the intrinsic activity of agonists / partial agonists was assessed in [35S]GTPgS binding assays conducted on striatal membranes. The experiments were performed in buffers containing Na+, and in buffers where Na+ was substituted for N-methyl-D-glucamine (NMDG), as this would enhance the activity of low efficacy partial agonists at the D2 receptor. Besides, in behavioural assays, we evaluated whether rats pre-treated with haloperidol would show enhanced dopaminergic stereotypies upon the administration of aripiprazole.
Results: The agonist profile of aripiprazole was not evidenced in [35S]GTPgS binding assays on striatal membranes from naïve rat. More surprisingly, in the buffers with or without Na+, its intrinsic activity was not revealed on haloperidol-treated rat striatal membranes. Aripiprazole behaves as an antagonist of the D2 receptors. However, the agonists such as dopamine, R(–)-Propylnorapomorphine hydrochloride, and the partial agonists such as R(+)- and S-(-)-3-(3-Hydroxyphenyl)-N-propylpiperidine hydrochloride, showed an enhanced efficacy on striatal membranes of rat pre-treated with haloperidol. In the behavioral assays, pre-treatment with haloperidol could not reveal the dopaminergic agonist properties of aripiprazole. But, on the other hand, catalepsy could not been registered.
Conclusions: In our experiments, aripiprazole behaves as an antagonist of the dopaminergic D2 receptors, although it does not induce catalepsy, as the typical neuroleptics. Other targets should be investigated in order to explain the clinical profile of the compound.

P-49-004

Comparative evaluation of the predictors that diferentiate Valproate's effect in the long-term treatment of Bipolar Disorders (BD)

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Objectives: Comparing Valproate's effect versus Lithium's and Carbamazepine's for BP treatment and defining predictors which differentiate its effect.
Methods: 235 patients, males and females, 19-65 years old, with at least 2 episodes of BD (I and II). The prospective open comparative randomized study has 3 parallel groups of 60 patients, 2 years follow up period. Primary outcome measure was time to recurrence/relapse of any mood episode. Survival Analysis, Cox Proportional Hazard Regression with Log-Rank and Breslow test is performed for statistical analysis. BD subtypes (I, II, mixed, rapid cycling), comorbidity, life's stressors, and number of episodes have been evaluated as implicated predictors of treatment.
Results: For all the spectrum of BD cumulative survival for the Valproate's group was 26% higher than Carbamazepine's group (p=0.001) and 4.3% than Lithium's group (p=0.4304). The mean and median survival time for Valproate's group was respectively 35% and 53% higher than Carbamazepine's group and 10% and 14% higher than Lithium's group, Hazard ratio of Carbamazepine's group has been 108.5% higher than Valproate's group (B=0.735, p=0.001), and for Lithium's group was 20.4% higher than Valproate's (B=0.186; p=0.434). Concerning the predictors: Valproate was more effective than Lithium in non-classic BD-I (p=0.0312), also superior to Lithium in mixed, rapid cycling subtypes and in comorbidities. Valproate was more effective than Carbamazepine in classic BD-I (p=0.0312) and Lithium slightly superior in BD with comorbidities. Valproate has better outcomes as monotherapy compared to Carbamazepine, especially after the first year of treatment (p=0.0388)
Conclusions: Valproate is significantly more effective than Carbamazepine in long-term treatment of BD, and Valproate is superior to Lithium in non-classic form of BD

P-49-005

Efficacy comparison of Lamotrigine versus Lithium Carbonate in Bipolar Disorder II (BP II) patients treated for the first time with mood stabilizer

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Objectives: Comparing Lamotrigine's versus Lithium's efficacy, tolerability and safety in treatment of BP II.
Methods: 30 patients 19-60 years old, diagnosed with BP II according to DSM IV-TR, followed for 24 weeks. HAM-D≥18 and Y-MRS≤10 were used for the diagnosis of depression and hypomania; CGI for severity and improvement. 28 patients were analyzed for efficacy and 30 patients for safety. Response to treatment was defined the reduction 50% of values from starting point measured by HAM-D and Y-MRS, and CGI-I for values <2. Remission was considered HAM-D≥7 evaluated on week 12 and 24. Paroxetine and lorazepam were allowed to be used during the study. Time and dose used were compared between two parallel groups. Statistical analysis evaluated through Student test (X2) and Z test variable changes on week 0; 12; 24;
Results: After statistical analysis on validity of comparison considering gender, number of past episodes, type of actual episode and age the groups were evaluated as comparable without significant statistical differences. Lamotrigine and Lithium resulted efficacious treatments for BP-II ((p=0.001). They resulted equal efficacious for treatment of depression symptoms and hypomania, for the response and remission rate. There was not statistical significant difference between groups on weeks 8 (p=0,787), 12 (p=0,124) and 24 (p=0,348) for Y-MRS, reflecting comparable efficacy on hypomania symptoms. On week 12 six patients (21.2%) resulted in remission in lamotrigine group and four (14.3%) in lithium group. Statistical analysis showed no difference for dose and time respectively for paroxetine (p=0.953); (p=0.701) and lorazepam (p=0.937); (p=0.411). Lamotrignie has higher tolerability rate. Side effects prevalence during study period was 12.5% for lamotrigine and 57.14% for lithium groups.
Conclusions: Lamotrigine and lithim resulted equally efficacious for both episodes of BP-II during acute and maintained treatment. Lamotrigine manifested less side effects, better compliance and satisfaction.

P-49-006

Evaluation of anxiolytic properties of the diethyl ether extract of Gentiana kochiana

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Objectives: The aim of our study was to examine possible anxiolytic potency of Gentiana kochiana.
Methods: The diethyl ether extract of aerial parts of this herb, rich in xanthones (76.1% gentiacaulein, 14.2% gentiakochianin) was administered in 3 doses (5; 10; 20 mg/kg, i.p.) to the two-month-old Wistar male rats. Diazepam (1 mg/kg) was used as a reference drug. The rats were subjected to the elevated plus-maze test 45 min after injection and their behavior was registered by video camera during 5 min interval. The parameters of the total distance traveled (TDT), than, distance traveled, number of entries and time spent, all in open arms (DOA, NOA and TOA, respectively) were analyzed and quantified (AnyMaze software, 4.50). The inter-group differences of these parameters were evaluated by one way-ANOVA followed by Dunett's test (GraphPad Prism, 4.0).
Results: Only the medium dose of the extract (10 mg/kg) induced significant elevation of all these parameters, the same as diazepam, while the dose of 20 mg/kg raised only TOA.

Conclusions: This pattern of changes imply a complex dose related influence of the extract, where the both higher doses, as well as diazepam, show anxiolytic effect (by TOA increase), while only 10 mg/kg dose may induce hyperlocomotion (by increase of TDT, DOA and NOA) and, thereby, seems to stimulate exploratory behavior of animals. Suchlike variations may indicate more complex and opposite influence of the extract and, probably, of the xanthones, on the distinct neurotransmitter systems involved in the expression and regulation of anxiogenic/anxiolytic and motor behavior (i.e. GABA, 5-HT, Ach). However, except the previously registered direct MAO A inhibition, not any other substantial interaction of the extract with certain components of these systems has been found by pharmacological in vitro tests.

P-49-007
Long-term efficacy and saftey of galantamine in outpatients with mild cognitive disorder

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Objectives: Galantamine is a reversible, competitive cholinesterasa inhibitor that also allosterically modulates nicotine acetylcholine receptors. Inhibition of acetylcholinesterase, the enzyme responsible for hydrolisis of acetylcholine at the cholinergic cognitive impairment. To evaluate the efficacy, safety and tolerability of galantamine in long-term in Mild Cognitive Disorder.
Methods: A multicenter, open label, prospective, observational study enrolled 800 patients, more 50 years old with Mild Neurocognitive Disorder (DSM IV criteria), during 24 months of treatment with galantamine 16 mg./day. Assessments included the Mini Mental State Examination (MMSE), Clinical Dementia Rating (CDR), Alzheimer's Disease Assessment Scale (ADAS-GOG), Seven minutes test, Wiscosin card sorting test, Boston naming test, Token test, Raven Test, Brow-Peterson test, Trail making test, Functional Activities Questionnaire (FAQ), GO-NO-GO test, Global Deterioration Scale, Global Clinical Impression (GCI) and UKU scale of Adverse Effects.
Results: A total 800 outpatients were treated with 16 mg./day galantamine during 24 months, the therapeutic response evaluated with CDR, MMSE and the tests and scales of function cognitive measuring, GCI and UKU scale of adverse effects, comparing the baseline to final scores.
Conclusions: Mild Cognitive Disorder is being examined, so there aren't enought treatment for this. A long-term treatment (24 months) galantamine improves cognition and global function, behavioural symptoms and the general state well being of patients with Mild cognitive Disorder. With incidence of adverse effects not significant and a very good profile of safety, the final results of the study suggest that galantamine may be particularly appropiate in the Mild Cognitive Disorder.

P-49-008
Mild cognitive disorder and depression: Treatment with association between Galantamine and Escitalopram

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Objectives: To evaluate the efficacy of galantamine-escitalopram association in patients with Mild Cognitive Disorder and Depression. So there is a possible relation between the deficit of cerebral oxygenation and depression or relation between the serotonin system and cholinergic system in relation with disease comorbidity cognitive-depression. To evaluate the therapeutic response in patients with comorbility between Mild Cognitive Disorder and Depression in treatment with Galantamine, Escitalopram and the two drugs associated.
Methods: A group of 300 patients with symptoms of Mild Cognitive Disorder and Depression (DSM IV-R criteria) were separated in 3 groups of 100 patients. Each group received different treatment in an 8 months period: Group 1: Galantamine 16 mg/day. Group 2: Escitalopram 20 mg/day. Group 3: both drugs, same dose.
Results: The therapeutic response evaluated in Hamilton Scale for Depression(HAM-D), Montgomery and Äsberg Depression Rating Scale (M.A.D.R.S.), Mini Mental State Examination (M.M.S.E.) and Global Clinical Impression (G.C.I.) scores during 8 months. In the third group who received the two drugs associated, had much better response than the others and "brain enhancer".
Conclusions: The group who received the association of the nootropic agent Galantamine with antidepressant (SSRIs) Escitalopram had a relevant satisfactory therapeutic response (the best result), so there is a possible relation between the deficit in cholinergic systems and depression. Could be cerebral cholinergic systems deficit a generator of Depressive Disorder?

P-49-009
Therapy of addition for Alzheimer's disease: Combination with Galatamine and Memantine

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Objectives: To demonstrate with use the association memantine - galatamine in neurocognitive disorder: Alzheimer's disease, improve cognition, behavioural symptoms, and the general state recognized as neurocognitive disorder. The efficacy, safety, and tolerability of nootropic cholinergic agent: GALANTAMINE (with a dual mechanism of action on the cholinergic a system) and moderate affinity NMDA- receptor antagonist: MEMANTINE, were assessed taking into account the profile of patients with neurocognitive disorder: Alzheimer's disease, from the clinical aspects and the different classifications.
Methods: The experience included 380 patients who were enrolled in a prospective, observational, multicenter, and open-label study to receive 16 mg/day of galantamine and 30 mg/day of memantine for 12 months of treatment of addition.
Results: The therapeutic response was measured using the Mini Mental State Examination (MMSE), Clinical Dementia Rating (CDR), Alzheimer's Disease Assessment Scale (ADAS-GOG), Functional Activities Questionnaire (FAQ) the Clinical Global Impression Scale (CGI) and the UKU scale of adverse effects taking into account the efficacy, safety and adverse events of the treatment.
Conclusions: The final results of the study showed that galantamine with addition memantine improves cognition, behavioural symptoms, and the general well-being of patients with cognitive impairment: Alzheimer's disease. The incidence of adverse events was not significant and a very good profile of tolerability and safety was observed.

P-49-010
Limited anti-apoptotic activity of valproic acid on leukemic cell line

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Objectives: Modern treatment of bipolar disorder includes normothymic drugs such as lithium (Li), valproic acid (VA) and other anticonvulsant drugs. We have shown before that Li exerts a dose-dependent, either pro- or anti-apoptotic activity on leukemic cells (Pietruczuk et al, Ann NY Acad Sci 2009 in press). On the other hand, some studies show induction of apoptosis of the leukemic cell lines by VA. Considering the similarities between the mechanisms of action of Li and VA (e.g. inhibition of GSK-3 in therapeutic concentrations and increased expression of Bcl-2 in nerve cells), which may suggest their common cytoprotective effect, we test here the hypothesis of anti-apoptotic activity of the VA, using broad concentration range and various means of apoptosis induction.
Methods: Molt-4 leukemic line was used throughout. Spontaneous, camptothecine or hydrogen peroxide – induced apoptosis was analyzed in cells treated with 0-300μg/ml valproic acid over 24 hours. Apoptosis was identified by flow cytometry as either mitochondrial depolarization (JC-1), membrane symmetrization (annexin V) or DNA degradation (propidium iodide).

Results: In case of spontaneous apoptosis we have not observed any influence of VA on mitochondrial depolarization (cells stained with JC-1) but both the proportion of annexin-positive and sub-G1 (late apoptotic) cells increased proportionally to the concentration of valproic acid. In case of camptothecine - induced apoptosis, valproic acid had a significant beneficial (anti-apoptotic) effect, confirmed with all three methods detecting consecutive phases of the apoptotic process. Contrarily, all stages of Molt-4 apoptosis induced by hydrogen peroxide were resistant VA.
Conclusions: Valproic acid exerts anti-apoptotic effect which strongly depends on the method of apoptosis induction, suggesting the VA involvement only in some (specific) anti-apoptotic pathways, requiring further study.

P-49-011
New perspectives: Atypical anxiolytics block the development of ethanol -and benzodiazepine withdrawal-induced anxiety in experiment

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Objectives: It has been shown that GB-115 (Ph(CH2)5CO-Gly-Trp-NH2), a retropeptide analogue of endogenous tetrapeptide cholecystokinin (CCK4) and afobazol (2-(2-morpholino)ethylthio)-5-ethoxybenzimidazole dihydrochloride) produced selective anxiolytic action in animals with genetically determined "freezing" reaction to emotional stress (Balb/c mice, MR rats) with no effect in animals with active type of behavior (C57Bl/6 mice, MNRA rats). The aim of the present study was to investigate the effects of new anxiolytics on ethanol-and BDZ withdrawal-induced anxiety.
Methods: The effects of GB-115 (0.0125-0.1 mg/kg, i.p.) and afobazol (1.0 – 5.0 mg/kg, i.p.) were examined on the anxiety-related behavior induced by withdrawal from chronic ethanol and DZP treatment, using the "elevated plus maze" test.
Results: In randomly bred rats experienced to 15% ethanol in free-choice paradigm during 12th month period GB-115 at the low doses 0.0125 - 0.025 mg/kg and afobazol at the dose of 1.0 mg/kg reduced anxiety level within alcohol deprivation period, increasing the time spent on the open arms (%) and the number of entries into these arms (%). There were no signs of tolerance (aggression, pain sensitivity, corazol-induced seizures and attenuation of anxiolytic effect) after chronic treatment with GB-115 per se. The discontinuation of daily administration of Diazepam (4.0 mg/kg, i.p., 30 days) induced withdrawal anxiogenesis and proconvulsant effect. In contrast, no such effects were seen following withdrawal from similar administration of GB-115 (0.1 mg/kg, i.p.). However, both anxiolytics at high doses GB-115 (0.1 mg/kg) and afobazol (5.0 mg/kg) antagonized only the anxiogenesis, but not the proconvulsant effect following diazepam-withdrawal.
Conclusions: The results show that GB-115 and afobazol block withdrawal-induced anxiety in ethanol-dependent and benzodiazepine experienced rats.

P-49-012
Anxiety disorders in primary care: Effects of anxiolytic treatments on cognitive functions, a French naturalistic study

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Objectives: Anxiety disorders are among the most common mental health problems seen in primary care. More than half of patients with a psychiatric problem receive treatment for their symptoms from a primary care physician and approximately one third of patients with anxiety disorder are treated with anxiolytics (mainly benzodiazepines and Hydroxyzine in France). The amnestic and cognitive effects of benzodiazepines are well-known. However few studies of these effects have been conducted in primary care. The current study was designed to assess the cognitive effects of benzodiazepines and non benzodiazepines treatments in primary care patients with anxiety disorders.
Methods: 69 primary care sites in France participated to the study. Inclusion criteria were the following: patients aged from 18 to 60 years, suffering from generalized anxiety disorder, without current depressive disorder. Exclusion criteria were: patients with past or present organic or traumatic CNS disease, suffering from any addictive disorder. Clinical and cognitive assessments were done at baseline (V1) 30 days after psychotropics washout and at V2 a month later with Clinical Global Severity for GAD and 3 cognitive tasks: Digit Symbol Sub-Test (DSST), story recall task from the Wechsler and a 30-words recall task. At V1 the primary care physicians had to choose between two options: 1) an anxiolytic prescription (benzodiazepine or Hydroxyzine), or 2) waiting a month before introducing a medication.
Results: Of 223 patients included, 131 completed the clinical and cognitive assessments. Performances on recall tasks revealed that patients treated with Hydroxyzine were significantly higher compared to those of patients treated with benzodiazepines. Patients treated with benzodiazepines showed more false memories than patients treated with Hydroxyzine.
Conclusions: This study underlines that benzodiazepines were responsible for amnestic effect and false memories whereas Hydroxyzine did not induce such cognitive impairments.

P-49-013
Pentoxifylline Ameliorates Methamphetamine-induced cognitive deficits

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Objectives: Methamphetamine (METH) is a popular abused psychostimulant. Repeated administration of METH to animals produces a long-term damage to dopaminergic and serotonergic neurons in central nervous system and also causes cognitive dysfunction. Pentoxifylline, an inhibitor of phosphodiesterases and tumor necrosis factor alpha (TNFα) and a non-selective antagonist of adenosine receptor, has been shown to be a potential therapeutic agent in neurodegenerative disorders. In the present study, we compared the effects of neurotoxic and sensitizing regimens of METH and investigated the effect of pentoxifylline on METH-induced cognitive deficits.
Methods: In neurotoxic regmen, male ICR mice were either treated with saline or METH (4×5 mg/kg s.c., 2 hr apart). In sensitizing regimens of METH, mice were given saline or METH (2.5 mg/kg, s.c.) every other day for 8 injection. Subsequently, pentoxifylline (10 mg/kg, i.p.) was injected once a day for seven consecutive days. Novel object recognition test (NORT) was performed 1 week later.
Results: Mice treated with neurotoxic and sensitizing regimen of METH exhibited deficits in NORT. Pentoxifylline significantly reversed the cognitive deficits induced by both neurotoxic and sensitizing METH treatment regimens.
Conclusions: The results suggest the therapeutic potential of pentoxifylline for METH-induced cognitive deficits.

P-49-014

Yokukansan supresses methamphetamine-induced hyperlocomotion in mice

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Objectives: Behavioral and psychological symptoms of dementia (BPSD) are commonly seen in patients with Alzheimer's disease (AD) and other forms of senile dementia. An effective drug therapy for BPSD has not been established. Recently, a traditional Japanese medicine Yokukansan (YKS, Yi-gan san in Chinese) has been reported to improve BPSD, such as aggression, agitation, irritability and hallucinations, in a randomized, single-blind, placebo-controlled trial. However, the psychopharmacological effect of YKS remains unexplored. N-methyl-D-aspartate(NMDA) receptor antagonists, such as MK-801 have been used as pharmacological models of schizophrenia. In rodents, NMDA receptor blockers induce hyperlocomotion. On the other hand, methamphetamine-induced hyperlocomotion has been used as a classic dopaminergic model for identification of antipsychotics. In the present study, we investigated the effect of YKS on methamphetamine- or MK-801-induced hyperlocomotion in mice.
Methods: Five-week-old male ddY mice were housed in groups. All procedures regarding animal care and use were carried out based on the regulations established by the Experimental Animal Care Use Committee at Fukuoka University, Japan. Mice were singly placed in the centre of a circular open field(grey iron, diameter=60cm) enclosed by a parapet(height, 50cm) with an upper opening(diameter=90cm). The numbers of line crossings were recorded during a 3-min test session. YKS(100 and 300 mg/kg, p.o.) was injected 60 min before the test. Methamphetamine(1mg/kg) or MK-801(0.3 mg/kg) was administered i.p. 30 min before the test.
Results: YKS(300mg/kg, p.o.) suppressed the methamphetamine-induced hyperlocomotion, while YKS at the same dose had no effect on the MK-801-induced hyperlocomotion.
Conclusions: These findings suggest that YKS might be useful for the treatment of agitation, and that psychopharmacological effect of YKS might be mediated, in part, by inhibiting the activity of dopaminergic system.

P-49-015

5-HT2C receptor activation inhibits stress-induced increase in 5-HT transmission: Relevance of receptor desensitization to the anxiolytic effect of chronic parocentine in mice

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Objectives: 5HT2C receptors are well known to be involved in anxiety, but their implication in stress-induced changes of 5HT transmission remained to be investigated. Our studies aimed to assess the behavioral and neurochemical effects of 5HT2C receptor activation in naïve and stressed mice, and after a long term paroxetine treatment known to exert anxiolytic effects in humans.
Methods: The effects of the preferential 5HT2C agonists m-chlorophenylpiperazine (mCPP) and RO600175, the selective 5HT2C receptor antagonist SB242084 and restraint-stress on anxiety-like behavior in mice were assessed using the social interaction test, while the neurochemical effects of these treatments on 5HT turnover (5HIAA/5HT ratio) and extracellular 5HT were determined using HPLC and microdialysis. Data were analyzed using ANOVA.
Results: Both mCPP and restraint-stress increased anxiety-like behavior in the social interaction test ($P<0.01$), and these effects were blocked by pretreatment with the selective 5HT2C receptor antagonist SB242084. Restraint-stress increased 5HT turnover in various brain areas (hippocampus, nucleus accumbens, ventral tegmental area/substantia nigra, frontal cortex), and this effect could be prevented by the 5HT2C receptor agonist RO600175 ($P<0.01$). Acute administration of SB242084 potentiated the stress-induced increase in 5HT turnover and blocked the inhibitory effect of RO600175. In contrast, the latter agonist was ineffective under basal conditions, in the absence of stress. Microdialysis studies in frontal cortex revealed that RO600175 had an inhibitory effect on the stress-induced increase in extracellular 5HT levels ($P<0.01$), but not on basal 5HT levels. Paroxetine prevented the anxiogenic effect of mCPP as well as the inhibitory effect of RO600175 on restraint stress-induced increase in 5HT turnover.
Conclusions: These data strongly suggest that 5HT2C receptor activation mediates the anxiogenic effect of restraint-stress in mice. In addition, the anxiolytic action of long term treatment with SSRIs might be causally related to a clear-cut 5-HT2C receptor desensitization.

P-49-016

Effect of memantine and lamotrigine chronic administration in rats submitted to the elevate T-maze

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Objectives: In order to study the effect of chronic lamotrigine and memantine admistration in the elevate T-maze (ETM), an animal model to study anxiolytic and antipanic drugs. Pre-administration with veratrine was used to evaluate the role of voltage dependent sodium channel
Methods: Male Wistar rats (220-250g) were treated chronically (24 days) with memantine (5 mg/Kg ip.), lamotrigine (20 mg/Kg ip.) or saline, until 1h before the behavioral tests (day 21). Between days 21 and 24, the animals continued being treated. Veratrine (0.1 mg/Kg ip.), a voltage dependent sodium channel opener, was injected 10 min before the administration of these drugs on day 24. The animals were resubmitted to the ETM and open field
Results: Memantine administered chronically impaired the inhibitory avoidance, indicating an anxiolytic effect, which was blocked by veratrine. It was observed that memantine didn´t change the one-way escape in comparison to the control group, but the group memantine plus veratrine facilitated it in comparison to the memantine group. In the open field, the memantine group showed a stimulant effect in comparison to the control group. Lamotrigine impaired the inhibitory avoidance in comparison to the control group, indicating an anxiolytic effect, but lamotrigine did not alter the one-way escape or the locomotor activity.

Conclusions: These results suggest a potential anxiolytic effect in the chronic administration of antiglutamatergic drugs (lamotrigine by the inhibition of glutamate release and memantine by non-competitive antagonism of NMDA receptors), but they did not indicated an antipanic-like effect. Moreover, they suggest a role for voltage dependent sodium channel.

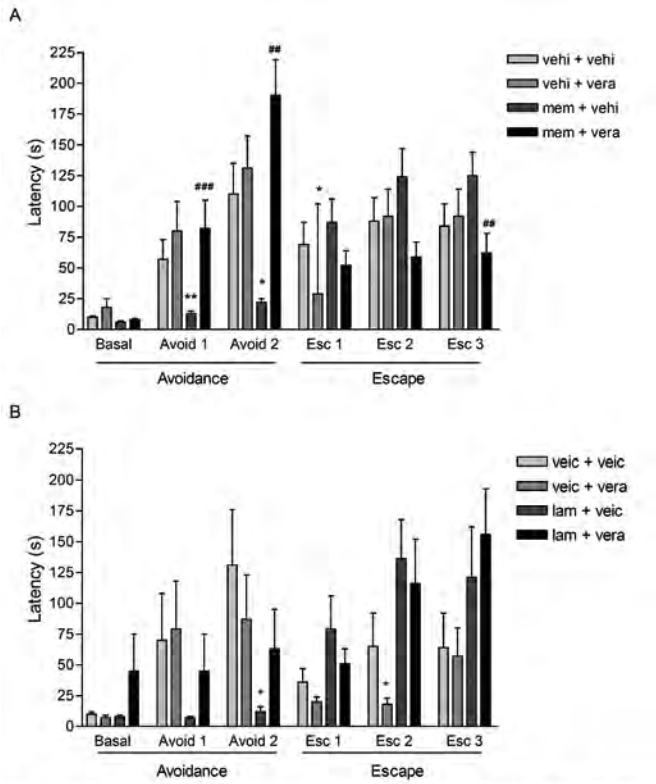

Figure 1: Effect of (A) memantine (mem) or (B) lamotrigine (lam) in rats submitted to the ETM with veratrine (vera) or vehicle (veh) pre-administration (Kruskal-Wallis ANOVA followed by Mann-Whitney test), mean±S.E.M. *p<0,05 vs veic; **p<0,01 vs veic; ##p<0,01 vs memantine ###p<0,001 vs memantine

P-49-017

Mineralocorticoid receptor antagonist enhance extinction on post-traumatic stress disorder animal model

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Objectives: There is evidence showing an association between Hypothalamus- Pituitary – Adrenal (HPA) axis and Post-Traumatic Stress Disorder (PTSD), such as patients with PTSD with hyporeactivity of the HPA and case reports showing improvement of PTSD with low doses of cortisol. Since cortisol may act trough mineralocorticoid or glucocorticoid receptors (MR and GR respectively), the objective of the present study was to evaluate the effect MR (spironolactone) or GR (mifepristone) antagonists and GR agonist (dexamethasone) in the extinction of the contextual conditioned fear, an animal model of PTSD. Propranolol was used as positive control. Additionally, we evaluated if the effect of high dexamethasone dose, which was associated to hippocampus lesion, before conditioning session can decrease memory extinction.

Methods: Adult male Wistar rats were treated with spironolactone (10 mg/kg, sc), dexamethasone (1, 5 or 10 mg/kg ip), mifepristone (10 mg/kg, sc), and propranolol (10 mg/kg, sc) or their vehicle before the session trials. In the training session of the contextual fear conditioning test the rats were placed singly in the conditioning chamber for three minutes and received an electric footshock (1.5 mA, 1s). After the shock the animals still remained in the box for one more minute, after which they were returned to their homecages. During three consecutive days the animals were re-exposed to the conditioning chamber (9 min), without receiving the shock, and the freezing behavior was measured (test sessions).

Results: The results showed that neither dexamethasone treatment nor mifepristone modified immobility time in test sessions. On the other hand, spironolactone before each test session decreased immobility time (increase extinction). Propranolol before each test sessions increased extinction (reduction of immobility time).

Conclusions: The results indicted that MR receptors play a role in conditioned fear extinction and that MR receptor antagonists may be an option to PTSD treatment.

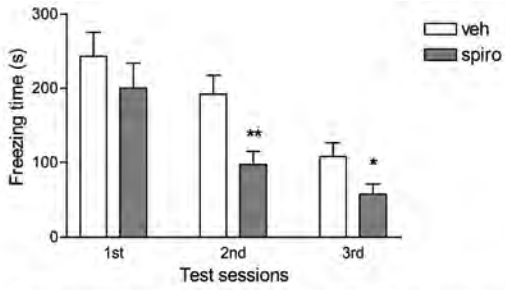

Fig 1- Effect of spironolactone (spiro, 10 mg/kg, sc) administrated 60 min before each test session on the extinction of contextual conditioned fear. Data represents mean + SEM; n= 10/ group. * P<0.05 and ** P< 0.01 vs vehicle (veh)

P-49-018

Sodium Fluoride induced memory impairment is associated with changes in striatal monoaminergic levels

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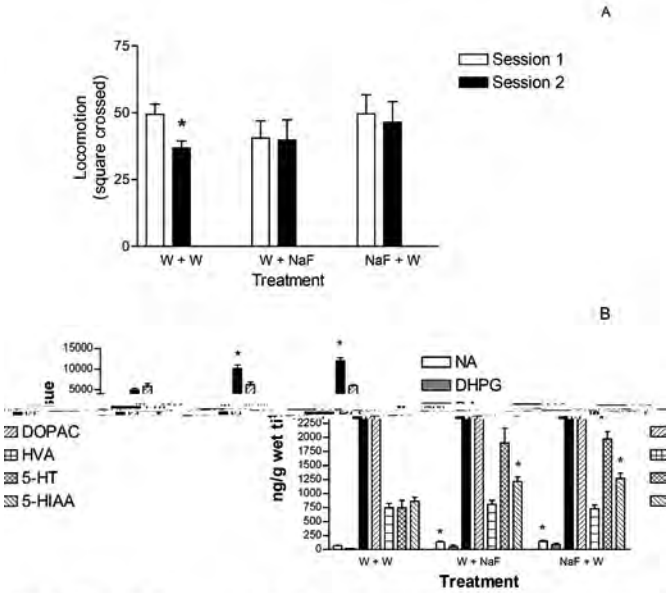
Objectives: Since previous work indicated that chronic (30 days) sodium fluoride (NaF, 100 ppm) intake impairs memory (Chioca et al., 2008, Eur J Pharmacol 579:196), we evaluated: (1) whether the NaF withdrawal reverts this impairment; (2) the impact of NaF intake and its withdrawal in monoamine levels (and their metabolites) in the hippocampus and striatum; (3) teeth fluorosis.

Methods: Adult male Wistar rats were treated with: (a) 45 days of tap water (W+W); (b) initial 15 days with tap water following 30 days of NaF (W+NaF); (c) initial 30 days with NaF following 15 days of tap water (NaF+W). NaF was administered in drinking water. The rats were tested in the open-field and re-tested 24h later. Total ambulation was recorded during 5 min. Dental fluorosis was scored by visual inspection of central incisors. The data were analyzed by Chi-square test, Student t-test for paired samples or ANOVA followed by Newman-Keuls test. $P < 0.05$ was considered statistically significant.

Results: There is a decrease in the total ambulation (an indication of habituation and memory acquisition) in the W+W group only (Fig.1A). There is a significant increase in dopamine, noradrenaline, serotonin and 5-HIAA levels in striatum of NaF treated groups (Fig.1B). In the hippocampus, there is only a trend to increase noradrenaline level. Increase in fluorosis was seen only in the NaF+W group.

Conclusions: The results indicated that NaF impairs habituation (a non-associative learning), as showed in our previous study, and that short-term withdrawal did not revert this impairment, which was associated with an increase in DA, NA, 5-HT and 5-HIAA striatal levels. Thus, the present study suggests that the NaF-induced memory impairment may be long lasting and may be related to central monoaminergic changes. Based on this last finding, drugs that reduce monoaminergic neurotransmission may be useful to revert this effect of NaF.



ntake in habituation in
3). * P<0.05 vs session

Fig 1- Effect of chronic sodium fluoride (NaF 100 ppm) i
the open-field (A) and monoaminergic level in striatum (
1 (A) or vs control (W+W; B)

P-49-019
Management alopecia induced by mood stabilizers

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Objectives: Medication-induced alopecia is an occasional side effect of many psychotropic drugs. Most of the mood stabilizer and antidepressant drugs can lead to this condition. Some antipsychotic and antianxiety agents induce alopecia. The authors provide a case to illustrate the common presentation of a patient with mood stabilizer -induced alopecia. Case Report - 40 years old female, diagnosed with Type II Bipolar Disorder, clinically stabilized with lithium 800 mg/day and lamotrigine 200 mg/day, for 8 months. The patient started complaining of diffuse hair loss 7 months after lithium was introduced in treatment. Thyroid function tests were normal. The evaluation and therapeutic attitude in the presence of alopecia in patients needing mood stabilizers are also discussed.
Methods: The literature on alopecia as a side effect of psychotropic medications is reviewed.
Results: Alopecia is a common side effect in patients managed on the mood stabilizers lithium, valproate, and carbamazepine. Clinicians may be reluctant to discontinue medications in patients suffering from alopecia if the mood stabilizer is otherwise efficacious. Therefore it is important to be familiar with the epidemiology, diagnosis, and management of alopecia.
Conclusions: Management of alopecia includes reassurance, hair care techniques, trace mineral supplementation, and hair replacement pieces. Alopecia due to mood stabilizer drugs can be managed without medication discontinuation

P-49-020
Translocation of sigma 1 receptors from the cytoplasm to vicinity of the plasma membrane in response to Afobazol treatment

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Objectives: Afobazol (5-etoxy-2[2-(morpholino)ethylthio]benzimidazole dihydrochloride) was registered in Russia in 2005 as a selective anxiolytic. The radioligand in vitro studies show that afobazol interacts with MT1 (IC50=2,7*10-5 M), MT3 (IC50=9,9*10-9 M), sigma 1 (IC50=7,1*10-6 M) receptors and MAO-A (IC50=6,2*10-6 M) (Cerep, France). It is known that sigma 1 receptors are localized to the endoplasmic reticulum. Ligands of sigma 1 receptors affect its transport to plasma membrane. The main purpose of this study was to investigate the influence of afobazol on localization of sigma 1 receptors in neuronal cells.
Methods: We used an immortalized mouse hippocampal cell line (HT-22). Neurons were treated with afobazol in concentration of 10-8 M for 30 min and 1 h before fixation. For immunofluorescence staining cells were incubated with specific antibodies directed against sigma 1 receptor and calnexin. Images were acquired by confocal microscope equipped with a helium-neon laser (wave-length 494 nm).
Results: Analysis of acquired images indicated that afobazol induced translocation of sigma 1 receptors in the cells. In the control conditions sigma 1 receptor immunoreactivity colocalised with the staining for calnexin, which is a protein of endoplasmic reticulum. After 30 min and 1 h of afobazol treatment the immunofluorescence staining against sigma 1 receptor was detected in the cytoplasm and axons whereas calnexin was associated with the membrane of endoplasmic reticulum in neuronal bodies.
Conclusions: These results confirm the data obtained in radioligand studies of interaction of afobazol with sigma 1 receptors.

P-11
Other / Eating Disorders

P-11-001

Treating binge eating disorder and substance use problems effectively with mindfulness based cognitive behavioral group therapy

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Objectives: Individuals with binge eating disorder (BED) frequently abuse substances to cope with negative feelings directly and indirectly resulting from binge eating. Substance use also frequently raises the susceptibility to binge eating by lowering both mood and inhibition against binge eating which often results in an endless cycle of problematic eating, negative feelings, and problematic substance use. The efficacy of a Mindfulness Based Cognitive Behavioral Group Therapy in individuals with concurrent BED with obesity and substance use disorders (SUD) was investigated.
Methods: Out patients with obesity and concurrent BED and SUD, as determined by the Structured Clinical Interview for DSM, were administered a psychiatric interview and psychometric measures to assess mental health (including binge eating) and substance use prior to starting the 16-week treatment and after completing the treatment. Using mindfulness, cognitive behavioural skills, meal and physical activity plans, the treatment focused on mindfulness, balanced and mindful eating, physical activity, emotion regulation, assertiveness, and coping strategies.
Results: Repeated measures univariate analyses of variance tests corrected for multiple comparisons with Bonferroni adjustments suggested that patients were more able to control their negative moods (p<.001), resist urges to use substances in high relapse risk situation and eat in response to emotions (p<.001). They also showed a decrease in scores on the Eating Disorders Examination, Alexithymia (p<. 007) and other mental health symptoms (p<.005); and an increase in self-efficacy (p<.001) and soothing receptivity (p<.006).
Conclusions: Mindfulness based group CBT can reduce binge eating, urges to eat in response to emotions, and preocupation with shape. It can help enhense efficacy to resist substances as well as general self-efficacy and general mental health. Strategies to provide effective treatment will be presented. Factors bolsters related to relapse prevention will be discussed.

P-11-002

Eating disorders – types of obsessive-compulsive disorder

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Objectives: Both anorexia mentalis and bulimia nervosa are types of eating disorder (F 50.) Anorexia is a disorder characterized by deliberate loss of body weight. Bulimia is a disorder featured by repeated attacks of excessive eating as well as preoccupation with body weight. Obsessive-compulsive disorder is qualified by recurrent obsessive thoughts and/or actions which repeatedly appear in ones' mind. **Objectives:** A display of a 25 year old female with an eating disorder and obsessive-compulsive disorder conjoint on the basis of an anancastic personality, followed by combination of pharmacotherapeutic and psychotherapeutic treatment.
Methods: psychiatric interview, psychological tests (personality test, IQ evaluation test), psychiatric treatment (involving both individual psychodynamic therapy and family therapy; support therapy was applied throughout the whole treatment, due to the subjects' extreme insecurity.) At the beginning of the treatment, the patient had low body weigh (BMI 18), was depressed and dysfunctional, further to occasional bulimic behavior and obsessive-compulsive behavior (obsessive thoughts of dirt and constant house-cleaning.) Previously she had been treated with antidepressants and basal neuroleptics, clinically and in a dispensary, for a year. After successfully creating a contact and forming a therapeutic alliance, she was submitted to an individual psychiatric treatment as well as family therapy. In addition, pharmacotherapy, which included small doses of atypical neuroleptic and a tricyclic antidepressant, was introduced.
Results: During the first two months of treatment, the subject's body weight increased (BMI 18), symptoms of obsessive-compulsive disorder disappeared, depressive symptoms reduced, and functionality restored. The patient is still being psychiatrically treated.
Conclusions: Different types of obsessive-compulsive disorder may be developed in an anancastic personality at the same time. However, this does not obstruct psychotherapeutic nor pharmacotherapeutic treatment.

P-11-003

Psychiatric comorbidities and childhood personality traits associated with subthreshold eating disorders in a population-based longitudinal study of adolescent girls

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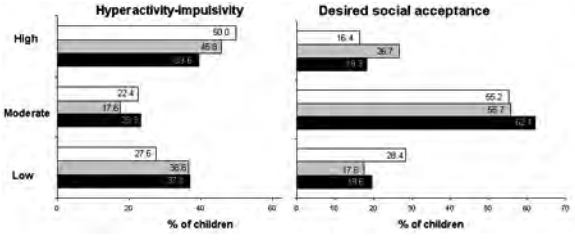
Objectives: Information is lacking about subthreshold eating disorders (EDs) during adolescence (Eddy et al., 2008). The aims of the study were to investigate the prevalence of subthreshold EDs at 16 years of age and to examine the psychiatric comorbidities and childhood personality traits associated with subthreshold EDs.
Methods: Longitudinal data on 1420 girls were collected from 6 to 16 years of age. At 16 years of age, 833 adolescent girls completed the Diagnostic Interview Schedule for Children (DISC-version 2) based on DSM-IIIR criteria. Childhood personality traits were measured by teachers annually through the Social Behavior Questionnaire from ages 6 to 12 years. Frequency analyses were used to calculate the prevalence of subthreshold EDs. Univariate logistic regressions were performed to measure the associations between subthreshold EDs and psychiatric disorders (e.g., depression, dysthymia, generalized anxiety, and panic disorders). Trajectories of childhood personality traits (e.g., hyperactivity-impulsivity, anxiety and desired social acceptance) were modeled with Proc Traj. Multivariate logistic regression was used to evaluate the associations between subthreshold EDs and childhood personality traits.
Results: The prevalence was 3.5% for subthreshold of anorexia and 3.8% for subthreshold of bulimia. At 16 years of age, girls suffering from subthreshold of bulimia reported greater major depression (57% Vs 7%, P=<.001), dysthymia (20% Vs 4%, P=<.001) and panic disorders (40% Vs 11%, P=<.001) compared to controls. A high desired social acceptance in childhood was significantly associated with suffering from subthreshold of anorexia at 16 years (Odds ratio (OR)=2.0 (1.2-3.2), P=.007) whereas exhibiting a childhood hyperactivity-impulsivity trait was significantly associated with suffering from subthreshold of bulimia at 16 years (OR=1.5 (1.0-2.3), P=.05) (see Figure).
Conclusions: Investigating subthreshold EDs, mood disorders, anxiety disorders, and personality traits in school services could play an important role in the early detection and prevention of eating disorders in adolescence.



P-11-004
Body image in adolescent boys and girls: A 4-year longitudinal study

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Marie-Eve Blackburn, Julie Auclair, Luc Laberge, Suzanne Veillette, Marco Gaudreault, René Lapierre, Michel Perron

Objectives: Considering the high prevalence of body dissatisfaction (BD) and its negative consequences on eating disorders, this research aimed to identify predictive factors of BD in adolescence.
Methods: Longitudinal data was collected in 337 boys and girls between the ages of 14 and 18 years. At ages 14 and 18, subjects selected pictures ranging from thin to fat to depict their current and ideal body images. Figure dissatisfaction is defined by the discrepancy between the selected current and ideal figures. All subjects completed a general BD scale (physical appearance, body appearance, clothing style) and measures of social and psychological well-being. Multiple regressions were performed separately for girls and boys to identify factors at age 14 that predict BD at age 18, and factors at age 18 that are associated to BD at age 18.
Results: At age 14, about 70% of adolescents were unsatisfied with their body. In addition, about one in two girls and one in five boys have tried to lose weight. Not eating (31%) and purging (10%) were amongst unhealthy methods of weight loss in girls. Predictive factors of BD at age 18 in girls were a desire to be thinner and negative comments regarding their weight at age 14 ($p<.001$, $R^2adj=.27$). At age 18, factors associated with BD were low self-esteem, higher BMI, figure dissatisfaction, and marijuana consumption ($p<.001$, $R^2adj=.44$). In boys, predictive factors of BD at age 18 were figure dissatisfaction, lower frequency of physical activity, and negative health perception at age 14 ($p<.001$, $R^2adj=.27$). At age 18, factors associated with BD were low self-esteem, figure dissatisfaction, maternal education, and non-smoking ($p<.001$, $R^2adj=.41$).
Conclusions: Figure dissatisfaction is prominent at age 14. The identification of factors at age 14 that predict BD four years later enables health professionals to help prevent the development of body and self-image concerns.

P-11-005
Translation of the SCOFF questionnaire and validation of this French version for the screening of eating disorders in a student population

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Sebastien Grigioni, Emmanuelle Houy-Durand, Elodie Allais, Gilles Merygnac, Florence Thibaut, Pierre Dechelotte

Objectives: To translate SCOFF questionnaire in French and evaluate its metrological features for the screening of eating disorders (ED) in a student French population.
Methods: SCOFF questionnaire is composed by 5 questions and it has been developed for the screening of ED and Its French version isn't currently available. The translation and the transcultural validation were done using international criteria. The validation study employed the Mini International Neuropsychiatric Interview as the gold standard and the French version of SCOFF questionnaire (QD-TCA) paper and pencil form was applied to female students attending yearly evaluation in the Students Health clinic.
Results: The sample was composed of 120 women with a mean age of 20 years (standard deviation – SD – 3.1 years, range 18-35). Thirteen cases (10.8%) of ED were diagnosed having ED (3 cases (2.8%) of anorexia nervosa and 10 cases (8%) of bulimia nervosa). Diagnostic threshold was calculated using the receiver operating characteristics (ROC) curve and fixated at two positive answers. The sensitivity of QD-TCA was of 92% with a specificity of 91.5%. Its positive and negative predictive values for ED were 57.1% and 99%, respectively. Similar results were obtained for AN and BN. Intraclass correlation-R was of 89%
Conclusions: The French version of SCOFF questionnaire developed by our team (D-TCA) seems to be a reliable and practical eating disorder's screening tool in a moderate risk student setting.

P-11-006
Using EAT to identify risk factors for Eating Disorders in a sample of Brazilian students

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Objectives: This study was developed to identify risk factors for Eating Disorders (ED) using the Eating Attitudes Test (EAT). It is of common knowledge that we may have a continuum between sick and healthy population regarding the ED. Taking this into account, subjects who scored above the cut-off point on EAT can meet criteria to fill-in an eating behavior or an ED. We can find here the partial syndromes that properly treated in advance can have a better evolution. The identification of risk factors is an essential step to developing effective preventive interventions. The EAT application is justifiable because it doesn't take much effort.
Methods: 1450 students from 6 to 18 years old, from 20 randomized schools in the city of Belo Horizonte, Brazil, were submitted to the EAT, Body Image Test and Sociodemographic Test. Al the students had their weight and height measured to obtain the body mass index (BMI). The students who scored above the threshold point were compared to the negative students according to clinical and socioeconomic variables by a multivariate analysis in order to find possible risk factors for ED. The sample was stratified in 3 age groups (6-9, 10-14, 15-18).
Results: From 1450 students, 1195 fill-in the criteria for the study. A hundred and six students (8,9%) have positive score in EAT. From all the variables, obesity (BMI ≥ p95) and female sex in group 3 (15-18 years) were considered significant.
Conclusions: We can see that these risk factors are common to developed countries showing that Brazilian population may not differ from those. Besides, the association between BMI and eating behavior suggests a potential link between ED and overweight. The prevalence of obesity in children and adolescents is growing all over the world, and this phenomenon could explain the increase of ED in this population.

P-11-007
Eating behavior: The role of family configuration

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Objectives: There are hereditary and environmental family influences on eating disorders. Eating behavior in Russian families has not been studied.
Methods: About 650 student's families with one-two children aged 13-24 were tested by EAT-26. Basic statistics, Correlation, and Regression (Statistica-6) have been used.
Results: EAT-26 scores demonstrate comparatively high risk in female groups (9.9% mothers and 8.6% daughters exceeded the critical value). Significant similarity between parental and children's EAT-26 scores have been found. Regression coefficients are dependent on gender and family configuration. Daughter-to-mother regression is 0,44 ($N=328$, $p<0.0000$), son-to-mother regression is only 0.18 ($N=152$, $p=0.02$). Son-to-father regression is 0.39 ($N=116$, $p<0.0000$), daughter-to-father regression is only 0.14 ($N=191$, $p=0.06$). Correlation between spouses is also significant ($R=0.33$, $N=250$, $p<0.0000$). Largest values of daughter-to-mother regression have been identified for first daughters in families with two children (Beta=0.58, $N=44$, $p=0.000$ for "girl-girl" families; Beta=0.56, $N=39$, $p=0.000$ for "girl-boy" families; second child's regression was not significant: Beta=-0.003 for second daughter, and Beta=0.16 for son). The first daughters also have higher scores on EAT-26 bulimic questions relative to single daughters. Daughter-to-mother regression in families with single daughter was 0.37 ($N=214$, $p=0.000$). In families with "boy-girl" configuration son-to-mother regression was 0.29 ($N=72$, $p=0.013$), and daughter-to-mother regression was 0,33 ($N=76$, $p=0.004$).
Conclusions: Maybe mother feeding practices with first (but not second) daughter influences her eating behavior later. The further researches with larger samples are necessary to confirm the received results.

P-11-008
Cancer-related anorexia treatment program and quality of life in cancer patients

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Objectives: Cancer-related anorexia occurs in some people with breast cancer and may be caused by physical illness, pain, treatment drugs, being in the hospital, and emotional stress. The aim of this study was to test the efficacy anorexia treatment program based on diet, pharmaconutritional support, antidepressant drugs and psychotherapy in a population of breast cancer patients with cancer-related anorexia.
Methods: Data were collected from 56 breast cancer patients who underwent 4-week anorexia treatment program at Odessa Regional Cancer Hospital. The benefit obtained by treated patients was evaluated using the nutritional/functional tests (body weight, appetite) and Quality of life Questionnaire 40-item version 5.0 with the added breast cancer-specific module at baseline and predefined follow-up visits. The integrated treatment consisted of the following: diet with high polyphenol content (500 mg), antioxidant treatment, pharmaconutritional support, Δognitive-behavioral psychotherapy and fluoxetine in a doze of 0,02 g/day.
Results: The results of this study indicated that this 4-week cancer-related anorexia treatment program was effective in decreasing symptoms of anorexia and improving overall quality of life in this group of breast cancer patients. In all assessment patient's quality of life was significantly improved and increased nutritional/functional variables after 4-week cancer-related anorexia treatment (weight of at least 7%, appetite of at least 3 units, grip strength by dynamometer of at least 45% as compared with baseline value).
Conclusions: These preliminary results suggest that 4-week anorexia treatment program improved cancer-related anorexia.

P-11-009
Nutritional state related to the corporal mass index in patients admitted to a psychiatric hospital with mental and behavioral disorders in Mexico City

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Objectives: To establish the obesity's prevalence in adult psychiatric hospitalized patients, with a maximum stay period of 30 days.
Methods: An exploratory study collecting the information of a 24 hour period in the year 2008. The nurses previously trained in the technique of measuring size and weight, collected information about every hospitalized patient, excepting those patients who couldn't be measured because of their physical state. 212 patients were measured and weighed and the corporal mass index was obtained and the nutritional state was determined using the International Classification of the Nutritional State of WHO (World Health Organization)
Results: Dates of 95 females and 117 males were analyzed more than a half had overweight with 61% of cases and 40% in males there were only 3 cases of low weight found in females under 40 years of age.
Conclusions: There isn't any meaningful statistic difference in obesity prevalence among psychiatric population and non psychiatric population; therefore it can be supposed that cultural components and eating habits lead more efficiently to obesity than any other factors. Longitudinal obesity studies are recommended in this population, including medical treatment, eating habits and physical activation.

P-11-010
Methabolic syndrome prevalence in patients admitted to Fray Bernardino Alvarez Psychiatric Hospital

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Objectives: Detect metabolic syndrome´s prevalence in a group of patients with psychiatric diagnose and with or without pharmacological treatment. The metabolic syndrome (MS) is integrated by: blood pressure elevation, hypercholesterolemia, hypertriglyceridemia, hyperglycemia and abdominal obesity; Mexico is located in the second place worldwide in obesity prevalence; It has also been reported that the use of psychiatric drugs increases the metabolic syndrome risk.
Methods: A descriptive screening study was designed. The following variables were measured: blood pressure, weight, height, abdominal circumference, triglycerides levels in serum, glucose and High Density Lipoproteins Cholesterol, by colorimetric enzymatic test on a Roche analyzer. Statistic analysis: t student, Fisher's exact test and Cochran-Matel-Haenszel.
Results: 50% of the sample group had an abdominal circumference higher than 88 cm, 10% glycemia higher than 110mg/dl, 30% triglycerides higher than 150mg/dl; 14% complies with MS criteria. When grouping patients with and without MS and comparing glucose and triglycerides, a p= 0.0001 is obtained. With a 93.4% of confidence a relationship between sedentarism and MS is accepted. Women between 40-69 yo have a higher prevalence of MS with a 98.4% of confidence. The only family history factor associated with MS was obesity with a 97.7% of confidence. There is a positive relationship between metabolic syndrome and the use of typical or atypical antipsychotic drugs, the selective serotonin recapture inhibitors (SSRI) are related to MS significantly p=0.072 and 91.5% of confidence. The benzodiazepines were significantly linked with p=0.073 and 92.7% of confidence.
Conclusions: MS appeared only in the 14% of the sample group, quite opposite to what was expected considering obesity prevalence in Mexico; psychiatric drugs were associated with MS in the sample group, women between 40-59yo presented the highest risk, the heterogeneous nature of the sample limits the results but it is adjusted to reality.

P-11-011
Sleep quality and quality of life in multiple sclerosis

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Objectives: The severity of multiple sclerosis (MS) presents significant challenges to the healthcare professional. The aim of the present study was to evaluate the sleep quality and quality of life in MS patients.
Methods: A purposive sample of 30 patients diagnosed with varying degrees of MS was selected for the study and compared with a group of normal matched controls. A demographic data sheet along with Pittsburgh Sleep Quality Index and WHO Quality of Life questionnaire and Coping styles questionnaire were administered to all participants.
Results: Findings reveal that when compared with the non-clinical controls, the patients with multiple sclerosis had slightly lower quality of life scores for two of the dimensions: overall perception of health, and physical functioning. In addition patients reported greater somatization and lower mental health. The scores were similar, however, for anxiety, depression, and social functioning. No significant differences emerged with regard to sleep quality and coping methods used. Persons who engaged in more emotion-focused coping styles were more likely to experience poor psychological adjustment than were those who employed more problem-focused strategies. Women in general, both with and without MS, were more likely to focus on the positive and seek social support than were men.
Conclusions: It appears that MS patients have unmet needs and attempts at improving quality of life may help meet those needs.

P-11-012
Prevalence of obsessive beliefs and intolerance of uncertainty among college students

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Objectives: The purpose of the present study was to explore the prevalence of obsessive compulsive beliefs and intolerance of uncertainty among college going youth and to explore for any possible associations.
Methods: A multistage cluster sampling procedure was used to collect data from a sample of 200 students (100 boys and 100 girls) ranging in age from 18 to 26 years. Data was collected using a socio-demographic information sheet, Obsessive-Compulsive Beliefs questionnaire and the Intolerance of Uncertainty questionnaire.
Results: Findings revealed obsessive thoughts in 20.8% of males and 11.5% of females. Extreme intolerance of uncertainty was reported by 16.7% of the males and by 7.7% of females. Males and females differed significantly on perfectionism and importance regarding control of thoughts, with females reporting greater perfectionism and males endorsing greater beliefs regarding thought control. Significant age differences emerged only with regard to uncertainty regarding one's ability to perform, with greater intolerance reported by male students. In both groups, obsessions regarding responsibility and threat estimation correlated with stress of uncertainty and expectation of negative events. Perfectionistic beliefs were associated with expectation of negative events in both groups and in the female group they were also associated with uncertainty regarding performance and stress of uncertainty. Obsessive beliefs regarding loss of control over thoughts were related to all the components of intolerance of uncertainty only in males. Regression analysis indicated that intolerance of uncertainty can be predicted by beliefs about perfectionism in females and by beliefs of thought control in males.

P-11-013
Electro-acupuncture diagnostic method for assessing of adjustment disorders in breast cancer patients

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Objectives: Electro-acupuncture diagnostic method according to Dr. Voll based on correlation between electro conductive qualities of measuring points by R. Voll and functional condition of the related organs and systems. The purpose of the present study was to develop a simple and reliable method for assessing adjustment disorders in breast cancer patients.
Methods: 340 breast cancer patients of the Odessa Regional Cancer Hospital participated in the research. All participants were assessed within 2 weeks of the completion of the chemotherapy in combination with mastectomy in a common protocol via a psychiatric interview, standardized psychological tests (Hospital Anxiety and Depression Scale (HADS), a 14-item self-assessment questionnaire) and electro-acupuncture diagnostic method according to Dr. Voll. Electro-acupuncture diagnostic measurements were made at 24 acupuncture points at the ends of the meridians of the fingers and toes of a subject and were made by the same operator and equipment.
Results: The analyses showed adjustment disorders were diagnosed after psychiatric interview and standardized psychological tests in 280 breast cancer patients (depressed mood in 28.2%, anxious mood in 10%, mixed emotional features in 20%), major depression in 117 patients (41.8%). The adjustment disorders were diagnosed after electro-acupuncture diagnostic method according to Dr. Voll in 340 breast cancer patients (depressed mood in 28.5%, anxious mood in 12,1%, mixed emotional features in 23,2%), major depression in 123 patients (36,2%).
Conclusions: Electro-acupuncture diagnostic method according to Dr. Voll allows, due to revealed information-functional interconnections of biological active points and biological active zones of skin with internal organs and tissue systems, to determine their functional condition, perform functional and topic diagnostic. Electro-acupuncture diagnostic method according to Dr. Voll allows assessing adjustment disorders related with treatment of breast cancer at preclinical stage of disease development when its symptoms are not expressed or absent.

P-11-014
Cognitive functioning, emotional state and quality of life in prediabetic persons

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Jurate Lasiene

Objectives: evaluate cognitive functioning, emotional state, quality of life in prediabetic persons.
Methods: Glucose tolerance test was performed for 39 males (56,1±9,4 years), 64 females (54,9±8,1 years). 57 healthy persons with normal glycemia, 25 persons with impaired fasting glycemia >6.1mmol/l (IFG), 21 with impaired postprandial glycemia >7.8mmol/l (IGT). Cognitive functioning - by Trail Making Test (TMT) and Wais-R Digit Span Test (DST) of Wechsler Adult Inteligence Scale, emotional state - by Profile of Mood State (POMS), quality of life (QoL) – by WHO Brief Quality of Life Questionnair.
Results: No significant differences were between healthy persons and persons with IFG. In patients with IGT cognitive functions, but not emotional state and quality of life were worse than in healthy persons: DSTforwards - 7.9±2.7 vs. 6.2±1.7, p=0.020, DST raw score -13.3±4.5 vs. 10.8±3.1, p=0,024. In patients with IGT only tendency of worse, than in persons with IFG, cognitive functions were found: DST forwards - 7.9±2.8 vs. 6.4±2.3, p=0.084. Significant correlations. In group of healthy persons: between postprandial glucose level and DST raw score (r=0.307, p=0.024), between postprandial glucose level and DST backwards (r=0.272, p=0.047), between postprandial glucose level and POMS tension-anxiety (r=-0.336, p=0.017). In persons with IFG: between fasting glucose level and DST raw score (r=-0.447, p=0.037), between fasting glucose level and DST forwards (r=-0.507, p=0.016), between postprandial glucose level and POMS anger-hostility (r=-0.464, p=0.026). In persons with IGT: between body mass index and POMS anger-hostility (r=0.552, p=0.018).
Conclusions: Cognitive functions, but not emotional state and quality of life in prediabetic persons are worse that in healthy controls. Some aspects of emotional state and cognitive functioning in prediabetic persons could be related to glycemia.

P-11-015
Neurosarcoidosis psychiatric disorder

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Objectives: Sarcoidosis is a multisystemic affection whose pathogenesis implies the presence of a characteristic inflammatory lesion, the epithelioid and giganto-cellular granuloma. Its clinical frame is polymorphic. Based on a clinical case of a 41 years old patient, who was initially hospitalized in a psychiatric unit ; which the evolution was marked by the appearance of neurologic disorders ; we highlight the fact that sarcoidosis belongs to the principal diagnosis to be evoked in the occurred brutal psychiatric disorders, at the youth subject without notable antecedent.
Methods: case study
Conclusions: we highlight the fact that sarcoidosis belongs to the principal diagnosis to be evoked in the occurred brutal psychiatric disorders, at the youth subject without notable antecedent.

P-11-016
Body dysmorphic disorder: Case report, relations with physical illness and diagnostic categorization

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Objectives: Classification of body dysmorphic disorder (BDD) remains the object of debate as it can be regarded either as a somatoform or a delusional disorder, depending on the presence of psychotic features. Moreover, BDD has also been considered as an obsessive compulsive (OCD) spectrum disorder. Much of this controversy probably stems from the fact that little is known about the causes and pathophysiology of BDD. We report a case of BDD and discuss the possible biological factors involved as well as the limitations of the current classification.
Methods: We report a case of an 18 year old female with BDD with intermittent psychotic features. Her psychiatric condition was greatly exacerbated following a medical illness, raising the question that the later may act as a biological stimulus for BDD.
Results: Most studies agree that there is no significant difference on most variables between patients with delusional and nondelusional BDD. Also, recent reports suggest a link between physical diseases and BDD via serotonin synthesis suppression, mediated through inflammatory cytokines.
Conclusions: The majority of papers support the thesis that BDD may have a closely related psychotic subtype or even that there is a spectrum between these two disorders. Whether delusionality is a dimensional construct or both a dimensional and categorical construct is an important classification issue with clinical implications. The phenomenology of BDD, its family history, and comorbidity with OCD support conceptualizing it on the OCD spectrum. However, the recent discoveries concerning the underpinnings of the physiology of BDD point to a different type of neuroanatomic abnormality. This report also raises the question about the role of inflammatory processes as a trigger for the neurochemical dysfunction in BDD. Additional studies are needed to further analyze these issues, with possible future implications for other disorders with both delusional and nondelusional variants in the current classifications.

P-11-017
Body dysmorphic disorder and its psychological correlates

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Objectives: Objectives: The purpose of the study was to determine the prevalence of body dysmorphic concerns, sex differences and the extent of comorbidity with social anxiety and obsessive beliefs.
Methods: The universe of the study comprised all high school and college going youths, enrolled in various educational institutions in Ardebil and East Azarbaijan during the academic year 2007. Initially a sample of 1200 individuals were selected through a stratified cluster sampling procedure and questionnaires tapping body dysmorphic concerns, social anxiety and obsessive beliefs were administered. The hypotheses were explored using MANOVA, independent samples t test, chi square and Pearson's correlation coefficient.
Results: Findings revealed body dysmorphic concerns in 2.19% of the sample, with 72% of them being university students and 91% being girls. Body dysmorphic concerns correlated significantly with both social anxiety and obsessive beliefs. About 27% of those reporting body dysmorphic worries reported obsessive beliefs and 73% reported social anxiety. The major worries among females were concerns about face (65.5%) followed by concerns about body weight (31%), while the predominant worries among males were about body weight (24%). Regression analysis revealed that social anxiety and obsessive beliefs accounted for 42.6% and 12% of the variance in body dysmorphic concerns, respectively.
Conclusions: Findings will be discussed with regard to cultural factors.

P-11-018
Cryoglobulinemy revealed by insanity syndrome

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Objectives: The vascular insanities are considered to be the second cause of insanity of the elderly, after the Alzheimer disease. They often carry out a clinical presentation of mixed insanity. The cryoglobulinemy belongs to the most unusual causes of vascular insanity. Through a clinical case of a 63 years old patient, who was hospitalized for psychiatric disorders that was complicated by a functional impotence of the right hemi-body with brutal installation. We illustrate problem of etiologic diagnosis caused by the vascular insanities due to the cryoglobulinemy, which constitute one of its rare causes. Its research must be conducted systematically in presence of any vascular insanity symptoms, with an unspecified etiology
Methods: case study
Results: Through a clinical case of a 63 years old patient, who was hospitalized for psychiatric disorders that was complicated by a functional impotence of the right hemi-body with brutal installation. We illustrate problem of etiologic diagnosis caused by the vascular insanities due to the cryoglobulinemy, which constitute one of its rare causes.
Conclusions: the search of cryoglobulinemy must be conducted systematically in presence of any vascular insanity symptoms, with an unspecified etiology

P-11-019
Aripiprazole - Anorexia

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P-11-020
A survey study of the social abnormality among the university students

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Objectives: Objectives: Overall Goals: Investigating and distinguishing the factors which leads the youths to social abnormality Goals: 1. Knowing the social abnormality related to the economical status of the families 2. Knowing the social abnormality related to the educational status of the families 3. Knowing the social abnormality related to the youth occupational status 4. Knowing the social abnormality related to the social welfare and facilities
Methods: Methodology In this survey the method is based on the descriptive – measurement. The questioners and interviews were used in this research and the selected samples are university students from various disciplines. By distributing the questionnaires among students and interviewing with them we are going to gather data. The sample is selected randomly from the university students according to their disciplines.
Results: Predictable results according to applying this plan 1. Modifying the new and scientific methods for encountering with youths of Qom Province 2. Formulating the suitable solutions for guiding the youths of Qom Province 3. Creating the motivation, self-esteem, life expectancy and self- controlling among the youths of Qom Province In addition it is expected that the implementation of this plan leads us to find other applicable solutions, nationally used.
Conclusions: Since in most cases the social abnormality exist among youths who have the identity-crisis and this leads them to low morale; consequently, the psychological problems will be created. This survey which is an inquiry from the university students seems to be more useful and beneficial. It is concluded that they are partial relationship between the social abnormalities and parents educational level, economic & social status. Abnormality is observed more among males than females.

P-11-021
Studying the relationship between emotional intelligence and principals' performance

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Objectives: The main of this research is to identify emotional intelligence factors of high school principals in Tehran's 9th pedagogy district and its relationship with their performance. To identify the relationship between emotional intelligence ad principals' performance, we tried to answer four questions. First, what are principals' emotional intelligence factors? Second, is there any relation between principals' emotional intelligence and their performance? Third, is there any relation between emotional intelligence factors (self-awareness, self-regulation, self-motivation, empathy and social skills) with principals' performance? Third, is there any difference between the emotional intelligence of male or female principals and between the principals in public and nonprofit schools? Finally, is there any difference between emotional intelligence factors among male and female principals?
Methods: survey descriptive
Results: The findings show that there is a strong and meaningful relation between emotional intelligence and principals' performance. Besides, there is a positive and meaningful relation between emotional intelligence factors and their performance (except than self-motivation). Among emotional intelligence factors, the relationship between self-awareness with performance was relatively strong and the relations between principals' social skills and self-regulation with their performance were mean to high.
Conclusions: Afterwards, we concluded that there is no meaningful difference between emotional intelligence of male and female principals and also between principals' emotional intelligence in public and nonprofit schools. Finally, by studying the relations between all emotional intelligence factors with gender, we concluded that male principals have higher social skills than females and there is no difference among other factors and both genders.

P-11-022
The psychology of job stress from legend to reality

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Objectives: Job stress in organizations is one of the current global problems which was considered by management and psychology connoisseurs since the beginning of industrial revolution, mass production and shaping big governmental entities and corporations. It includes various issues such as health, human values, safety, anxiety, frustration, disillusionment, spiritual crisis, unemployment, professional static, feeling/non-feeling of success, etc.
Methods: Survey Descriptive
Results: In the present article, we are willing to investigate job stress in two perspectives: legend and reality. We address stress indicators while reviewing its terminology as well as its background and its connoisseurs especially in modern world.
Conclusions: The indicators include physical, mental and behavioral symbols. Then we point out job stress legends and through the second part of the article, we address scientific guidelines to illuminate job stress.

P-21
Other I

P-21-001
FAHR syndrome revealed by neuro-psychiatric disorders

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Objectives: The Fahr syndrome is characterized by the presence of intracerebral, bilateral and symmetrical non-arteriosclerotic calcifications, located in central grey nuclei. One of its main etiologys is the pseudohypoparathyroïdism (PHP), which reflects a resistance to the action of the parathormone, with especially a hypocalcemia and a normal or a high rate of parathormone.
Methods: case study
Results: We report in this study, the case of a 36-year-old man affected by PHP, revealed by a FAHR syndrome, discovered after several years of evolution of persistent and refractory psychiatric and neurological disorders. For this patient, alcoholism, use of typical antipsychotics, of antiparkinsonien drugs and some antiepileptics, contributed to perpetuation and exacerbation of symptoms.
Conclusions: This study underlines the interest of searching phosphocalcic metabolism disturbances, in presence of neuropsychiatric symptoms, to detect a PHP; or any other FAHR syndrome etiology; in order to improve, or at least, not to aggravate the symptomatology.

P-21-002
Relationship between skin and psychopathology: Review of the literature

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Objectives: The relationship between dermatologic disorders and psychiatric disorders exists in the domains of pathophysiology, semiology and therapeutics. The goal of this study is to describe the disorders that present with both psychic and dermatologic manifestations in their pathophysiology, clinical presentation and treatment.
Methods: A literature's review was made via a Pubmed research of the published articles between January 1967 and May 2008 that were interested in the disorders belonging to both disciplines at the same time.
Results: Psychodermatologic disorders belong to four main groups: 1) Psychophysiologic disorders that are dermatologic disorders declenched or exacerbated by a psychologic factor, i.e. psoriasis 2) Primary psychiatric disorders that manifest in dermatologic disorders, i.e. the delusion of parasitosis 3) Secondary psychiatric disorders caused by a primary dermatologic disorder, i.e. the social anxiety secondary to vitiligo. 4) Psychodermatologic disorders not otherwise classified.
Conclusions: These are, in the majority of cases, chronic disorders that need a multidimensional approach for treatment.

P-21-003
Prevalence of psychiatric disorders during Peg - Interferon and Ribavirin therapy in patients with chronic hepatitis HCV - correlated

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Objectives: Peg-Interferone (PegIFN) and Ribavirin (Rbv) therapy in patients with HCV chronic hepatitis is associated with the onset of psychiatric symptoms and syndromes in approximately 20% of the cases (Kraus et al. ,2004; Constant et al., 2005). The aim of the present study was to evaluate 1) the incidence of psychopathological alterations and psychiatric disorders during PegIFN and Rbv therapy and 2) whether psychiatric alterations were correlated to a specific type of PegIFN.

Methods: The onset of psychiatric disorders was evaluated through the administration of the SCID in 431 HCV patients, consecutively recruited and randomized to receive PegIFN-alfa2a and Rbv (212 patients, Group A) or PegIFN-alfa2b and Rbv (219 patients, Group B) therapy for 48 weeks.
Results: One hundred and forty patients (32%) developed psychopathological alterations during the therapy, regardless of the PegIFN administered (71 patients in Group A vs 69 patients in Group B). In 28% of the cases, patients developed depressive symptoms and 1/3 of these patients a Major Depressive Episode. Most common observed psychiatric symptoms were: aggressiveness, irritability, nervousness (51%), insomnia (50%), general anxiety, panic attacks and concentration difficulties (16%), dizziness and emotional instability (2%). Of the 140 subjects with psychopathological alterations, only the 16% (n=23) had a positive family history for psychiatric disorders, whereas in the remaining 84% (117 patients) psychiatric symptoms appeared for the first time. The 41% of the patients with psychiatric alterations (58 of 140) was treated with SSRIs and, occasionally, with benzodiazepines. The prevalence and type of treatments were similar in both treatment groups (41% vs 41%, p=ns).
Conclusions: PegIFN and Rbv therapy determined the onset of mood disorders and psychiatric symptoms in almost one third of the sample. The incidence of the symptoms did not seem to depend on the PegIFN administered.

P-21-004
Study oxidant and antioxidant systems in multiple sclerosis

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Objectives: Study of parameters of oxidant and antioxidant systems in different clinical forms and at different stages of MS current.
Methods: It is carried out complex clinical-biochemical research in 79 patients with MS, in 75 mentally and physically healthy persons. Parameters of an intensification of lipids peroxidation, conditions of enzymatic and not enzymatic parts of antioxidatic system (AOS) are analyzed at different clinical forms and stages of MS current. Oxidative stress is the essential feature of pathogenesis MS. The analysis of parameters of the peripheric blood at patients with MS has showed substantial increase of the pro-oxidant processes (malondialdehyde's level) and an expression of an endointoxication (spectrum "middle molecules") at the pathological process exacerbation, and also depending on the disease gravity. Rising of background "middle molecules" in the blood's serum also reflects intensifying the pro-oxidant processes. These oxidant breaches can point out an opportunity of a continuity of the demyelination's process development.
Results: The failure AOS is found out at patients with MS. It is lowered glutathione's level in a phase of remission and at an exacerbation both at relapsing-remitting (RRMS) as well as at secondary progressive (SPMS). It is accompanied by very low erythrocyte activity of glutathionereductase, the only enzyme which provides restoration of the oxidized glutathione. The compensatory activation of a catalase of serum is fixed only at exacerbation RRMS.
Conclusions: Obtained data confirm the importance of the oxidizing stress in development of pathological process at the MS.

P-21-005
Temperament and character-myocardial infraction predisposed personality traits

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Objectives: Patients diagnosed a cardiovascular disease, particularly ischemic disease or myocardial infarction, display the increased frequency for depressive disease in relationto those who do not suffer from coronary diseases. The analysis of the influence of personality factor in relation to myocardial infarction incidence is the main goal of this study.
Methods: Patients hospitalized at the Coronary Ward of the Intern Clinic at the Clinical center "Kragujevac" in the period October 2003 until July 2006, with acute myocardial infarction diagnosed (I-21, MKB 10). Acute myocardial infarction is defined by means of positive tropinine blood test in the setting of angina symptoms, as well as according to electrocardiographic changes. Patients between the age of 35 and 65 were included in the research (63 patients). Control group - healthy individuals between the age of 30 and 65 (52 patients). We also used TCI test to provide myocardial personality type.
Results: Personality traits such as NOVELTY s. HARM AVOIDANCE, SELFTRANS., ANTICIP and FATIGAB significantly influence myocardial infarction incidence. Individuals with lesser NOVELTY SEEKING value (odds ratio is 0,961,p=0,000), and SELF-TRANSPARENCY (self transparence-odds ratio is 1,036,p=0,000) value are myocardial infarction predisposed.
Conclusions: TCI test may also play an important role in predicting emotional responses in the course of various challenges imposed upon a person. An opportune and preventive introduction of diverse therapeutic procedures (psychopharmacological, first and foremost) would yeald numerous benefits for the individuals suffering from CVD. Antidepressant therapy (for example, SSRI) results in depression symptoms reduction in patients with infarction, which ih to lead to lifestyle quality improvement, decrease in the mortality rate, decrease in the number of days spent in a hospital, as well as to the reduction of health insurance costs.

P-21-006
Features of application of psychotherapy in psychosomatic

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P-21-007
Investigation of job burnout between employees and managers

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P-21-008
Studying the relationship between A & B personality types and managerial style

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Objectives: Owing to the fact that managers' personalities are among the effective factors on their managerial style, present research tries to investigate the relationship between A & B personality types and managerial style. The research population includes managers of Training and Education Organization and Agricultural Jihad Organization in Qom Province. Its sample includes 48 managers of Training and Education Organization and 60 managers of Agricultural Jihad Organization studied by polling method. 42 filled questionnaires in Training and Education Organization and 55 ones in Agricultural Jihad Organization were gathered. On this basis, two questionnaires were applied: A & B personality-types questionnaire which includes four aspects namely competitiveness, work addiction, hostility/angriness and impatience/restlessness; and leadership style questionnaire of Bardenz and Metzcas whose aim is to evaluate the managers based on task-orientation and relationship-orientation through studies in Michigan State University.
Methods: Survey-Descriptive
Results: Task-oriented leadership style was the dominated leadership style and A personality type was dominated personality type in both populations.
Conclusions: The findings show that there is no meaningful relationship between leadership style and personality type in both population in terms of studying paradigm.

P-21-009
Studying the relationship between propensity to team-building and managers' personalities based on McKerry and Costa' Big-5 Model

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Objectives: Managers' individual differences that are mainly rooted in their personalities can be a source of creativity development or a source of conflict, frustration and unavoidable organizational problems. Unavoidable individual differences in organization are representing themselves in the format of important contradictions in life. One of such conflictions is balancing among individual personality, needs and aims with collective collaboration which can be one of the most important factors in creating the tensions and also one of the most significant managerial tasks in the organization. In this research, studying the relation of managers' personality with McKerry-Costa's five-factor model with neuroticism, extroversion, conscientiousness, agreeableness and openness to accept experiences with the propensity to team-building and joining them are considered.
Methods: Survey-Descriptive
Results: The results of researches in Training and Education Organization and Medical University supports the major hypothesis namely the existence of relationship between personalities based on selected model and their propensity to team-building. In studying sub-major, it was revealed that there is no meaningful relation between neuroticism and propensity to team-building.
Conclusions: Other aspects of personality have meaningful relations with propensity to team-building except than agreeableness in Medical University that has no meaningful relationship with propensity to team-building.
Keywords: personality, personality five-factor model, team-building

P-21-010
Application of "proteasome tolerance" to a novel therapy for neurodegerative diseases

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P-21-011
Time selective attention in a visual context. An event related potentials study

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Objectives: It has been demostrated that "time selective attention" modulates the amplitud of the N1 and CNV component elicited by auditive stimuli. However, until now we did not know if this process is also implemented in the visual system. Our objective was to determine if the duration of a visual stimulus can be used as the selection feature in a visual time selective attention task.
Methods: We designed a time visual selective attention task based on the dichotic listening task. The duration of the foveally presented standard visual stimuli could be 400 (short) or 1000ms (long). Participants (N=13) had to attend to one or the other duration in alternating runs. A response was required only to an infrequent luminance change marking the end of the relevant duration (Target). The ERP data was analyzed by a repeated measures analysis of variance design (ANOVA) with duration, attention and electrode site as factors.
Results: We found that N1 amplitude was modulated by attention to a specific duration, it being larger when elicited by all of the stimuli presented on attended short than on attended long blocks. We also observed that the CNV component shows significantly larger amplitude when it is elicited by stimuli belonging to an attended long compared with and attended short block.
Conclusions: We demostrated that relevant stimuli duration can be used as selection feature in a time visual selective attention task and that this process is reflected by the amplitud modulation of the same ERP component seeing in auditive time selective attention studies, suggesting a cross-modality time selective attention neural mechanisms.

P-21-012
Pathogenetic immunomodulating therapy in patients with neurotic disorders

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Objectives: To determine the efficacy of immunomodulating therapy in adult patients with neurotic disorders.
Methods: The psychotropic effect of the mielopid, licopid and T-activin was investigated in the complex therapy for patients with neurotic disorders with help of multivector analysis of main clinical and immune parameters. Studies of influence of some immunomodulators were hold according to clinical condition of patients with neurotic disorders.
Results: Increasing activity of some interleukins (IL-1, IL-2) and macrophage lymphokines (α-INF, α-TNF) biosynthesis, as well as high level of IgG and increasing of number of CD2+, B-Ig+, B-IgG+, B-IgA+ cells were detected during the monitoring of the immune status of patients with neurotic disorders. More active effect in the direction of anxiety and fear was noted for mielopid, and in direction of psyhoasthenic disorders – for licopid were noted during competitive analysis of psychotropic effect of above mention peptides.
Conclusions: Presented dates are confirming new possibilities of the immune peptides in complex therapy for patients with neurotic disorders.

P-21-013
Electroconvulsive therapy and schizophrenia

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Objectives: The authors propose to talk about the use of ECT in schizophrenia.
Methods: The authors make a literature revision with clinical data available in Pub-Med and several books on this matter.
Results: The evidence suggests that ECT, combined with treatment with antipsychotic drugs, may be considered an option for people with schizophrenia, particularly when rapid global improvement and reduction of symptoms is desired. This is also the case for those with schizophrenia who show limited response to medication alone. The optimal number of ECT sessions in patients with schizophrenia remains controversial, such as the identification of those patients who would benefit from ECT-C and ECT-M.
Conclusions: The induction of a seizure for therapeutic purposes by the administration of an electrical stimulus (electroconvulsive therapy or ECT) remains a common treatment option for people with schizophrenia. Substantial proportions of patients with schizophrenia do not achieve acceptable levels of response with antipsychotic therapy alone. It is difficult to draw conclusions or treatment recommendations from available data because of small sample sizes and widely divergent study designs.

P-21-014
Neuropsychiatric manifestations of HIV disease

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Objectives: In this work, the authors review the clinical disorders associated with HIV infection, psychopharmacologic treatment options and drug interactions.
Methods: The authors made a literature revision with clinical data available in Pub-Med.
Results: With the recent advances of antiretroviral therapy and the consequent increase of the life expectancy of people living with HIV infection, psychological and psychiatric issues associated have received considerable attention owing to the emotional impact of the disease and it´s effect on an individual´s personal, sexual, occupation and social life.
Conclusions: Disorders associated to HIV may be as varied as depression, phobias, post-traumatic stress and the whole gamut of cognitive disorders. Substance abuse is also a very common disorder. The pharmacological treatment of these disorders have important interactions with HAART leading to collateral effects witch can lead to psychiatric disturbances.

P-21-015
Psychiatric symptoms associated with anabolic steroids and alimentary supplements

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Objectives: The authors want to alert psychiatrists about patients who show these syndromes and physical evidence of AAS effects. We think that we are facing a new "addictive disorder".
Methods: Based on literature revision on this subject, we found that body misperception, anxiety, impulsivity, aggressivity, headache, mood oscillations and sexual dysfunction have been frequently described. The authors define these substances, describe the action mechanisms, the real benefits and side effects. Also refer to the multiple substances used as alimentary supplements by these people, who mystify their benefits, when there is no scientific evidence of their real advantages.
Results: The modern society incite to the body image cult. Athletes and non-athletes seeking a better performance and gains in strength and appearance use anabolic-androgenic steroids (AAS) out of their medical indications. They generally use the combination of multiple AAS drugs beyond their therapeutic doses. This has multiple adverse medical effects.
Conclusions: Many studies have found evidence that AAS may lead to important psychiatric collateral effects, such as mania, psychosis and depression, when in high doses.

P-21-016
Oxidative stress and neuroprotection at experimentaly induced Parkinson's disease

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Objectives: Oxidative stress was shown to be implicated as a common pathogenic mechanism at the central nervous system diseases such as cerebral stroke, Parkinson's disease, and Alzheimer's disease. The development of oxidative stress is characterized by activation of free radical reactions being cause to structural and functional changes of cell membranes. The objective of this study was to determine the lipid peroxidation in nuclear and mitochondrial fraction of brain cells of animals under the experimental Parkinson's disease and treated with new synthesized compound containing lithium, nicotinic acid and cysteine.
Methods: The experimental Parkinson's disease was done using injection of N-methyl-1,4 phenyl-1,2,3,6-tetrahydropyridine. In the bases of method for determination of lipid peroxidation is the quantitative evaluation of hydroperoxides and malonic dialdehyde in the total homogenate of nuclear and mitochondrial fraction of brain cells.
Results: Obtained data shows that injection of new synthesized compound at the dose of 10 mg/kg brings to normalization of lipid peroxidates.
Conclusions: Anti oxidative effect of synthesized compound is conditioned by its chemical structure containing cysteine and lithium. The cysteine participates in metabolism of glutathione which is a component of glutathione peroxidase and glutathione reductase. Both enzymes play a crucial role in protecting cells from formation of highly reactive free radicals, and particularly from lipid peroxidation.

P-21-017
Demonstration of inhibitory processes in the central nervous system

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Objectives: To research the influence of stimulation of thalamus on the spinal reflex time and to demonstrate the inhibition in the central nervous system (CNS) and its reversibility.
Methods: 1. Suspend the thalamic preparation by its lower jaw. Wait until the frog's preparation comes out of shock. 2. Determine the reflex time when a hind paw is in acid. Wash off the paw. 3. Put one sodium chloride crystal on the dry surface of thalamus. Determine the reflex time several times. Wash off the hind paw. 4. Take the crystal off, wash off the incision with physiological solution and determine the reflex time.
Results: Initial reflex time: 1.24 seconds Reflex time during the action of sodium chloride crystal: 5.16 seconds Reflex time after the removal of sodium chloride crystal: 2.60 seconds
Conclusions: There is presence of inhibition in the central nervous system when the sodium chloride crystal is placed on thalamus. The inhibition is proved to be reversible process because inhibition becomes gradually weaker when the crystal is removed from the thalamus.

P-21-018
Neurophysiological characteristics of patients with alcohol epileptic syndrome

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Objectives: Differential diagnosis of alcohol epileptic syndrome (AES) with idiopathic and symptomatic epilepsies is very urgent. Implementation of a comparative analysis of electroencephalograms (EEG) of patients with AES and patients with non-alcoholic ES can be used as an additional criterion of differentiated diagnosis.
Methods: With the goal of study of EEG of patients with AES, 251 persons (18-76 y.o.) have been examined: I group included 89 patients with AES – with primary generalized attacks of wakefulness and ÀWS symptoms without the brain limited organic injuries in anamnesis; in II group – with non-alcoholic ES: 22 persons with - symptomatic – with primary generalized and secondary generalized attacks of sleep and wakefulness and the brain organic limited injuries with ÀWS symptoms; 56 – with idiopathic – with primary and secondary generalized attacks of sleep and wakefulness without ÀWS symptoms; III gr. - comparisons – 84 neurological patients without ES and ÀWS.
Results: EEG of all the patients in I gr. had the following accents: low-amplitude alpha-rhythm with absent zonal differences and modulations as well as regular dominating activity; diffusive changes in the form of slow waves from the delta range above both brain hemispheres, high frequency beta-rhythm primarily in frontal abductions; record plural artifacts; overlapping of "muscular tremor" and "floating electrodes" as AWS manifestation; epileptic and focal slow wave activity was not present on any EEG, but reduced activation after hyperventilation, photo- and phonostimulation has been detected. At the same time in 44.4% of cases, the EEG of the patients with idiopathic and symptomatic epilepsy was notable for focal slow-wave activity in the brain injured hemisphere, in 22.2% - epileptic activity.
Conclusions: Thus, EEG of the patients with AES had definite neurophysiological characteristics, this can be used as an additional criterion of AES differential diagnosis.

P-21-019
Application of ultralow temperatures in rehabilitation

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P-21-020
Neurobiological mechanisms of ecology-induced mental retardation

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Objectives: During the last few years a number of investigations were made in the field of pathogenic influence of unfavourable ecology to children's health. The aim of present research was to determine the role of neuroimmune factors in genesis of ecology-induced mental retardation in children.
Methods: 120 children 4-8 years old with mental retardation (MR) from the region of East Zabaykalye with unfavourable ecology have been included into the study (main group). As a comparison 42 children of the same age with MR from the region of Zabaykalye region with relatively favourable ecology were examined. All the children involved underwent a neuropsychological examination to determine a maturity of cognitive functions. Control group involved mentally sane children from Zabaykalye territorial centre (Chita). Their neuroimmune status was estimated by blood levels of brain-derived neurotrophic factor (BDNF), neuron-specific enolase (NSE), autoantibodies to neuron growth factor (NGF) and autoantibodies to myelin-associated glycoprotein (MAG). Listed parameters were determined by hardphase immune-enzyme assay. The organic origin of the mental disorders stated was confirmed neurophysiologically by EEG-mapping.
Results: It was revealed that children with ecology-induced MR studied had decrease of BDNF blood levels, increase of NSE and high antibody titre to neron-spesific peptides (NGF & MAG) – as compared to control group and children from relatively favourable region of Zabaykalye. Shown abnormalities are evidence of autoimmune mechanisms in genesis of MR in children residing in the district with unfavourable ecology.Those children also demonstrated domination of slow (delta and theta- activity) constituents in the electroencephalograms, which testifies to organic brain damage. Children from relatively favourable region of Zabaykalye had no statistically significant differences of laboratory indices from control group. Neurophysiological assessment showed less of delta and theta- activity.

P-30
Other / Suicide / PTSD

P-30-001
What do we really know about mindfulness meditations?

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Objectives: In the last decades, the scientific community showed an increasing interest towards a group of meditations called Mindfulness meditation (MM). The aim of the present work is to give an integrative overview of MM, considering neurobiological, genetic and clinical features, and providing a relationship between these data.
Methods: A literature search was conducted using MEDLINE, ISI web of knowledge, the Cochrane database and references of selected articles. Articles in English language, published until may 2008, were included
Results: The neurobiological and clinical modifications induced by MM are mainly modulated by an activation of the prefrontal cortex and a deactivation of the amygdala, results suggesting a more conscious reflexive rather than automatic reactive awareness. Electroencephalographic studies evidenced an increase in alpha and theta activities, findings related to relaxation states. MM showed efficacy in the prevention of depression relapses, in anxiety disorders, substance/alcohol abuse, heart diseases and chronic pain, in the reduction of stress, anxiety, depressive levels and in the improvement of quality of life in many disorders and in healthy people. These effects could be mediated by both psychological mechanisms, as a development of meta-cognition and of a non judgemental awareness of experiences, and biological ones, as reduction in cortisol levels and release of endogenous beta-endorphin.
Conclusions: MM appears to be a promising tool for many mental and physical disorders. Even though several limitations affect available studies such as small samples size, lack of randomizations and double blinding, present evidence is encouraging and further better designed studies are needed.

P-30-002
Mindfulness based stress reduction for stress management in healthy people: A review and meta-analysis

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Objectives: Mindfulness based stress reduction (MBSR) is a clinically standardized meditation which showed consistent efficacy for many mental and physical disorders. However smaller attention was given to the benefits that it could have in healthy subjects, in particular as a tool for stress reduction. Thus, the aim of the present review and meta-analysis is to better investigate current evidence about the efficacy of MBSR in healthy subjects with a particular focus on its benefits for stress reduction.
Methods: A literature search was conducted using MEDLINE, ISI web of knowledge, the Cochrane database and references of retrieved articles. The search included articles written in English language published until September 2008, identifying 10 relevant studies. Cohen's d effect size between meditators and controls on stress reduction and spirituality enhancement values were calculated.

Results: MBSR was significantly more efficacious than inactive control groups both in reducing stress and in enhancing spirituality values. A direct comparison-study between MBSR and a standard relaxation training found that both treatments showed comparable efficacy. Furthermore, MBSR showed significant efficacy in reducing ruminative thinking and trait anxiety as well as in increasing empathy and self compassion.
Conclusions: MBSR could represent an efficacious tool for reducing stress in healthy people. However many limitations of current studies including small samples size, self selection bias and heterogeneity of scale used to assess measures of stress and spirituality reduce the significativity of our finding and underline the necessity for future research.

P-30-003
Executive Functions with affective involvement in patients with suicide attempt

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Objectives: Some studies have shown that patients with suicide attempt present deficit in executive functions; these functions have been related to dorsolateral prefrontal cortex integrity. However, results are not conclusive. In this study, the aim was to identify deficit in executive functions in tasks with high and low affective involvement in patients with suicide attempt. In addition, executive function deficits in social behavior were evaluated.
Methods: Outpatients with non-violent suicide attempt, with depressive and anxious symptoms were compared to patients with depressive and anxious symptoms, without history of suicide attempt and healthy subjects. The groups were matched in age, education, and sex. Stroop Test (Stroop), emotional version of Stroop Test (E-Stroop), Wisconsin Card Sorting Test (WCST), emotional version of WSCT (ECST), Gambling task (Iowa, Bechara, et al., 1997) and Behavior Rating Inventory of Executive Function (BRIEF- A) were applied to the subjects.
Results: Significant differences between groups were observed neither in the Stroop, nor in WCST in any version. A trend to choose higher number of disadvantageous decks in the Gambling task was observed in suicide attempt patients in comparison with the control group. In addition, suicide attempt patients showed higher scores in almost all the Brief-A scales.
Conclusions: Present results suggest that patients with suicide attempt did not show deficit in executive functioning, with or without affective stimuli. However, they showed a trend to take disadvantageous decisions in the Gambling task, suggesting that these patients have difficulties in decision making when personal affection is involve. Deficits in Gambling task performance have been associated with a dysfunction of the ventral and medial parts of the prefrontal cortex. Additionally, the differences in the Brief-A reflect executive function deficits in social behavior in patients with suicide attempt that may contribute to increase suicide risk.

P-30-004
Suicidal behavior associated to obsessive compulsive disorder in a mental health institution

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Objectives: determine suicidal behavior prevalence in out-patients with diagnosis of Obsessive Compulsive Disorder (OCD) assisted in ambulatory and emergency services of National Institute of Mental Health along last five years
Methods: descriptive trial in Obsessive Compulsive Disorder out-patients assessing suicidal behavior, using DSM-IV criteria and instruments like Yale Brown Bocs, Hamilton for Depression Scale and Beck Inventory for suicidal ideation, carried out by a multidisciplinary professional team
Results: In a sample of 44 patients, 20 males and 22 females, aged between 18 and 45 years old, it was found suicidal ideation in 55 %, while suicide attempt in 23.7 % of them, mostly by medicine overdose. Comorbidity of OCD and Major Depression Disorder was about 50 %.
Conclusions: in this trial we found OCD patients with suicidal ideation and suicide attempt in higher percentages than reported in foreign literature,becoming OCD an important risk condition for suicidal behavior not only by itself but for its association to Major Depressive Disorder

P-30-005
Suicidality and Phagophobia

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Objectives: to study suicidal behavior in out-patients with diagnosis of an specific phobia like Phagophobia along last decade in a mental health institution
Methods: descriptive and prospective trial in out-patients with diagnosis of Phagophobia according to DSM IV criteria and assessed by application of instruments like Sheehan Scale, Hamilton for Depression Scale and Beck Inventory for suicidal ideation by a multidisciplinary group of professionals in a mental health institution
Results: we found 12 out-patients with diagnosis of Phagophobia, nine of them (75 %) reported suicidal ideation, and 3 of them (25 %) presented suicide attempt requiring emergency intervention. Also we observed comorbidity with Social Anxiety Disorder in 8 patients (66.6 %), and with Major Depressive Disorder in 9 patients (75 %). At least 2 female patients were hospitalized because high suicidal risk and important weight loss
Conclusions: in this study we observed that Phagophobia is a dramatic entity related to suicidal ideation and suicide attempt, not only by its clinical features and consequences, but also by comorbidity with Social Anxiety Disorder and Major Depressive Disorder

P-30-006
Effectiveness of a practice guideline for ambulatory treatment of Colombian patients with suicide risk

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Objectives: The aim was to study the effectiveness of a practice guideline for the ambulatory treatment of Colombian patients with suicide risk.
Methods: This study used a quasi-experimental design. The practice guideline for the ambulatory treatment of patients with suicide risk has been developed by a private mental health institute in Colombia. The patients were classified in four different suicide risk levels, low, middle, high and high immediate. The guideline established that patients with suicide risk lower than high immediate could be treated in home with medical care. The control group was established with those patients who their insurance service did not allow the application of the guideline; therefore, usual care was offer to them. The outcome was measured by suicide attempts or suicide within the first 30 days of the treatment.
Results: 111 patients were included in the intervention group and 88 in the control group. The patients in the intervention group had a mean age of 31.4 years (SD = 13.8) and 32.4% were male; the patients in the control group had a mean age of 31.7 years (SD = 15.3) and 46.6% were male. The relative risk for suicide attempt within the first month was 0.22 (CI95%; 0.04-1.11, p=0.04). None patient died by suicide. Formal survival analyses revealed a significantly lower suicide rate in the intervention group for the first 30 days (p=0.045). The median for hospitalization days was 2 in the intervention group and 7 in the control group (p<0.001).
Conclusions: The use of the practice guideline was protector for suicide attempt and also diminished the hospitalization days compared with the usual care. Randomized clinical trials should be conducted to confirm these results.

P-30-007
Predictive validity of the suicide behavior questionnaire – revised in Colombian psychiatry patients with suicide risk

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Objectives: The aim is to establish the psychometric properties of the Suicide Behavior Questionnaire-Revised in psychiatry patients with suicide risk and its predictability for suicide or suicide attempt.
Methods: This was a validation study. Patients who assisted to psychiatry consult and their attending psychiatry found them to have suicide risk were assessed with the Suicide Behavior Questionnaire-Revised, a four item version; reasons for living inventory; and a semi-structured interview for suicide risk. A 30 days follow up were completed to all patients to establish the predictive validity with suicide attempt or suicide.
Results: 211 patients were surveyed. The mean age was 31.5 years old (SD=14.48). 37.44% of the sample were male. The Cronbach's alpha was 0.664. The Suicide Behavior Questionnaire-Revised showed a correlation of -0.546 with the Reasons for Living Inventory ($p<0.001$) and 0.380 ($p<0.001$) with the semi-structured interview for suicide risk. With the cutpoint equal or higher than thirteen with a positive predictive value 10.17% and a negative predictive value 98.25%.
Conclusions: The Suicide Behavior Questionnaire-Revised was useful for the assessment of psychiatry patients with suicide risk. This scale could be applied as a screening instrument in psychiatry patients with suicide risk to predict suicide attempt in the first month of treatment, because of its excellent negative predictive value. Otherwise those patients who have a score higher than thirteen should be assess and follow by a specialized team in suicide.

P-30-008
Migraine comorbidity in Bipolar Disorder patients

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Objectives: The aim of this study was to establish the association of bipolar disorder with migraine.
Methods: a consecutive sample of 113 patients with bipolar disorder (85 bipolar disorder I patients and 28 bipolar disorder II patients) evaluated by the Structured Clinical Interview for DSM-IV of two mental health centers and a sample of 113 people selected from Bucaramanga's general population matched by sex, age, and socioeconomic status were obtained. Michel's Standardized Migraine Diagnosis Questionnaire was applied in both groups. Migraine prevalence were calculated and odd ratios were computed for case group and control group also for different bipolar disorder diagnosis.
Results: mean age was 41.9±13.6 years old and 80.3% were female. Migraine prevalence in bipolar disorder patients was 46.9% and 24.3% in control group (OR=2.22; CI95% 1.39-3.64). Also, bipolar disorder I patients had higher migraine prevalence than their matched control individuals (OR=2.53; CI95% 1.46-4.55). Bipolar disorder II patients showed a higher association with migraine than bipolar disorder I patients (OR=2.57; CI95% 0.98-6.98, p=0.003).
Conclusions: bipolar disorder patients show comorbidity with migraine, moreover, bipolar disorder II patients have a higher migraine prevalence than bipolar disorder I patients. This finding could implicate that bipolar disorder I and II are different conditions rather than a severity spectrum of the same disorder.

P-30-009
Occupational stress among administrative personnel in mental health hospitals

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Objectives: To evaluate levels of occupational stress in administrative personnel in mental health hospitals. According to NIOSH - The National Institute for Occupational Safety and Health - professional stress is a combination of negative physical and emotional reactions that occur in the mismatch between job requirements and capabilities, resources or needs of the worker. Psychiatry has been considered as one of the most stressful medical specialties. Most of the studies in the literature consist of samples of nurses and physicians and, while comparative studies amongst these groups are scarce, research comparing mental health professionals and administrative staff are practically non-existent. The purpose of this study is identifying those work situations which are potentially powerful stressors, as well as the nature of their consequences for health. The design of the study should allow us to examine the potential specific differences among occupations.
Methods: A sample of 100 administrative personnel was chosen from different state mental health care services. Design – A pilot postal questionnaire was drawn up from the most frequently-mentioned issues in the psychiatric domain.The questionnaire comprised following aspects: Conflict situations; Sociodemographic aspects; Health; Job dissatisfaction.
Results: The response rate was 85 % (85/100). By occupation, the percentage of returned questionnaires was 52 % for administrative personnel, 38 % for psychiatrist and 10 % for internal staff. Pronounced differences were found between the respondents in the evaluation of potential stressors and the overall occupational stress score. The category of stressors with the highest mean severity of stress score was time-related stressors, falling behind schedule, constant time pressure. Two-third of all interviewed described moderate to severity high levels of emotional exhaustion
Conclusions: The results indicate that administrative personnel rank factors related to time management as major job stressor, they need additional training in time management and specialized training in techniques, enabling them to cope with stress in daily work.

P-30-010
Emotionally-strong-willed sphere of the person with information neurosis

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Objectives: experimental base of Rehabilitation and Diagnostic Center. In total research had been captured 93 persons. The first group was made by 62 persons (67 %) at the age from 20 till 53 years having the status working in sphere of intellectual activity. The second group included persons from 18 till 57 years in number of 31 persons (33 %), whose labour activity is connected with physical activities.
Methods: research included method use «primary interview» and a complex of psychodiagnostic techniques, such as: a technique of colour choice by Lusher, a clinical questionnaire of revealing and an estimation of neurotic conditions and multifactorial personal questionnaire MMPI.
Results: technique Lusher's, has allowed to reveal decrease in working capacity at 35 persons (56 %), presence mental breakedown and emotional stress at level of 10-12 points at 42 % (26 people) control group. The clinical questionnaire diagnosed prevalence of scales of neurotic depression and астении for 53 persons (85 %). As a result of diagnostics by technique MMPI, at control group (p=0,005) - deviations from norm are not present.

Conclusions: considering increase of the diseases making on etiologic sign an information pathology of the higher nervous activity (HNA), the attention of optimisation HNA, to information overloads and psychopreventive maintenance of preservation of working capacity and psychological readiness for activity in various extreme conditions is paid. Measures of preventive maintenance of this pathology can be divided conditionally on two big groups: one of which is directed on increase of stability of nervous system to increasing information loadings (a relaxation method, aytogenic trainings), and the second - on creation of optimum conditions of interaction of an environment with an organism, by regulation of factors of an environment - the dosed out impellent training which can make preventive impact in initial stages of development of the neurosis caused by long psychophysiological loadings.

P-30-011
Psychological and neuroendocrine responses in male residents after an overnight hospital call

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Objectives: exposure to excessive or cumulative stress can result in damaging physiological and psychological changes that may occur singly or in combination.
Methods: to assess the neuroendocrine impact of a night-call, we studied eight healthy male residents (MEAN AGE=33 YEARS SEM=2) by measuring salivary cortisol concentration as well as circulating concentrations of total testosterone, FSH, LH, T4, T3U, TSH, prolactin, and proinflammatory cytokines such as c-reactive protein, ICAM-1, and VCAM-1. validated psychologic instruments—the STAI-S and STAI-T—were used to measure state anxiety and subjective stress and arousal. studies were conducted in the morning and on 3 separate days (pre-call, on call, and post-call). each subject functioned as his own control, and anova was used for statistical analysis
Results: salivary concentration of cortisol was significantly increased after a night call (0.423 ± 0.06 MG/DL), and on call (0.236 ± 0.03 MG/DL). this was associated with significantly lower post-call serum concentrations of total testosterone, when assessed in relation to pre-call and on call values (419 ± 59 versus 495 ± 50 versus 464 ± 54 NG/DL; P=0.04). the lower circulating concentrations of total testosterone after a night on call were accompanied by lower serum concentrations of FSH (4.1 ± 0.6 versus 4.8 ± 0.8 versus 4.7 ± 0.8 MIU/ML; P=0.02) and LH (2.9 ± 0.3 versus 3.9 ± 0.3 versus 3.6 ± 0.4 MIU/ML; P=0.055).
Conclusions: stress of a night call is of significant intensity to stimulate the hypothalamic-pituitary-adrenal axis and to centrally suppress the male gonadal function. the dissociated activity of the two axes is presumed to be due to inhibition of the gonadotropin pulsatility by endogenous opiates (beta-endorphin), which are known to be concomitantly released with acth, both at baseline and in response to stress.

P-30-012
Treatment emergent sexual dysfunction related to antidepressants: A meta-analysis

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Objectives: Sexual dysfunction is an important under-estimated side effect of antidepressant drugs. Patients, in fact, if not directly questioned, tend to scarcely report them. Thus, the aim of the present meta-analysis is to quantify sexual dysfunction caused by antidepressants on the basis of studies where sexual functioning was purposely investigated through direct inquiry and specific questionnaires.
Methods: A literature search was conducted using Medline, Isi web of Knowledge and references of selected articles. Selected studies performed on patients without previous sexual dysfunction were entered in the Cochrane Collaboration Review Manager Software (RevMan version 4.2). Our primary outcome measure was the rate of total treatment emergent sexual dysfunction. Our secondary outcome measures were the rates of treatment emergent desire, arousal and orgasm dysfunction.
Results: Our analyses indicated significantly higher rates of treatment emergent sexual dysfunction as well as specific phases dysfunction compared to placebo for the following drugs: citalopram, escitalopram, fluoxetine, fluvoxamine, paroxetine, sertraline, duloxetine, venlafaxine, clomipramine, imipramine and phenelzine, whereas no significant difference with placebo was found for the following antidepressants: amineptine, bupropion, moclobemide, mirtazapine and nefazodone. Nonetheless sufficient evidences (>100 subjects) are available only for bupropion, citalopram, fluoxetine, paroxetine, sertraline and venlafaxine.
Conclusions: Present evidence on treatment emergent sexual dysfunction caused by antidepressant is sufficiently studied only for few drugs. Furthermore some statistical limiting assumptions, as the inclusion of open label or small studies and the presence of an evident publication bias, could reduce the significativity of our findings. Thus, treatment emergent sexual dysfunction should be more deeply investigated.

P-30-013
Suicidal attempt cases admitted within a year in a general hospital

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Objectives: To report demographic and epidemiologic data concerning all suicidal attempts admitted in the various department wards of a general hospital within a year. "G. Gennimatas" is a general hospital admitting patients especially from within the county of Attica (population about 5 million) in Greece, but from the rest of Greece as well.
Methods: In a retrospective study, files of 136 cases performing suicidal attempts and being admitted in our hospital within the period from March 2007 until March 2008 were examined. Specifically, gender and country of origin, as well as age, marital status, existence of descendants, presence of previous psychiatric history and calendar month at time of attempt were noted. Mean values were calculated and appropriate statistical tests were performed where possible.
Results: Out of 136 cases performing suicidal attempt, 106 were female and 30 male. 104 were of Greek and 32 of foreign origin. Concerning marital status, 44 individuals were married, 69 were never married, 17 were divorced and 6 had lost their spouse. Concerning descendants, 58 patients had children whereas 78 didn't. 47 individuals had a positive previous psychiatric history and 89 not. Concerning the month the attempt was performed, 2 peaks were noted, 18 attempts were performed in March and 18 in August. Statistically significant peaking during August and March was observed (P<0.02, chi-square test).
Conclusions: Distribution of suicidal attempts in our sample within a year was greater among female gender, Greek nationals, unmarried people without descendants, individuals with an absence of previous psychiatric history. Statistically significant peaking concerning calendar month the attempt was made were found during August and March.

P-30-014
Environmental enrichment rescues the behavioural phenotype of BDNF heterozygous mice

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Objectives: Environment as well as genetic variability influence the behavioral and physiological phenotype of mice. Especially group housing in impoverished "standard" conditions is a crucial stress factor in male C57Bl/6 mice. The brain derived neurotrophic factor (BDNF) appeared to be a prospective target considering that its expression is known to be regulated by several external factors, including physical exercise, early social enrichment and housing conditions in general. Moreover, the "Neurotrophin Hypothesis" of depression and anxiety postulates that stress causes a reduction of BDNF, whereas chronic antidepressive treatment increase the levels of BDNF and its receptor, tyrosine kinase B (TrkB).

Methods: We investigated the effects of a genetic vulnerability – a heterozygous deletion of BDNF - combined with the modulating influence of two different group housing conditions on emotional behaviour. For that purpose, we subjected male and female mice to a battery of standardized test for locomotor, exploratory, anxiety- and depression-like behaviours. Furthermore, we measured BDNF protein levels in by ELISA in several brains areas, such as hippocampus, frontal cortex, hypothalamus and striatum.
Results: Standard impoverished group housing affected emotional behavior in male and female BDNF heterozygous mice, causing an increase in anxiety, changes in exploration and nociception. Environmental enrichment led to a rescue of alterations of emotional behaviours. Housing conditions affected significantly the BDNF levels, mainly in the hippocampus, correlating with the behavioral alterations.
Conclusions: These findings demonstrate that the potential pathological phenotype in BDNF mutant animals - as predicted by the "Neurotrophin Hypothesis" - could have been masked in former studies and a more stressful environmental context might elicit changes in emotional behaviour. The importance of environmental factors, especially of gene-environment interactions in animals with a special vulnerability seems often to be underrated and underestimated.

P-30-015
Is allergen exposure a contributing factor to suicidality?

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Objectives: Consistent evidence has shown seasonal peaks in suicide incidents but the explanation remains elusive. We proposed that seasonal aeroallergens represent environmental triggers for suicide through the association between depression and allergy as well as the depressogenic and prosuicidal effects of certain cytokines, and therefore examined the association between allergy and completed suicides in this large population study.
Methods: Using data from Danish population longitudinal registers, we included all defined suicide deaths of 27262 cases over a 26-year period in Denmark and the comparison population of live individuals. We retrieved personal information on history of hospitalization for allergy, psychiatric illness and socioeconomic status and data of pollen counts from various registers. We analyzed the data with conditional logistic regression.
Results: We have found that a spring peak of suicide was present in all suicides, and was significantly more prominent in those with a history of mood disorders, independent of gender, suicide method and personal socioeconomic status. We have also noted that significantly more suicide victims, compared with sex-age-matched population controls, had a history of allergy treated in hospitals, and that the overall allergy predicted suicide completion with odds ratio of 1.35 in men and 2.02 in women and such association remained after controlling for personal socioeconomic status and history of mood disorders. When modeling the frequencies of suicide deaths with the seasonal data of pollen counts suicide frequencies, we have observed a significant dose-response correlation between pollen counts and suicide incidents.
Conclusions: These findings support a biological connection between allergy, mood disorder and suicidality for which pollen may act as a triggering factor. However, additional studies are necessary to confirm this novel hypothesis which carries a promising potential for suicide prediction and prevention.

P-30-016
Suicidal ideation and hopelessness – is this the psychological marker?

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Objectives: Suicide is a leading cause of avoidable death. There are not much findings in this area in Malaysia due to religious sensitivity. This study has two major aims, firstly to obtain the prevalence of suicidal ideation in the population and secondly to identify factors that are significantly associated with the presence of suicidal ideation.
Methods: This is a sub study from the Malaysian Mental Health Survey (MMHS). Presence of suicidal ideation in the past one year period was assessed using two items from WHO mental health risk factors questionnaire. The questions were first if in the past year the respondents have thought about serious endings their own life and second if in the past one year period they have planned to end their own live. Factors associated with suicidal ideation were determined using descriptive statistics and logistic regression analysis.
Results: In the past one year prior to the study, 2.9% (n=108) of the total 3666 respondents had serious thought of ending their lives and 1.5%(n=56) had planned to end their lives. Being aged between 16-19 years old, belonging to Indian ethnic group, presence of family history of mental illness, alcohol problems, presence of common mental disorders and dispossession of own transport increased the rates of suicidal ideation. Hopelessness was also most strongly associated with both ideation and attempt.
Conclusions: It is showed that there would be 8-25 suicide attempts for every death from suicide. In line with this the findings show that the rate ideation is much higher than that of the suicidal rates of 0.4-0.6%. Further research on suicidal attempts with hopelessness as a predictor should be carried out and high risk groups should be targeted for interventions to avoid suicidal behaviours in future. Would there be biological associations with this marker and can this be detected?

P-30-017
Risk factors of suicidality in patients with social phobia

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Objectives: It has been reported that social phobia(SP) is generally begins in early or late adolescence. Therefore SP is commonly comorbid with other mood and anxiety disorders. It is also reported that suicide risk is elevated in social phobia if other psychiatric disorders are present. However, most of these reports were result of epidemiological studies which did not evaluate severity of depression or anxiety. The aim of this study is to elucidate risk factors of suicidality in patients with SP by evaluating both comorbidity of SP and its severity.
Methods: SP and its comorbid disorders were diagnosed by a trained psychiatrist according to DSM-IV with the aid of MINI Neuropsychiatric interview(MINI). Suicidality was evaluated by assessing items of module C(Suicidality) in MINI. Liebowitz Social Anxiety Scale(LSAS), Hamilton Anxiety Rating Scale(HAM-A), Beck depression inventory(BDI), Trait form of Spielberg State and Trait Anxiety Inventory(STAI-T), Retrospective Self-Report of Inhibition(RSRI) and Global Assessment of Functioning(GAF) were also evaluated in 180 SP patients.
Results: 24 of 180(13.3%) SP patients showed suicidal ideation or behavior. Suicidal patients were younger($t=3.912$, $p<0.001$) and more likely to have depressive disorder($x2=6.859$, $p=0.009$) as well as any other comorbid psychiatric disorder($x2=4.143$, $p=0.042$) than non-suicidal patients. Suicidal patients also scored higher in STAI-T($t=-2.776$, $p=0.006$) and BDI($t=-2.655$, $p=0.009$). However, after controlling interactions between variables by multivariate logistic regression analysis, only higher score in BDI($p=0.021$) was remained significantly associated with suicidality.
Conclusions: Suicidality of patients with SP is associated with current severity of depression and not with severity of SP itself nor any other clinical and psychometrical measures. These results suggest that thorough evaluation of current depressive symptoms is crucial to assess suicidal risk of SP patients.

P-30-018
Social factors in the prevention of suicidal attempts in Saudi Arabia

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Objectives: to find out the social factors that influence the prevention of rates of suicide attempts in saudi arabia.
Methods: This is a retrospective study of patients who attempted suicide and were admitted to General Hospital in the Industrial Eastern region of Saudi Arabia (2004-2005).
Results: In age distribution 35% were below 20 years and 28% were between 41-50 years and 17% were between 31-40 years. Percent distributions of marital status 53% were single and 47 % were married. As to the "state of mind" prior to the suicidal attempt, the majority was impulsive at 86% and only 14% were planned. Attempts were due to interpersonal relationship problems 34%, marital problems 17% and occupational problems 24%. The majority were referred for follow up to Psychiatric Outpatient Clinic (80%), 61% were referred to the Community Counseling Clinic for counseling and 3.8% were followed by their Family Physician. Age was found to be significantly related to a diagnosis of acute situational reaction. The female gender was significantly related to the same variables. Marital status, family problems, mental illness were found to be significantly related to age, gender, nationality and employment status,
Conclusions: there was a reduction of the parasuicide rate from 20.7 per 100,000 to 14 per 100,000. We claim that this reduction in rate may be related to improved psychiatric services. We have found that in addition to young females aged 20 there is a peak in females aged 40+. marital problems 17% and interpersonal relationship problems 34% The Provider has a program helping employees with stress called the Employee Assistance Program (EAP). We feel that increased public awareness in addition to improved medical and psychiatric services can make more significant effect.

P-30-019
Laboratorial findings in 300 fibromyalgia patients. A review

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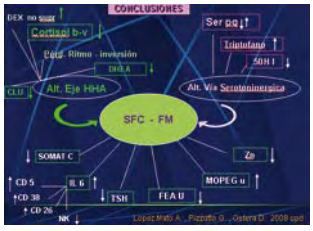
Objectives: to determine a shared pattern of biologycal alterations shown in more than 300 patients with fibromyalgia and related syndromes
Methods: The sites of the study are the Center for Family Medicine (CEMIF) and the Clinical Biochemical Institute at the city of Rosario and the Institute of Biological Psychiatry (ipbi) in Buenos Aires, Argentina in an interdisciplinary setting with psychiatrists, family doctors, psychologists, biochemistry specialists, statiscal engineer and medical residents intervening in the present work. 311 patients were screened for different biochemical alterations corresponding to clinical, rheumatologic, immune, endocrinological, neurological and psychiatrical entities. Patients with psychiatric, endocrinological, immunological or neurological pathologies were excluded.
Results: The clinical and biochemical results are presented in different posters and free communications, correlated and divided according to each form of presentation. Here we present a picture summary of the principal findings.
Conclusions: Fibromyalgia has plenty of biochemical alterations revealing dysfunction of the endocrine, immune and nervous but none is patgnomonic of the illness.



P-30-020
Malignant evolution of fibromyalgia. About one case

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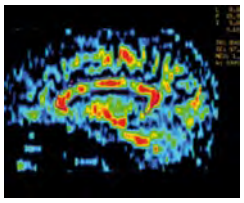
Objectives: To present a case of malignant evolution of a complicated fibromyalgia patient
Methods: One female patient of 60 years old is presented
Results: A history of traumatic life events including childhood sexual abuse, divorce, family violence, and loss of her sons by emigration, fire with partial destruction of her material belongings was detected. Her clinical records revealed hysterectomy, dyslipemia, hypothyroidism, allergies and frequent infections. She consulted different professionals between 1996 to 2000 complaining for insomnia, diarrhea, headaches, tremor, asthenia, erratic rheumatic and widespread pain,. She was medicated for depression and somatoform disorder and had received different psychotherapeutical treatments. As pain and other symptoms persist she receives a final diagnosis of fibromyalgia in 2002 and later produces diabetes. She now undergoes treatment with different drugs with partial response. On 2007 she is included in a complete diagnostic protocol (presented by us in different communications) and is studied with brain imaging. Abnormal brain involvement was shown via static and functional neuroimaging. Decreased blood flow within the thalamus and elements of the basal ganglia and hypothalamus, corpus callosum and trigonum was detected. Studies using single-voxel magnetic resonance spectroscopy showed reduced brain metabolite ratios with NMA and choline diminished and glutamine and glutamic metabolites increased. An inversion of creatine in white matter has been demonstrated. The insular cortex was particularly involved. The main difference with the normal age-related brain atrophy was the normality of morphology and functionality of the hypocampus in her case. Uncomplicated diabetes of 3 year evolution does not produce such abnormalities. In various tracthographies performed, myelinic association fibers destruction was clearly demonstrated.
Conclusions: Although considered a non neither complicated nor degenerative disease, fibromyalgia when overlooked can end in a sort of dementia with a very poor prognosis



P-30-021
Fibromyalgia and children abuse stress in circa 300 cases

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Objectives: to determine if patients with fibromyalgia were exposed to any kind of stress during their early life due to the fact that in a total population of more than 300 cases 90% occurred during childhood and adolescence
Methods: The sites of the study are the Center for Family Medicine (CEMIF) at the city of Rosario and the Institute of Biological Psychiatry (ipbi) at Buenos Aires, Argentina in an interdisciplinary setting with psychiatrists, family doctors, psychologists, biochemistry specialists, statiscal engineer and medical residents intervening in the present work 298 patients entered the study. Patients with DSM IV axis I psychiatric entities, endocrinology cal, immunological or neurological pathologies were excluded. Statistical Measure of position or trend, and ANOVA T distribution was performed
Results: Family violence was present in 92%, discriminated in: physic violence in 59% (mostly determined by mother aggression compared to father aggression) and parental divorce in 33%. Sexual abuse represents 47%, (ages 4 to 16 with a statically peak between 5 and 10 years old) Most sexual abuse does not imply coitus but is related to petting, licking and kissing of genitalia between siblings and parental figures.

Conclusions: Fibromyalgia patients as a group show a heavier history of child abuse than that published for other populations. This may be the first published work with so many cases of very early traumatic life events.

P-30-022
Eponyms from the Nazi era of relevance to biological and neuropsychiatry: Remember some, change some

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Objectives: Eponyms are titles of medical disorders linked to individuals who originally described the condition and serve a valuable role in remembering and identifying the disorder. While use of eponyms is widespread, often the change or discarding of such eponyms becomes important on ethical grounds. This would arise when research associated with the disorder and individual was carried out under such overt unethical conditions that it would be wrong to perpetuate and thus "reward" the memory of the individual after whom the disorder is named. Thus ethical considerations should be introduced into medical nosology just as they exist in patient care and research.
Methods: A search of all neuropyschiatric eponyms was made with those identified related to the Nazi era either as victims or perpetrators.
Results: Several eponyms exist of relevance to the biological and neuropsychiatry community named after individuals who lived and worked during the Nazi era. The names of several of these individuals are associated with explicit crimes of the medical community during the Nazi era. In addition, examples were identified of neuropsychiatric eponyms named after Nazi era victims, eponyms of those who protested such injustices and eponyms of those who had to flee prejudice and death.
Conclusions: Alternative medical nomenclature is suggested for the former conditions. In contrast, it is suggested that the latter eponyms should be remembered and even strengthened as opposed to the former group, which should be abolished. Since the greatest accolade a physician can earn from colleagues is the honor of an eponym entrenched in ones name, the medical profession in general and the neuropsychiatry field in particular should remove any respect given to physicians involved in or associated with crimes to humanity.

P-31
Other / Mental Health

P-31-001
Epidemiology

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P-31-002
Evolution of psichiatric emergencies

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Objectives: Over the past 25 years the system of centralised management of emergency psychiatry has disappeared and re-appeared. Since 2000 improvements have been made in the logistics, organisation and quality of emergency care. In the same period, however, there has been a horrendous increase in the number of patients attended in hospital emergencies during each year. Some authors hypothesise that this increase may be due partly to organisational changes in the psychiatric emergency services and partly to the introduction of a new mental health act and changes in society. This study aims to document the pattern of psychiatric emergencies in a psychiatric hospital during a year.
Methods: A cross-sectional study was made during 2008 with patients attended in the hospital emergency department during the year. Our study took place in Reus (Spain) in 2008 in the Institut Pere Mata. Demographic and clinical characteristics were obtained from the databases of the Hospital. The software used in analyses was v.16 SPSS.
Results: The main conclusion of our study is that there has been an important increase of the number of patients attended in the hospital emergencies department. This fact may lead us to a concern about a mental health emergency system which is not efficient enough to supply the needs of the population.
Conclusions: Recommendations for the future should be to adapt the emergency system to the needs of the patients and provide our service with a larger professional group. Thus, both patients and professionals would be able to get and give a better psychiatric attention.

P-31-003
Psychiatric consultation in a general hospital – Biological and clinical data: Prospective study

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Objectives: The aim of this study is to evaluate clinical, biological and treatment variables of a sample of patiens which were visited by a psychiatrist during their hospitalisation in a general hospital over a period of one year.
Methods: In a prospective way, data were collected from clinical interviews and further clinical reports.
Results: 33 patients (16 men, 17 women) were visited in one year period. Mean age 63,7 years, range from 25 to 84 years, Median 69 years, Sd 15,49. Main Psychiatric diagnoses (DSM-IV) were Depressive Disorder on 12 patients, Adaptative disorder on 5 patients, Anxiety Disorder on 4 patiens Psychotic Disorders on 3 patients. Other diagnoses on 3 patients (Delirium, Dementia and Alcohol Addiction). No diagnoses in Axis I in 1 patient. Cognitive deterioration was detected on 21,2% of patients. Previous psychiatric disorder in 60% of patients. Psychiatric hospitalisation was required in 2 cases. After hospitalisation 39,4% of patients continued psychiatric treatment. Antidepressant, Antipsychotic and Sedative Drugs were given in 69,7%, 15,2% and 66,7% of cases respectively.

Conclusions: People visited in psychiatric consultation regime were suffering mainly from anxiety and depressive symptoms in relationship with their medical situation and to their hospitalisation period. Age (50% are over 69 years old) and organic disorder were important to determine their mood and mental status as well as social stress factors- economic, work and familiar factors. The wide use of farmacology is probably due to the need to improve quality of life in patiens wich suffer from organic illness, some of them were not previously identified by general practitioner on a need of psychiatric treatment.

P-31-004
Mental Health Recovery: An illusive concept

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Objectives: There is an effort in the western world to present Mental Health Recovery as fact, even though as a concept is still unheard of in many parts of the world. Recovery is presented as a journey of healing and transformation for a person with mental health problems and as a complex personalized process. We tried to investigate the concept to real life conditions and implementation of mental health services to western world countries.
Methods: Thorough research of the main databases (Medline, Embase, Psychinfo), and web search engines such as Goggle, for relevant studies, agencies and organizations, interested in recovery issues.
Results: Although recovery appears a concept with a well defined justification and theoretical background it doesn't correspond to highly expected promising results in patients' everyday life. As a concept has great appeal to the mangers and health policy makers who are contacting tactics' exercises and cost benefit analyses, emphasizing at the numbers that prove their theoretical structures, without taking into consideration that mental health workers and service users discussed in low voice: Pharmacotherapy is non adequate for negative symptomatology, social isolation and stigma is evident, as lack of employment and need for increased number of inpatient beds and admission days. Recovery is elusive to mentally ill patients who are guided to the penal system in an increasing rate.
Conclusions: There is a swift in community psychiatry and short admissions of mentally ill and a constant flow of funds and support aiming at the recovery of mentally ill. But at the same time we should listen to the patients needs and find the balance between in and out patient care in a more personalized way doing practice the old and forgotten idea of treating individuals and not numbers, concepts or theories.

P-31-005
The non government organization in the process of psychiatric attention, the case of a hospital in Mexico City

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Graciela Lopez, Jose Luis Garcia Aguire

P-31-006
Translating biological parameters into clinically-useful diagnostic tests

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Objectives: Psychiatry has lagged behind other specialties in developing laboratory tests to confirm or rule out a diagnosis. However, biological research into the pathophysiology of psychiatric disorders has yielded a number of highly replicable abnormalities. These abnormalities have the potential for being developed into clinically-useful diagnostic tests. To achieve this goal, a process for systematic translation must be developed and implemented.
Methods: A four-step process is proposed and compared to currently existing processes for reporting diagnostic tests (STARD), evaluating evidence-based medicine (EBM) and developing guidelines (AGREE).
Results: The first step is the biological test is repeatedly observed to differ between a narrowly-defined patient group and healthy controls using masked procedures. The results are then independently replicated. The second step examines the initial clinical usefulness of the finding for a range of patients whose management might benefit from the test. The third step is to establish the performance criteria of the test for the target population using realistic patients. The fourth step is to establish its utility, including cost effectiveness and patient outcomes, in at least one multicenter clinical trial. These steps are further expanded based upon reporting requirements and principles of EBM and guideline developments.
Conclusions: Biological parameters currently face challenges in their pathways to becoming diagnostic tests due to the premature release of tests and premature abandonment of tests. Attention to a systematic translation process aided by principles of EBM and guideline developments may help avoid these problems.

P-31-007
Mental healt primary attention model experence

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Objectives: To make public the characteristics and results of a mental health primary care pilot study applied in the State of Mexico community. Although mental disorders are among the diseases that cause more disabilities among the population, this area of medical care does not receive enough financial resources. In addition, in the last few years their frequency has increased so much that the World Health Organization estimates that in 2010 there will be around 176 million people suffering from some neuropsychiatric disorder. Likewise, despite global morbidity, mental health does not receive the attention it deserves.
Methods: A mental health primary care team was formed. This included a psychiatrist, a general medical practitioner, a social worker and an assistant nurse. A community close to the hospital was selected and the needs of both the health personnel and community were assessed through direct interviews and conferences on mental health.
Results: The training of the DIF (Whole Family Development) personnel was reflected in a higher sensibility to deal with patients that looked for medical care. Communitary talks lead to integrate workshops and specific psycho-educative groups if also helped to refer persons who presented a mental disorder to a psychiatric hospital.
Conclusions: This pilot study revealed the need of a mental health primary care program in communitarian health centers and general hospitals. Likewise, it prove that is highly important to form mental health teams interested in getting involved with the community without them feeling any pressure to assume such a task. Since this program has showed its efficacy, its implementation in other centers is suggested.

P-31-008
The coercive measures in psychiatric emergency service. Differences on different diagnoses

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Objectives: The aim of this study is to analyse factors and diagnose which can have influence on applying of physical restraint in mentally disordered patients in PES. Description of specific circumstances in which physical restraint is used can help in the optimisation of psychiatric treatment.
Methods: We evaluated a total of 11578 consecutive patients seen over a 5-year period, from January 2001 to January 2006, at the PES of a university general hospital in the city of Barcelona. We prospectively studied all admissions following a routine computerised protocol that comprised socio-demographic, clinical and interventional data (including the use of physical restraint). The severity of illness was assessed by the Spanish version of the Severity of Psychiatric Illness (SPI) scale. For this study we play special attention to suicide risk, danger to others and severity of symptoms items. Data were analysed using the SPSS 14.0 version

Results: The preliminary results show 843 (7,3%) patients who required the use of coercive measures. 39,7% of them will be psychotics, 17% drug consumers, 16.8% affective disorder and personality disorders 10%.

P-31-009
Therapeutic adherence clinic: An alternative to make psychiatric treatment efficient

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Carlos Castañeda

P-31-010
Psychiatry illness and medical comorbidity, do they really prolong the length of stay?

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Objectives: Several studies have doccumented high rates of comorbid medical disease in psychiatryc illness. medical comorbidity has measurable effects on the psychopathological outcomes of psychiatric inpatients, and may increase the lenght of stay. 1.To describe the impact of medical comorbidity on psychiatric patients 2.To demonstrate that medical (non psychiatric)comorbidity will be associated with a longer stay in our psychiatry inpatient unit
Methods: N=640 patients. We retrospectively examined patients' features over a 11 month period (Jan to Nov 2008). Independent variables(demog features, psychiatry diagnosis and treatment, consultation with medical departments). Comparison with the dependent-respond feature:days of stay of discharged patients.Multiple lineal regression. SPSS 13.0
Results: 64%males; Schizophrenia42%; High prevalence pf dual pathology with substance abuse disorder(73%).39% of inpatients had comorbidity with nonpsychiatric diagnosis, most prevalence consultation: internal medicine(72%). The aim of this study is confirmed by regression analysis, and it explains eight more days of lenght of stay for the equation (R2=0,69; p=0,003). OR=2.4 for comorbidity. No significant differences for sex, medication and psychiatry diagnosis.These results confirm the hypothesis we suggested before.
Conclusions: Patients with psychiatry disorders who have significant medical illness generate more costs due to increase in lenght of stay and other factors. Regarding to our results, the development of a medicine and psychiatry inpatient unit (as Roger Kathol described) should be taken into account in our country for better treatment and management of these patients.

P-31-011
Hospital re-admission of patients with mental and behavioral disorders in Mexico

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Objectives: As a part of the internal supervision program the studied hospital implements the monitoring of the user's re-admission to generate specific methodologies to attend resistant psychotic clinical cases or social networks that help to keep the disorders controlled through ambulatory services.
Methods: A sample of 3,600 subjects was analyzed during 2007; diagnosis, age, civil state, occupation and education were included to analyze the data as influential variables in the evolution of the psychopathology.
Results: The total of discharges was divided in 3 groups: male, female and geriatric patients. In the first and second groups, 76% was hospitalized once, the rest was hospitalized more than once and only .07% needed to be hospitalized more than 4 times. In case of the geriatric patients there wasn't any meaningful difference, and those who needed more than 4 hospitalizations were reduced to .05% the dominant pathology in the re-hospitalization was paranoid schizophrenia, the civil state unmarried, the status unemployed, and education didn't show any statistic difference.
Conclusions: Re-hospitalization is limited statistically to the timing of the disorder, and not to inappropriate treatment, therefore it can be suspected that the adverse social context leads to lack of attention to the psychopathology and to continuous hospitalization.

P-31-012
Rapid tranquillisation practice in Zambia: A survey

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Objectives: To survey rapid tranquillisation practices in the psychiatric emergency department at Chainama Hills College Hospital, Lusaka, Zambia.
Methods: The survey was carried for five consecutive weeks between June and July 2008. The survey questionnaire was developed in collaboration with local clinicians, approval was sought from the local drugs and therapeutic committee and data was gathered by trainee clinical officers and medical students who were not involved in decision making. All patients requiring rapid tranquillisation as decided by the treating clinician were included in the survey.
Results: 105 patients needed rapid tranquillisation. No patient was lost to follow up. 68% of patients were male with a mean age of 32 years. Treating clinicians rated agitation as being mild in 53%, moderate in 30% and severe in 16%. Various combinations of medications were used as outlined in figure 1. The commonest provisional diagnosis was non-affective psychosis (37%), followed by substance misuse (25%). 27% of patients were brought in under restraint, of which 61% of the time they required retraining to administer medications. 20% of patients receiving rapid tranquillisation received a second dose to calm them down.
Conclusions: Surveys of rapid tranquillisation practices are difficult to conduct and more so in developing countries where resources are stretched and record keeping is poor. Multiple medications were used often in high doses and there were huge variations in clinical practice as has been in other parts of the world. Evidence base for recommending interventions are thin. This remains an under-researched area and in much need for further evaluative studies tailored to local needs. Pragmatic randomised trials of rapid tranquillisation interventions have been done recently in resource poor settings in Brazil and India, why not in Zambia or for that matter developed countries such as UK or France? Let the evidence river flow two ways!

P-31-013
Common mental disorders among immigrants in Santigo de Chile

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Objectives: In the last century, Chile has received immigrants coming mainly from Europe, Asia and Africa but currently immigrants come mostly from other Latin American countries. In Santiago, the County of Independencia, located north from the downtown, has the largest immigrants population. The objective of this study is to determine the prevalence of Common Mental Disorders (CMD) among immigrants who consult in the primary care clinic in the County of Independencia and its potential related factors.
Methods: A cross sectional study was carried out in a primary health care clinic located in Independencia. The sampling frame used was the register of immigrant patients aged 15-64 years(1030 immigrants). During November 2007, 282 immigrants aged 15 to 64 were contacted in the waiting room of the primary health care center. They were asked to answer, after signing an informed consent, a detailed structured questionnaire. The CIS-R was used to measure common mental disorders

Results: 282 persons (78.7% women and 21.3% men) were interviewed. They were young people with an average age of 30 years. Most of them came from Peru. The prevalence of CMD was 14.2% (women 17.1 (12.4-22.7) / men 3.3 (0.4-11.5)). The most common symptoms were fatigue (13.8%); depressive ideas (11.4%); concerns (11%), depression (10.3%) and irritability (10.3%). CMD were significantly associated with female gender, age 55 or more, living in a several dysfunctional family and have experienced a drop of their income in the last year. The prevalence of common mental disorders among immigrant population surveyed (14,2%) is lower than that described for non-immigrants who attended primary care centers (50%)
Conclusions: The results of this study are consistent with the international literature that informed lower prevalence rates of CMD among immigrants populations compared to people born in the host country

P-31-014
Immigration in Chile: Mental health problems. A comparison between immigrants and local population

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Objectives: People came to Chile, mostly, for increasing their salaries. The majority are Peruvian. Women work as housekeepers and men as laborer. They live in poor conditions, they have poor education and social support. In this study, we describe immigrants coming from Peru, Ecuador and Venezuela.The purpose of this study is to describe mental health problems (and risk/protective factors) suffered by immigrants in Santiago of Chile and compare them with similar studies on local population.
Methods: During November 2007, 282 immigrants aged 15 to 64 were contacted in a primary health care center in the most popular zone for immigrants in Santiago (Independencia). They were asked to answer a detailed structured questionnaire and we applied sociodemographic (Holemes and Rahe, Sarason, APGAR, etc), quality of life (EQ-5D), and mental health (MINI, CIS-R, GHQ-12) scales.
Results: 282 persons (78.7% women and 21.3% men) were interviewed. The prevalence of mental health disorders was 14.2% (women 17.1 (12.4-22.7) / men 3.3 (0.4-11.5)). The most common diagnosis were affective and anxiety disorders (6,7%) The prevalence of mental disorders among immigrant population surveyed (14,2%) is lower than that described for non-immigrants who attended primary care centers (50%). This finding is consistent with similar published studies. Nonetheless, in children (second generation) prevalence and distribution of mental disorders is similar between immigrants and local population. Risk factors related with presence of mental health diseases are: Family disintegration, provisional residential status, overcrowding, hardworking, integration difficulties, and the absence of health insurance.
Conclusions: On future studies, it will be interesting, to compare these kind of immigration (Latin American to Latin American country) to the phenomena occurring in Europe, in order to discuss of the influence of sociological factors on the epidemiology and treatment of mental health disorders.

P-31-015
Physical illness and common mental disorders in primary care

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Objectives: Psychiatric disorder has emerged as an important source of comorbidity in medical and somatizing patients in primary care. Many psychiatric patients are not accurately diagnosed at the primary care level or do not receive treatments in accordance with standardized guides or protocols. Comorbidity may be the result of an overlap of symptoms, a simultaneous presentation of disorders or an artefact amplified by the diagnostic systems. The objective is to estimate the comorbidity of the most common mental disorders with medical diseases in primary care practice in Spain.
Methods: A systematic sample of 7940 adult primary care patients was recruited by 1925 general practitioners in a large cross-sectional national epidemiological study in Spain. The PRIME-MD was used to diagnose psychiatric disorders.
Results: 53.6% of the sample presented one or more mental disorder, and 30.3% of the patients had more than one current mental disorder The most prevalent were affective (35.8%), anxiety (25.6%), and somatoform (28.8%) disorders. 59.4% of the sample presented one or more medical disease. The most prevalent were musculoskeletal (27.2%), vascular (18.4%) and gastrointestinal (16.7%). Prevalence of any mental disorder was higher among patients presenting liver (75.7%), neoplastic (68.0%), gastrointestinal (67.2%), metabolic (58.2%), respiratory (57.9%) and musculoskeletal (57.8%) diseases, respectively (Chi-Square test, $p<0.05$).
Conclusions: The study provides further evidence of the high comorbidity of mental disorders with medical diseases in primary care. Prevalence of mental disorders was particularly high among patients with liver, neoplastic, gastrointestinal, metabolic, respiratory and musculoskeletal diseases.

P-31-016
Contemporary ethics and informed consent in psychiatric research: seeking the truth or attempting to override it?

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Objectives: Over the last three decades the principle of respect of mentally ill individuals has become central to the debate on the ethics of psychiatric research. Informed Consent (IC) procedures represent one of the most salient ethical practices and is considered to be fundamental in the effort to develop safeguard practices of investigators. The aim of this study is the critical review of the Informed Consent concept.
Methods: This paper critically reviews the concept of informed consent as this is perceived by a large part of the research community.
Results: Modern multicultural societies are marked by a wide variety of beliefs and moral priorities. The embarrassment that rises during the attempt of the state to establish regulatory principles of a catholic authority has been recorded in numerous occasions in the past. Given this difficulty to establish the legislative provisions with a binding character, IC could serve as an acceptable solution. In this way, it is easy to override the attempt to seek a holistically recognizable and acceptable truth and the burden falls on the side arrangements and agreements between the parties involved. The question is no longer the truth itself but the detailed description of procedures and conditions that are considered necessary for the acquisition of consent for participation to a research. The aim is to create arrangements and not to reveal a satisfactory moral truth.
Conclusions: Although Psychiatry and Philosophy have for centuries been two different entities, the interests of the two sciences have never stopped overlapping. Bioethics and ethical dilemmas arising from the research that concerns psychiatric patients brought back into the limelight the need for cooperation and collaboration. IC could easily accept the criticism that it mainly facilitates the continuance of research without taking into account the morally correct – considering that such a thing does not exist – and it relegates ethics into a procedure promoting the technical rather than the human character of Psychiatry.

P-31-017
Emergency psychiatry

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Objectives: Through this presentation the different kinds of disorders that are treated in the psychiatric emergency are explained, they are: psycho-mobile disorder state, deep depression, suicide attempts, anxiety disorder, consumption of drugs and psychotropic substances, personality disorders, among others.

Methods: At the psychiatric emergency room the actions must be realized as quick as possible, realizing differential diagnosis that allow the rational took of decisions that include: the hospitalization in a psychiatric hospital, the reference to another specialized hospital, reference to extern consult or to the house. The take of those decisions is determined by the diagnosed pathology. Because many of the causes of a psycho-mobile excitement state or deep behavior disorder might be medical diseases, not psychiatric ones, (metabolic, traumatizing, infectious, or other kind of diseases) the patient must be referred to a specialized hospital where they can get the attention they need.
Results: In our country, Honduras, there are only two psychiatric hospitals, one located at the capital and the other one at Amarateca, 45 minutes away from the capital. Psychiatric spots are not included into general or specialized hospitals. Some hospitals offer the service of external psychiatric consult, but not hospitalization. To be noticed that even though the hondurian population has grown, both psychiatric hospitals remain with the initial amount of beds and the same infrastructure.
Conclusions: Even though the psychiatric medical diseases have a chronic course and they're not direct cause of mortality, except in the case of suicide where an opportune intervention might save a life, they limit the patient's functionality and carry suffering.

P-31-018
Strategies for the renewal of significance of psychiatric attention in Mexico

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Carlos Castañeda

P-31-019
Attitudes to psychiatric services and compliance in migrant families

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The Outpatient Clinic of Transcultural Psychiatry and Migration Induced Psychiatric Disorders in Childhood and Adolescence at the Department of Child and Adolescent Psychiatry, Medical University Vienna, Austria, was implemented in 1996 to emphasize treatment of children and adolescents from various countries with different experiences related to migration and flight.
This presentation will report the results of a survey with families from Turkey and former Yugoslavia, such as psychiatric disorders, the way of referral, help seeking behaviours, attitudes to psychiatric services and compliance in these migrant groups.

P-31-020
Essential fatty acids in inflammatory and immune response in psychiatric diseases

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Buenos Aires, Argentina
Aaron Epelbaum

Objectives: +We point out that inflammatory and psychoneuroimmunological processes are involved in major psychiatric diseases. The objective is to reduce chronic inflammatory and immune processes with omega 3 fatty acids that reduce the proinflammatory cytokines and eicosanoids which are responsible for inflammation and pain,since current therapies with anti inflammatory drugs have many side effects.
Methods: We did a double blind placebo controlled trial in patients with major depression with omega 3 fatty acids, with a group of patients with Chia oil ,and another with fish oil. Dose 2.5 g per day during 3 months. We evaluated depression scores and ratio TG/HDL as an indicator of inflammation.
Results: At the end of the trial the patients treated with omega 3 fatty acids showed a lowering of the ratio TG/HDL and at least a 50% reduction in depression scores compared with the placebo group with a stabilization of mood, remission of symptoms,with good tolerance.
Conclusions: We consider useful the implementation of omega 3 fatty acids ,to modulate the inflammatory and immune response in patients with depression and in other psychiatric disorders as adjuvants to standard psychiatric treatments and because of its multiple beneficial effects.

P-31-021
Influence of insulin and altered carbohydrate metabolism in psychiatric disorders

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Objectives: There is clinical evidence that metabolic abnormalities such as functional hypoglycemia, hyperinsulinism, resistance to insulin, metabolic syndrome, diabetes, that (all these) conditions can complicate latent predisposition, be associated or give rise to psychiatric disorders. The objective is to restore (altered metabolism) and to obtain a balance between insulin-glucagon and of (eicosanoids) with an adequate diet and nutritional supplements.
Methods: In psychiatric patients with metabolic syndrome due to the medication with atypical antipsychotics, we prescribed a diet with restriction of calories, refined sugar and (carbohydrates) with high glycemic index.(We indicated)an adequate proportion of carbohydrates-proteins in the diet in each meal, which control insulin, glucagon and blood glucose,and (eicosanoids). Also with mono and unsaturated fatty acids with the implementation of oligoelements and antioxidants. We measured the parameters that were abnormal in metabolic syndrome and also the ratio of TGL/HDL, which is also a substitute marker of the levels of inflammation and insulin.
Results: We found in (psychiatric) patients with metabolic syndrome a significant reduction of body weight and (lean) body mass index, in the measures of blood pressure, waist circumference, fasting blood glucose, in the ratio of TGL/HDL ,with an improvement (in the symptoms and in general nutrition).
Conclusions: We suggest (the) control of metabolic abnormalities, with the implementation of an adequate diet that regulates glucose in blood, insulin, glucagon and (eicosanoids) ,to prevent the risk of developing(functional hypoglycemia, hyperinsulinism, insulin resistance, metabolic syndrome) obesity, diabetes, cardio-cerebro vascular and psychiatric diseases.

P-40
Other / Pain / Stress

P-40-001
Stress-phase orientated conception of stress-related and neurotic disorders

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Objectives: To provide a theoretical conception of the mechanisms of the development of stress-related and neurotic disorders (stressogenesis).
Methods: It was carried out a clinical-psychopathological investigation of large sample of patients (F4), diagnosed according to ICD-10, who were affected by severe psychogenic factors and distressing situations, such as reminiscences of war, earthquake, painful losses, personal failures, family difficulties, poverty and social unprotectness. Using specially designed questionnaires the psychological states of the mentioned patients have assessed.
Results: There were differentiated the variants of memorization of traumatic event and observe the dynamics of the state of psychic traumatization and further development of post-stress disorders. It was discussed the main difference between "psychic trauma" and the "state of psychic traumatization". The general adaptation syndrome is differing on the level of organism and on the level of conscious person - the adaptative strategy of the phases (anxiety, strain and asthenization), performing as parts of a indivisible stress process on the level of organism, acquired the possibility to be launched independently each other, becoming independent mechanisms, engaging during any psychoemotional stress or even thoughts about them.

All the phases of the general adaptation syndrome became autonomic during the evolution, developing parallel to consciousness. The new quality set up new adaptative variants, retaining the main psycho-biological mechanisms: neurobiological – the anxiety phase (anxious, phobic, dissociative disorders), neuroendocrinological – the strain phase (somatoform, psychosomatic disorders or "strain deseases") and the asthenization phase (syndrome of tiredness and fatigue).
Conclusions: General adaptation syndrome had undergone to a evolutionary transformation in the form of autonomy of its each constituent phase.

P-40-002
Psychiatric treatment in neuropathic pain

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Objectives: Neuropathic pain is a chronic pain syndrome caused by drug, disease, or injury, induced damage or destruction of sensory neurons within the dorsal root ganglia of the peripheral nervous system. Treatment remains unsatisfactory despite a substantial increase in the number of trials. Anticonvulsants and antidepressants have demonstrated efficacy in improving neuropathic pain, but, the use of atypical antipsychotic in treatment of neuropathic pain is not well study. The purpose of the study was to evaluate the efficacy of atypical antipsychotic in different association of drugs, in this disease.
Methods: 15 patients, aged 43-55 years, diagnosis with neuropathic pain were divided in 2 groups: A - 7 patients received antidepressant with anticonvulsant (carbamazepine 400-600 mg/day), B - 8 patients received risperidone (4-6 mg/day) associated with the same medication used in group A. It was used Clinical Global Impression (CGI), Global Assessment of Functioning (GAF), Brief Pain Inventory (BPI). Period of study 6 month with visit at every 2 weeks in first month and monthly after that.
Results: Severity of illnesses and score on GAF were slowly improvement in group A in compare with group B. After 1 month of treatment, absolute mean (%) value of score improvement on CGI- S was 11. 76% for group A and 16.66 % for group B. For GAF, this value after 1 month of treatment, was higher with 7 in group B, in compare with group A. "Worst pain" or the mean of the 4 severity items, used as a measure of pain severity on BPI, were more improved in group B after one month but also at the endpoint.
Conclusions: The rapidity of improvement of scores on CGI, BPI and GAF in group B, in compare with group A, suggested a superiority of results at endpoint, if we use this combination of drugs.

P-40-003
The effects of prenatal morphine exposure on pain response

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P-40-004
Is fibromyalgia an overlapping of rheumatic, immunological and psychiatric entities? A clinical setting work with 400 patients

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Objectives: To determine if fibromyalgia (FM) is a real and unique entity or the sum of different entities belonging to different medical specialties
Methods: The sites of the study are the Center for Family Medicine (CEMIF) and the Clinical Biochemical Institute at the city of Rosario and the Institute of Biological Psychiatry (ipbi) in Buenos Aires, Argentina in an interdisciplinary setting with psychiatrists, family doctors, psychologists, biochemistry specialists, statiscal engineer and medical residents intervening in the present work. Epidemiology study comprised of 400 patients with fibromyalgia or related syndromes. Subjective reports were obtained after two or more directed interviews. Patients with DSM IV axis 1 psychiatric, endocrinological, immunological or neurological pathologies were excluded
Results: Patients reported that the most frequent factors perceived to worsen FM symptoms were emotional distress (90%), sleeping problems (88%), stressful activity (70%), psychosocial stressors (68%), and physical injuries (50%). Other factors included infections, allergies, lack of emotional support, perfectionism, side effects of medications, and chemical exposures. It is published that fibromyalgia may result from stress-induced changes in the response and adaptation to stress. Physical symptoms presented were chronic pain resembling rheumatoid diseases (80%) depressive or anxious symptomatology (89%), primary sleep disturbances 878%) and burst and wanning and waxing of signs as in immune diseases (50%) All refered many years of misdiagnosis by different physicians and disbelief by their family relatives and employers
Conclusions: Fibromyalgia configures a new clear disease presenting ubicuos symptoms which belong to many medical specialties and whose treatment is always interdisciplinary. Its clinical presentation includes rheumatological, immunological and psychiatric symptoms but also reveals an psychosocial disturbance in the way one is perceived by the milieu

P-40-005
Relationship between neuroendocrine and immunological abnormalities in 20 chronic fatigue syndrome female patients

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Objectives: To determine if there is any special relationship between neuroendocrine and immunological alterations demonstrated in chronic fatigue syndrome (CFS) patients
Methods: The site of the study is the Institute of Biological Psychiatry (ipbi) in Buenos Aires, Argentina in an interdisciplinary setting with psychiatrists, family doctors, psychologists, biochemistry specialists, statiscal engineer and medical residents intervening in the present work 20 female patients were selected, diagnosed under American College of Rheumatology criteria for CFS. Patients with psychiatric, endocrinological, immunological or neurological pathologies were excluded. No drug with immune, endocrinological or Central Nervous System action was authorized since one month prior to testing. Statistical Measure of position or trend, and ANOVA T distribution was performed. All patients underwent tests for plasmatic and urinary cortisol determinations under standard biochemical tests. They also underwent measures for basal TSH and anti-peroxidase antibodies, and also immunological markers like CD2, CD3, CD4, CD5, CD8, and CD16-56.
Results: Cortisol was high in 2 patients, low in 12 patients and within normal levels in 6 patients. Hemogram is normal in 14 patients and abnormal (with lymphocytosis) in 6 patients. On the contrary 10 patients showing altered cortisol did not present lymphocytosis and only 4 did show it. Immunological results showed that CD 5 and CD 16-56 were elevated and decreased respectively. Other immunological markers do not show significant alterations. In whole, alterations of cortisol and CD markers have been detected in 12 patients.
Conclusions: Of all chronic illnesses, CFS is one of the most intriguing. Dysfunction in the immune system has been proposed as a cause. Hypo or hyperactivity of Hypotalamus-Pituitary-Adrenal axis may be attributed to cortisol alterations shown in 70%. The immunologic alteration seems to be some way connected with psychiatric diseases and highly connected with neuroendocrine distortions. CFS is a Psycho-neuro-immune-endocrinological (PNIE) disease.

P-40-006
Salivary cortisol responses of patients with migraine in a psychosocial stress test

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Claudia Sommer

Objectives: Psychosocial stress is a major trigger factor of migraine attacks. In our study we investigate the salivary cortisol levels of patients with chronic and episodic migraine (CM, EM) before and after psychosocial stress.
Methods: To date n=11 patients with CM and n=10 patients with EM were tested interictally. Patients were diagnosed according to the IHS (International Headache Society) criteria. The mean number of monthly headache days was 17 in the CM and 5 in the EM. The stress test consists of a 20 minute speech and a mental arithmetic task under social evaluation. Saliva samples for cortisol measurements were collected at baseline and 15, 35 and 55 minutes after stress exposition. Cortisol levels were determined using a commercial enzyme immunoassay kit.
Results: Mean baseline cortisol levels did not differ between groups (mean = 6.67 nmol/l, SD = 3.37 nmol/l). Regarding the entire group of patients, only four patients (20%) had a cortisol response to the stress test. In these patients cortisol levels were still elevated after one hour. The EM group contained one responder (10%), whereas the CM group contained three responders (27%).
Conclusions: In the stress test salivary cortisol levels increased only in few patients, who were mostly patients with CM. The majority of patients with CM und EM turned out to be non-responders, which could be due to a generally blunted cortisol response of patients with migraine. Our findings are in accordance with previous data and may contribute to elucidate the pathophysiology of migraine. Altered interactions in neuroendocrine immune circuits with reduced hypothalamic-pituitary-adrenal axis activity may contribute to the known increased inflammatory responses in migraine patients.

P-40-007
Atypical facial pain

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Objectives: We report a longitudinal study of 20 patients with medically intractable atypical facial pain who were treated with tricyclic antidepressant and typical antipsychotic, and had a comprehensive follow-up for a mean 4 years.
Methods: Thirteen patients (65%) had improvement, another three (15%) showed mild improvement, and the remaining 4 patients (20%) showed either no change. Significant predictors of improvement were identified.
Results: Good prognostic indicators for successful treatment included: pain following and adverse life event, minimal previous surgical intervention, and freedom from pain after 9 weeks treatment.
Conclusions: This study suggests an association between facial pain without physical signs and atypical depression (with intensive fatigue, tension and sleep disorder superimposed upon-F60.5 anankastic personality disorder). Females = 14 patients = 70%. Males = 6 patients = 30%).

P-40-008
Does fibromyalgia syndrome exist?

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Gerson Ballester

Objectives: The symptoms of fibromyalgia are not specifically for the syndrome.
Methods: Between 2005 and 2008, 154 patients, who met diagnostic criteria for fibromyalgia, were referred to psychiatric assessment, when all current methods of treatments have been proved unsuccessful.
Results: We found a group of 76 patients that met ICD-10 diagnostic criteria for generalized anxiety, insomnia, anxiety and affect pain; 3 patients met ICD-10 diagnostic criteria for factitious disorder with predominantly physical signs and symptoms and severe personality disorder undergo to individual psychotherapy (psychotherapy is not curative but helps preventing further iatrogenic complications and high medicine utilization); 53 patients met ICD-10 diagnostic criteria for mixed anxiety and depressive disorder improved their pain when treated with imipramine and periciazine.
Conclusions: Fibromyalgia syndrome exists but nowadays is over diagnosed. In our sample 132 patients (85.71%) from 154 patients were misdiagnosed.

P-40-009
The sensitization of the acoustic startle response persists for a long-term after chronic variable stress

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Objectives: The acoustic startle response (ASR) is a model in the behavioral neurosciences for the study of anxiety and fear in rats. The ASR can be augmented by stress such as footshocks. This enhancement of ASR is regulated by the corticotropin releasing hormone (CRH) neurons in the central nucleus of amygdala. We have previously reported that the basal level of CRH immunoreactivity in the central nucleus of amygdala and the paraventricular nucleus are decreased after chronic variable stress (CVS) whereas CRH immunoreactive response is augmented by footshocks, corresponding to the sensitization of the ASR to footshocks after CVS. In the present study, we investigate whether the sensitization of the ASR to footshocks after CVS follows for a long time.
Methods: Male Wistar rats were used. Rats were treated with CVS for 13 days. The ASR was measured 1 day or 8 days after the last stress of CVS. All rats were placed in the startle test cages and after a 5 minutes adaptation period were presented with 120 startle stimuli. The startle amplitude was defined as the maximum accelerometer voltage that occurred during the first 200 ms after the startle stimulus was delivered. We performed all experiments based on guideline of St. Marianna University School of Medicine Center Experimental Animal Management Commission.
Results: There was no significant difference among these groups in the baseline. The enhancement of ASR to footshocks in CVS rats was augmented compared with control group. In the group of footshocks at 8 days after CVS, the enhancement of ASR was augmented as same as the group of footshocks at 1 day after CVS.
Conclusions: In summary, our present study strongly suggests that CVS produced a long-term sensitization of CRH response to footshocks.

P-40-010
Association of activity of antioxidative enzymes with level of thyroid hormones in patients with neurotic disorders

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Objectives: We have studied interrelationship of level of thyroid hormones and activity of antioxidative enzymes in patients with neurotic disorders.
Methods: Patients with neurotic disorders under treatment at Mental Health Research Institute and healthy people were examined. We have studied activity of antioxidative enzymes and level of thyroid hormones in peripheral blood. Results were processed using non-parametrical U criterion and correlation analysis with count of Spearmen's coefficient.

Results: It has been shown that in blood in healthy people level of triiodothyronine (T3) was 1,34±0,21 nmol/l, thyroxine (T4),- 17,64±1,60 pcmol/l. In persons with neurotic disorders we have detected increase of content of Ò3 up to 1,71±0,11 nmol/l;, T 4 up to 23,68±0,23. The decrease of activity glutationreductase by 1,5 times, glutationtransferase by 3,8 times and glucose-6-phosphatdehydrogenase by 3,6 times was shown for patients with neurotic diseases. The increase of activity was shown for catalase by 2,7 times and glutationperoxidase by 1,8 times as compared with control group. In patients with neurotic disorders we have revealed strong positive correlation association between of activity of catalase and content of thyroxin (R = 0,99) and negative correlation association between of activity of glutationtransferase and level of content of thyroxin (R = 0,43). There is no such interrelation in group of control.
Conclusions: These data suggest interrelationship of level of thyroid hormones with activity of antioxidative enzymes. It is known that emotional stress increases level of thyroxin in blood. Thyroxin increase content of frequency of respiration and pulse and consequently content of oxygen. This effect increases ROS in blood. Probably, this stress-induction of thyroxin triggers mechanism of oxidative stress at cellular level.

P-40-011
Effects of long-term increase of oxytocin levels on anxiety – like behavior and selected stress systems

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Objectives: Oxytocin is a neuropeptide, which is produced in the hypothalamus and secreted from the posterior pituitary in response to various stress stimuli. There is some evidence that peripheral oxytocin may exert certain central effects. We have tested possible central effects of prolong increase in plasma oxytocin as well as its action on selected cardiovascular functions.
Methods: Rats were implanted subcutaneously with osmotic minipumps and treated with oxytocin or vehicle for two weeks. Elevated plus-maze test was used for measurement of anxiety-like behavior. To investigate whether the hypertrophy of the heart was associated with cardiomyogenesis, we have evaluated the incorporation of 5-bromo-2-deoxyuridine (BrdU), an indicator of proliferation into DNA. We have investigated mean blood pressure (BP) response to pressor drugs phenylephrine and angiotensin II in animals bearing chronic catheters in the jugular vein and the tail artery. The data were analysed by one- or two-way analysis of variance, as appropriate.
Results: Oxytocin treatment resulted in a significant increase in plasma oxytocin. Long-term increase in circulating oxytocin was not associated with changes in the frequency and time spent in the open arms in the elevated plus maze test. Plasma concentrations of corticosterone and ACTH increased in response to oxytocin treatment. Oxytocin-treated animals exhibited higher relative adrenal weights and enlarged hearts. The incorporation of BrdU failed to be modified by the treatment with oxytocin. The rise in BP is an important part of the stress response. In rats treated with oxytocin, a reduced BP response to phenylephrine was observed.
Conclusions: The present results show that anxiety-like behaviour is not significantly modified by chronic increase in circulating oxytocin but the effects of oxytocin on stress hormone release and on the BP may play a role in the development of stress-related disorders. The presented studies were supported by grants of APVV (LPP-0194-06) and Vega 0098.

P-40-012
Exhaustive screening of acute psychological stress-responsive cytokines in healthy university students

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Objectives: Acute psychological stress stimulates neuroendocrine and immune responses. Stress-induced proinflammatory cytokines have been suggested to play a crucial role in the complex stress response. In this study, using multiple-suspension array system, we succeeded to confirm the significant changes of serum cytokines during psychological stress without any extra stimulation.
Methods: We recruited 20 male and 6 female freshmen (19.7 ± 3.1 years) in medical school who faced to their first regular 5 days-examination. Saliva and serum samples were collected for measurements of cortisol and/or cytokines 7 days before, the first day of, and 2 days after the examination. Normal range of each serum cytokine was determined from another 204 healthy students. The collections were always performed between 4:00 PM to 5:00 PM. Anxiety was also assessed every time by State-Trait Anxiety Inventory. Parent rearing attitudes were assessed by parental bonding instruments. Serum levels of 50 different cytokines were determined using the multiple-suspension array system (Bio-Plex). Repeated measures ANOVA were used for statistical analyses of time differences. Relationships between two different parameters were analyzed by Pearson or Spearman correlation coefficients. $P < 0.05$ was considered as significant.
Results: Among 50 cytokines, the levels of MIF, MCP-3, and ΔNGF were significantly increased in association with increases in anxiety and salivary cortisol concentration on the first day of examination compared to 2 days after. In contrast, serum IL-16 level was inversely regulated. All 26 subjects showed changes of these 4 cytokines within normal ranges except for one person. Interestingly, parental rearing significantly modified ΔNGF secretion in response to the examination: students recognizing their father's rearing attitudes as overprotective significantly displayed higher ΔNGF response.
Conclusions: We identified 4 cytokines as psychological stress-responsive cytokines. These cytokines may be useful markers for assessment of psychosocial stress responses.

P-40-013
Is Chronic Fatigue Syndrome a postviral disease? Quantification of antibodies and cytokines in Chronic Fatigue Syndrome

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Andrea Lopez Mato

Objectives: To determine if Chronic Fatigue Syndrome (CFS) can be reconceptualised as a variance of post viral diseases.
Methods: The sites of the study are the Institute of Biological Psychiatry (ipbi) sited in Buenos Aires and the Center for Family Medicine (CEMIF) and the Clinical Biochemical Institute at the city of Rosario, Argentina in an interdisciplinary setting with psychiatrists, family doctors, psychologists, biochemistry specialists, statiscal engineer and medical residents intervening in the present work 20 female patients were selected, diagnosed under American College of Rheumatology criteria for CFS. Patients with psychiatric, endocrinological, immunological or neurological pathologies were excluded. No drug with immune, endocrinological or Central Nervous System action was authorized since one month prior to testing Acute (IGM) and sequel (IGG) antibodies for herpes virus (HV), cytomegalovirus (CMV), Epstein Barr virus (EBV) were screened, Antibodies for streptococcus (ASTO) and some lymphocytes differentiation clusters were measured.
Results: Our study reported the existence of antibodies for CMV IGg in 17 patients, EBV IGg in 18, HV IGg in 9 and ASTO in 5 patients of the sample. More than 85 % patients have undergone an infectious disease which still had an impact on immune parameters. No one showed active markers of infectious disease (IGM). Immunological results showed that CD 5 and CD 16-56 were elevated and decreased respectively. The others immunological markers do not show significance alterations.

Conclusions: Of all chronic illnesses, chronic fatigue syndrome is one of the most mysterious. Unlike definite infections, it has no clear cause. Several possible causes have been proposed, including post viral infection such AC Epstein Barr, Herpes simplex, HHV6, CMV, HHV-6, and enterovirus. A group of chronic fatigue syndrome can be considered as a posviral illness. This finding is accompanied of modified values of immunological markers.

P-40-014
Relation between Chronic Fatigue Syndrome, Hypotalamus-Pituitary-Adrenal axis and lymphocytosis alterations in 20 female outpatients

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Objectives: to demonstrate the relationship between Chronic fatigue Syndrome (CFS) and the Hypotalamus-Pituitary-Adrenal axis disturbances and lymphocites alterations in 20 patients.
Methods: The site of the study is the Institute of Biological Psychiatry (ipbi) in Buenos Aires, Argentina in an interdisciplinary setting with psychiatrists, family doctors, psychologists, biochemistry specialists, statiscal engineer and medical residents intervening in the present work 20 female patients were selected, diagnosed under American College of Rheumatology criteria for CFS. Patients with psychiatric, endocrinological, immunological or neurological pathologies were excluded. No drug with immune, endocrinological or Central Nervous System action was authorized since one month prior to testing. Plasmatic cortisol and free urinary cortisol. was determined and related to lymphocytes count measured
Results: Cortisol measurement was high in only 2 patients, low in 12 patients and normal in 6 patients. Hemogram is normal in 14 and abnormal with lymphocytosis in 6 patients. On the other hand, with respect to altered cortisol samples 10 of them were without lymphocytosis and 4 with this abnormality. There was not a linear correlation between cortisol abnormalities and altered white blood functionality.
Conclusions: Of all chronic illnesses, chronic fatigue syndrome is one of the most mysterious. Unlike definite infections, it has no clear cause. Several possible causes have been proposed, including dysfunction in the immune system with reduced lymphocytes populations such as CD 16-56 (natural killers cells), CD5, CD4, CD3, CD2, CD8 y CD 26. Hypo or Hyperactivity of Hypotalamus-Pituitary-adrenal axis and disturbances in the autonomic regulation of blood pressure and pulse (neutrally mediated hypotension, or NMH) were common in CFS patients. 70 % of the sample presents cortisol alterations. These results indicate that HPA axis is clearly affected in CFS. Of these 70 % 28, 5 % shown lymphocytosis.Thus, only 30% of total patients have lymphocytosis but many more reveal immunological alterations.

P-40-015
Behaviour pattern, stress, and conformational properties of albumin binding sites in rats with experimental hemorrhage

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Objectives: Stress is one of the components in pathogenesis of many diseases, including hemorrhage. Earlier we showed that conformational properties of the main plasma carrier protein, albumin, differ in rats with different behaviour pattern in the open field test [Gryzunov 2006]. The objective of this work was to study how stress loading influences the course of hemorrhage in rats with different stress resistance and does the properties of albumin binding sites change during the disease.
Methods: The behaviour of 60 rats (Wistar, male, 270±60g) was characterized in the open field test by a ratio of the time spelt for an exploratory activity to the total latency. Active rats were regarded as relatively resistant to stress. All rats were subjected to an experimental hemorrhage. A subgroup of the animals was loaded with immobilization stress before hemorrhage. The ratio of fluorescence intensity of albumin-specific probe CAPIDAN bound to albumin in different pH (7.4 and 4.2) was an index of conformational properties of the protein. Fluorescence quenching method was also used to investigate the state of albumin binding sites. The fraction of fluorescence accessible to quenching (accessibility) was determined according to [Lehrer 1971].
Results: The ratio of fluorescence intensity of the probe was lower (p=0,095) in low active rats after stress than in ones without stress on the first day after hemorrhage. Animals with and without stress also had different patterns of the curves: conformational index versus the days after the hemorrhage. There were no such effects in rats resistant to stress. Accessibility to the quenching of CAPIDAN bound to albumin was increased in active rats with stress comparing with in stressed low active animals on the first day after hemorrhage (p=0.086).
Conclusions: The state of albumin binding sites in rats with experimental hemorrhage differs depending on behaviour pattern and the occurrence of previous stress loading.

P-40-016
Analgesic activity of bi - and polycyclic frame amines derivatives

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Objectives: In the real work analgesic activity of more than 60 derivatives of frame amines is studied. Carbox-, sulfon- and phosphonamides, ureas, sulfonylureas and aminoalcohols. They were got on the basis of stereochemically homogeneous frame amines (exo- and endo-2-aminomethylbicyclo[2.2.1]hept-5-enes and their saturated analogues, exo- and endo-5-aminomethyl-exo-2,3-epoxybicyclo[2.2.1]heptanes, and also deitiforin and amines of adamantane row by comparison to base amines, studied as hydrochlorides, are plugged into the investigated group. Rigid molecules with «fixed» in space substituents used as models for the study of connection of analgesic activity of compounds with their chemical structure.
Methods: The investigation of all compounds has been carried out on white mise. The toxicity (LD50) and analgesic activity («hot plate» method, 55°C) were determined. Explored compounds were entered in a dose equal 1/10 LD50 for 30 minutes prior to testing. Activity of preparations was estimated in % in relation to the control group of animals.
Results: Dependence of analgesic activity on the orientation of substituents in norbornene frame is marked: higher activity for endo-stereoisomers than for exo-form. Analgesic action decreases with disappearance of double bond and increase of number of cycles in carbon frame. The deitiforin derivatives are considerably more active than adamantane analogues.
Conclusions: More than 10 patents of Ukraine are got. Possibilities of the directed synthesis of new active analgesic preparates are certain.

P-40-017
Basical emotions in a cohort of 300 fibromyalgic patients in the first consultation

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Objectives: To determine which were the basic emotions referred by patients in their first visit to a primary care family doctor. Basic emotions do not always correspond to special psychiatric diagnosis

Methods: The site of the study is the Center for Family Medicine (CEMIF) at the city of Rosario, Argentina in an interdisciplinary setting with psychiatrists, family doctors, psychologists and medical residents intervening in the work. 302 patients with Fibromyalgia diagnosed under American College of Rheumatology criteria entered the study. Patients with psychiatric, endocrinological, immunological or neurological pathologies were excluded. Statistical Measure of position or trend, and ANOVA T distribution was performed. The emotion considered as basic was that referred subjectively or deduced by the primary care professional by means of some simple questions or the applications of very simple inventories during the first visit.
Results: Main symptoms referred in first consultation were: sadness in 93%, anguish in 90%, anxiety in 69%, dysthymia in 37%, depression in 27%, phobias in 8%, panic attacks in 7%, anger or hostility in 4%, suicidal attempt in only 3%, suicidal ideation in only 1% and anhedonia in less than 1%.
Conclusions: In further visits patients were interviewed with special scales for depression, anxiety, anhedonia, alexithymia, disthymia and these results did not necessarily match with their primary emotion which nevertheless needs urgent attention in order to achieve treatment adherence.

P-40-018
Fibromyalgia and clinical presentation in 300 patients. How many years of misdiagnosis?

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Objectives: To determine how much time fibromyalgia patients were misdiagnosed until they did receive a final and correct diagnosis. To consider relationship between their clinical presentations and other factors
Methods: The sites of the study are the Center for Family Medicine (CEMIF) and the Clinical Biochemical Institute at the city of Rosario, in an interdisciplinary setting with psychiatrists, family doctors, psychologists, biochemistry specialists, statiscal engineer and medical residents intervening in the work. Over 300 patients with Fibromyalgia diagnosed under American College of Rheumatology criteria entered the study. Patients with psychiatric, endocrinological, immunological or neurological pathologies were excluded. Statistical Measure of position or trend, and ANOVA T distribution was performed
Results: Main symptoms referred in first consultation were: asthenia and fatigue in 97%, sugar craving in 94%, pain in 93% (predominantly cervicalgia in 38%, dorsal pain in 29%, headaches in 22%, myalgias in 12%, rheumatic pain in 2%), irritable bowel and dyspepsia in 89%, voice alterations in 79%, hyperorexia and weight gain in 63%, non restorative sleep in 56%, forgetfulness (fibrofog) in 52%, sleep awakeness in 47%, libido loss in 45%, diarrhea in 41%, dermatological pruritus or skin alterations in 38%, tremor in 34%, urinary hesitation with urinary infection (UI) in 29%, urinary hesitation without UI in 22%, numbness and cerebelar inbalance in 23%, photophobia and noise intolerance in 21%, allergies in 18%, skin and mucosa dryness in 9%. Mean time to correct diagnosis for this cohort was 1 to 5 years in 38% of patients, 5 to 10 years in 42% of patients, more than ten years in 20% of them. More variance of symptoms refered, more time to diagnosis.
Conclusions: Fibromyalgia, as many chronic diseases presents itself as a variety and nonspecific symptomatology which (if not thought about and carefully looked for) can remain many years undiagnosed.

P-40-019
Relationship between chronic fatigue syndrome hypocortisolemia and indolamine and catecholamine alterations in 30 female patients

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Objectives: To determine if there is any special relationship between adrenal axis disturbances and indolaminergical alterations demonstrated in chronic fatigue syndrome patients
Methods: The site of the study is the Institute of Biological Psychiatry (ipbi) sited in Buenos Aires, Argentina in an interdisciplinary setting with psychiatrists, family doctors, psychologists, biochemistry specialists, statiscal engineer and medical residents intervening in the present work 30 female patients were selected diagnosed under American College of Rheumatology criteria for chronic fatigue syndrome (CFS). Patients with psychiatric, endocrinological, immunological or neurological pathologies were excluded. No drug with immune, endocrinological or Central Nervous System action was authorized since one month prior to testing. Statistical Measure of position or trend, and ANOVA T distribution was performed
Results: The study showed that serotonin presents low level in 13 patients and no modification in 7 patients, while 0 patients show high serotonin levels. Cortisol measurement is high in 2 patients, low in 12 patients and normal levels in 6 patients. Many showed a strong correlation.between cortisol and serotonin alterations may be presumed. Of 13 patients with low levels of serotonin we found 12 patients with high cortisol levels. On the other hand the only 2 patients with high values of cortisol none showed modified levels of serotonin.
Conclusions: Accuracy between cortisol alterations and indolamine dysfunction can lead a new way to the explanation of the pathophysiology of CFS

P-40-020
Treatment of fibromyalgia and related entities: Results in more than 300 patients

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Objectives: determine treatment received in of 300 patients with fibromyalgia and similar entities.
Methods: The sites of the study are the Center for Family Medicine (CEMIR) and the Institute of Biological Psychiatry (ipbi) sited in Argentine in an interdisciplinary setting with psychiatrists, family doctors and psychologists 302 patients in an open clinical setting were included. Treatment was aimed at symptom management, thus many received more than one drug.
Results: The drug mostly used and with better results was pregabalin (300-450 mgs/day) in 80 % of patients. Some did not tolerate sedative effect. 80% received antidepressants mostly duloxetine (60-90 mg/day) with few collateral effects. Others (before the approval of Cymbalta) were on amitriptiline, fluoxetine, sertraline, milnacipran or mirtazapine which were maintained if clinical efficacy had been achieved.. 60% had an add-on therapy with ibuprofen. Only benzodiacepines allowed were alprazolam and clonazepan (for restless leg syndrome). 75% received a combination of orthomolecular based prescriptions such as Same, DHEA, thyamine, cianocobalamine, aspartic and glutamic acid, magnesium and zinc. In all cases symptom amelioration was faster. Zinc was found to be extremely beneficial but not always tolerated. Corticoids and opiods were formally contraindicated. Alternative medicines such as movement therapies, Chinese herbs, ozonotherapy, massages, etc were not restricted. 10% responded to the addition of nistatine, under clinical supposition of presence of micotic infections due to sugar craving. In refractory cases, receiving more than three drugs, the waning and waxing of symptoms is always present. Different types of psychotherapies, including behavioral intervention, were performed in order to assure empathy and comprehension that enables the handling of a chronic illness
Conclusions: Fibromyalgia and other similar entities always require an interdisciplinary approach and many years of treatment may be necessary for the total recovery. Integrated treatment plans are imperative.

P-40-021
Traumatic stress and fibromyalgia. More than 300 cases

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Objectives: to determine history of traumatic life events in a group of circa 300 patients who consulted a primary care doctor as a first consultation on behalf of widespread pain of more than six month duration and nonspecific anxious or depressive symptoms, receiving diagnosis of fibromyalgia according to International Criteria
Methods: The sites of the study are the Center for Family Medicine (CEMIF) at the city of Rosario and the Institute of Biological Psychiatry (ipbi) at Buenos Aires, Argentina in an interdisciplinary setting with psychiatrists, family doctors, psychologists, statiscal engineer and medical residents intervening in the present work. 302 patients were evaluated in an open based and directed interviews performed with different professionals, mostly a family doctor. Clinical records were obtained, once each patient had developed a good emphathetic alliance. Patients with DSM IV axis I psychiatric, endocrinological, immunological or neurological pathologies were excluded. Statistical Measure of position or trend, and ANOVA T distribution was performed
Results: The population studied showed the presence of: familial violence in 92%; sexual abuse in 47%, emotional loss in 37%, surgery distress in 22%, car accidents in 19%. Nearly 99% of the patients belong to a matriarchal home. Childhood and adolescent traumatic stress events will be detailed in other communication.
Conclusions: Fibromyalgia patients have as a whole, undergone more traumatic stress than the general population. Most of them underwent various types of stress, mainly during early years.

P-41
Other / Women's Health and Gender

P-41-001
Psychiatric manifestations of antiphospholipid syndrome during pregnancy

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Objectives: Antiphosholipid syndrome (APS) is a systemic autoimmune disorder characterized by arterial, venous, or small vessel thrombosis and pregnancy morbidity. Although central nervous system involvement in APS is well acknowledged, limited scientific data are published on psychiatric morbidity in APS patients and none during pregnancy.
Methods: In the following case, psychiatric manifestations, as well as a peculiar sense of upcoming loss of pregnancy, preceded actual fetal loss and APS diagnosis.
Results: The patient, a 34-year- old woman, had no previous medical, OB/ GYN or psychiatric (individual or family) history. This was her first pregnancy and it was uneventful until the beginning of the 18th week when, in the absence of precipitating life events, she suddenly started being depressed, anxious, and sleepless with a sense of threat related to the "premonition that the fetus would die". Physical examination and fetal ultrasonoghaphy performed four days later, revealed no problems, but when she returned three days later, in a confusional state with delusions that her dead father wanted her to join him; fetal loss was verified by ultrasound. A clinical diagnosis of APS was established, based on both clinical events and laboratory findings (persistent presence of antiphosholipid antibodies and multiple high density foci in the subcortical white matter of the frontal lobes in brain MRI).
Conclusions: Perhaps unexpected psychiatric problems in pregnant women should sensitize health professionals working in the field of women's mental health to search for clinical (thrombosis, previous fetal losses, pulmonary embolism, livedo reticularis etc) and if needed laboratory features of APS.

P-41-002
Character and temperament – sex or gender related?

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Objectives: This research deals with temperament and character type in persons with heterosexual gender identity (HS) and transgender identity- namely transsexuals (TS). One of the author's main ideas was to search for synchronization between personality dimensions and sex or gender by comparison of (comparing) gender harmonized and disharmonized persons.
Methods: Research was carried out in two year period. Chosen sample consisted of 60 adult persons: target group 30 TS (9 female and 21 male) and control group 30 HS (15 female and 15 male). Groups did not differ significantly in age. We have used DSM-IV diagnostic criteria for homosexual transsexualism. We have used psychiatric examination, psychological evaluation and TCI-9 (Cloninger R., 1997). Investigation was performed in three stages: evaluation of personality dymensions in each of the group, comparisson between the groups and comparisson between the groups in correlation with sex. For statistic analysis we have used: c2 test, Value Spearman's correlation test and discriminant analisys.
Results: Both HS and TS group did not differ significantly in character and temperament type when compared each other. Comparison of personality dimensions between HS and TS identity in correlation with male sex have shown statistically significant difference in temperament type, while there wasn't any difference in character types. HS group of male sex differed from TS in Avanturistic and Passionate temperament type, while TS group of male sex differed from HS in Cautious and Methodical temperament type. Same comparison between the groups when correlated with female sex did not found any statistically significant difference in temperament and character type.
Conclusions: The results indicate significant correlation between gender identity and personality (character and temperament type). On the other hand there wasn't any relevance of personality and sex. In other words we could say that sex and gender does not influence in the same way personality dimensions.

P-41-003
The impact of maternal psychopathology on young females

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Objectives: To determine the relationship between mother and daughter psychopathology.
Methods: Ninety-six girls (mean age: 21.21±1.88 years, range: 17-27) and their mothers (mean age: 46.41±5.31 years, range: 37-64) participated the study. The girls were the students attending the School of Nursing at Gaziosmanpasa University in Tokat, Turkey. The girls and their mothers completed the Beck Depression Inventory (BDI), the Symptom Check List 90-R (SCL-90-R), and the 20-item Toronto Alexithymia Scale (TAS-20). The girls also completed the The Rosenberg Self-Esteem Scale (RSES).
Results: The mean score of the RSES was 1.37±1.11; of the 96 girls, 59 (62.1%) had high, 34 (35.8%) intermediate, only 2 (2.1%) had low self-esteem levels. Twenty-nine per cent of the girls and 25% of the mothers scored above the cut-off of 17. On the TAS-20, 39 (41.5%) girls and 8 (8.5%) mothers scored above the recommended cut-off of 61. The girls and their mothers did not differ with regard to depressive symptom or alexithymia levels (t= 1.250, p=0.213 and t=0.457, p=0.648, respectively). The mothers had significantly higher scores on somatization, obsessive-compulsive, and lower scores on interpersonal sensitivity and anxiety than their daughters. The girls' self-esteem had no significant relationship with the mothers' depression levels, measured by the BDI (r=0.129, p=0.214). The girls' depressive symptom levels were positively correlated with total alexithymia scores on TAS-20, and somatization, interpersonal sensitivity, depression, anxiety, hostility, phobic anxiety, paranoid ideation, psychoticism and global severity index on SCL-90-R.
Conclusions: This study supports an interaction between daughter and mother psychology, with a particular emphasis of the negative impact of maternal psychopathology on young girls' self-esteem.

P-41-004
Menstrual parameters and serine 9 glicinepolymorphism in PMDD

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Objectives: Compare the frequency of functional polymorphism D3R glycine serine 9 in PMDD women versus control group. To evaluate the association between this polymorphism with menstrual parameters in both groups.
Methods: Case control, epidemiological observational, longitudinal, prospective study, Sampling representing 99.99% female population of Belo Horizonte, 78 PMDD and 33 controls aged 18 to 50, regular menstrual cycles, with symptoms for at least 9 months last year, medication free, control group the same criteria without functional loss.Daily prospective during two menstrual cycles and blood collection for analysis of polymorphism of D3R.
Results: There is a statistically significant difference in prevalence of se 9 gli D3R polymorphism between the groups(p: 0004).There was no significant difference between the menstrual history in patients and controls regarding menarche, regularity, interval and cycle length.
Conclusions: The menstrual parameters above seem to be independent of the se 9 gli D3R polymorphism.

P-41-005
Serine 9 glycine D3R polymorphism and appetite changes in PMDD women

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Objectives: Compare the frequency of functional polymorphism D3R glycine serine 9 in PMDD women versus control group. To evaluate the association between this polymorphism with appetite changes in both groups
Methods: Case control, epidemiological observational, longitudinal, prospective study, Sampling representing 99.99% female population of Belo Horizonte, 78 PMDD and 33 controls aged 18 to 50, regular menstrual cycles, with symptoms for at least 9 months last year, medication free, control group the same criteria without functional loss.Daily prospective during two menstrual cycles and blood collection for analysis of polymorphism of D3R
Results: There is a significant difference in the Serine9 Glicine D3R polymorphism prevalence between the PMDD and control groups (χ 2 = 10.06, p value: 0004).Changes in appetite were found to be more frequent in Ser 9 Ser phenotype (OR: 5.92, 95% CI: 1,27-25,6) in PMDD women versus controls.Changes in appetite to be more frequent Ser 9 (OR: 5.92, 95% CI: 1,27-25,6).
Conclusions: In this sample, compared to a control group, there are significant differences between the groups in Ser 9 Gli D3R polymorphism which was foud to be related to appetite changes in PMDD group. Changes related to this dopaminergic polymorphism can be of importance in the synthesis of agents that can relief PMDD symptoms which so far are temporary and partially solved by the use of inhibitors of reuptake of serotonin.

P-41-006
Psychological reactions of woman with late pregnancy abortion

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Objectives: Woman with undesired pregnancy are in risk for various psychological reaction, especially when they are late for legal abortion. Abortion after 12 weeks of pregnancy can be completed only for medical reasons and severe psychiatric disorders.
Methods: Fifty pregnant woman addressed to Clinic for Mental Health for psychiatric evaluation in order to terminate undesired pregnancy for psychiatric reasons. We wanted to detect presence of psychiatric disorders, psychopathological reactions, psychological characteristics, socio-economic status and subjective reasons for missing the legal time for abortion. We have applied semistructured psychiatric interview, SCL-90, MINI, Questionnaire for socio-economic features, MMPI test. Six months after the women were contacted by phone to asses pregnancy outcome.
Results: 23 woman had no psychiatric indication for abortion. Anxiety -depressive reaction was present, without fulfilled criteria for depressive or anxiety disorder. In this group level of anxiety, depression, interpersonal sensitivity was>63. They were unemployed, with low income, 15 were unmarried, living with parents. Worries and distress due to conflict relation with sexual partner, was the most common reason for late pregnancy recognition. Late abortion was not approved, but 19 of them had illegally terminated their pregnancy. 27 woman had psychiatric indications and aborts was approved: 9 woman were depressed, 4 schizophrenic, 4 were heroin adductors,10 were under sixteen, some of them were sexually abused by older man.

P-41-007
Nonverbal fluency: Sex or gender characteristic

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Objectives: Who or what is responsible for sex caused differences in brain structure and functioning: our biological inheritance or is simply it the consequence and the result of learning, experience and socio cultural influence? Scientists with different approaches and different orientation agreed in one: responsibility for sex caused differences of cognitive capabilities share innate and acquired factors. Studies which consider cognitive abilities males and females are mostly done with heterosexual and homosexual individuals. The aim of this study was to asses some aspects of cognitive functioning of female-male transsexuals (FMT) and to compare it with the model of functioning of heterosexual female (HF) and male (HM) individuals.
Methods: experimental group consisted of seven FMT and 14 individuals were in HS group (seven in each, HM and HF). FMT were in stage of preparation for operative treatment, and transsexualism was diagnosed and guided within this program. We used Levin Test of Nonverbal Fluency as test of nonverbal fluency in which subjects must draw as many different senseless figures as he can in four minutes, and then the same, but using only four elements for drawing in three minutes.
Results: FMT group drew approximately the same number of senseless figures as HF in the first part of test, while HM group was less successful. On the second part HF and HM reached almost the same score, while less successful, more similar to HM group, by the number of drawn figure, was FMT group
Conclusions: results showed slightly unexpected finding the greatest success of female heterosexuals on both tests of non verbal fluency. F-M transsexuals were almost equally successful as female heterosexuals on the first part of the test. In the second part they've had the worst results. All together female transsexuals were close to male heterosexuals in second part of the test.

P-41-008
Domestic violence against the Iranian pregnant women

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Objectives: Domestic violence especially from intimate partner, is the most common type of violence against women that has many psychological, social and economic adverse effects. Domestic violence in pregnancy causes serious problems for the infant and mother. Considering the importance of this matter, the present study investigated the frequency and intensity of intimate partner violence against pregnant women.
Methods: This study is a cross- sectional research. Two hundred and ninety inpatient mothers in post-delivery sections in educational hospitals were assessed using Iranian version of "Conflict Tactics Scale"(CTS2) after establishing the validity and reliability of this scale.

Results: Results showed that 92.4%, 6.9% and 0.7% of women experienced very mild, mild and moderate intimate partner violence in their pregnancy, respectively. Verbal violence was rated as 40.9% and 0.7%, emotional violence as 81.1% and 1.7%, physical violence as 93.1% and 0.3% and sexual violence as 95.2% and 0.3%, as very mild and severe, respectively. Findings showed that there was a significant difference between the violence against pregnant women and their neonates' low birth weight (W< 2500 grams).There was not a significant difference between education of men and violence against their wives.
Conclusions: This research shows that many pregnant women experience the very mild forms of violence and mostly as the sexual violence. The rate of neonates' low birth weight has a significant relationship with the intimate partner's violence against Iranian pregnant women. These findings show the importance of this problem and the necessity of considering preventive strategies for that.

P-41-009
Sexual health in Parkinsons disease

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Objectives: The changes in sexual health of patients with Parkinson's disease must be a concern to the clinicians. The effects of functional cirurgy in sexual health of Parkinson's patients are still a matter of debate. Our aim is to describe and evaluate the sexual health of patients with Parkinson's disease following deep brain stimulation (DBS) of the subthalamic nucleus (STN).
Methods: Patients with Parkinson's disease bilaterally implanted for DBS of STN and those only pharmacologically treated, will be evaluated. Sexual functioning will be assessed using the international erectile function indices (IEFI) and the female sexual function indices (FSFI). Depression and anxiety will be evaluated using the Beck depression inventory and the brief symptom inventory.
Results: We have a control group with 23 normal volunteers matched for sex and age, a group with 19 Parkinson patients only pharmacologically treated, and a group with 20 Parkinson's patients bilaterally implanted for DBS of STN. Mean age was 61,3 years (SD 10,27), 90,3% were married and 70,0% have four years of school. The three groups have BSI scores higher than 64,8. Control group have higher somatization index ($p<0,05$), only pharmacologically treated group have higher somatization and phobic anxiety indices ($p<0,05$), cirurgy group have higher obsessive-compulsive, phobic anxiety, and psychoticism index ($p<0,05$). BDI score was 20,23 in cirurgy group ($p<0,001$). IEFI have was lowest in cirurgy group (26,3; $p<0,05$). The pharmacologically treated group have a higher orgasm score (15,7; $p<0,05$). FSFI was higher in the cirurgy group (44,0; $p<0,05$).
Conclusions: The sexual function of Parkinson patients is globally impaired. When submitted to cirurgy women suffer an improvement and men impairment. Patients submitted to functional cirurgy have a different psychopathological profile. These should take in to account in the follow up of these patients.

P-41-010
The dexamethasone suppression test and its relationship to entrapment and mental defeat in women experiencing intimate partner violence

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Objectives: Women experiencing intimate partner violence (IPV) may serve to model impacts of severe, chronic stress in a gender-specific manner and allow for further refinement of current models relating stress and trauma to health outcomes. The aim of the project was to assess the contribution of perceived stress and entrapment and mental defeat (EMD), as human analogues to inescapability in animal models, to neuroendocrine parameters associated with depression (MDD) in humans and chronic stress in animals. We hypothesized that EMD would modify basal and challenge-induced HPA axis parameters.
Methods: Women seeking support for IPV (N=39) were compared with women seeking other community services (N=36). A clinical interview and standardized tools were used to assess Axis I disorders, perceived stress and EMD. Biological measures included awakening levels of salivary cortisol and the low-dose dexamethasone (DEX) suppression test (DST). We mailed women DEX and an at-home collection kit to assess HPA axis output in a naturalistic setting. A radioimmunoassay method confirmed ingestion and quantified salivary DEX concentrations. A Kruskall-Wallace test was used to compare salivary cortisol levels and percent suppression between the two groups and a Chi-Square test (or Fisher's Exact where appropriate) was used to explore associations between scores on psychological and neuroendocrine measures.
Results: Positive relationships were found for the IPV group and perceived stress, EMD and DSM IV Axis I diagnosis. Neither morning cortisol levels nor the DST discriminated IPV from other non-interpersonal stressors. The predominant response to the DST in both groups was hypersuppression, independent of psychiatric diagnosis, type of stressor or psychological test scores.
Conclusions: IPV influences women's perceptions about EMD and may allow us to critically examine relationships between learned helplessness in animal models and IPV as a model of chronic, severe stress in women. By integrating neuroendocrine and psychological measures, further development of gender-specific stress models may occur.

P-41-011
Anxiety and depression in pregnancy: Relationship with sleep quality

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Objectives: Women become unstable easily mentally during pregnancy such as anxiety, depression.Δsleep problems are common in pregnant women, and it is reported that mental health and sleep are related. However, there are limited data on pregnant women. The aim of this study was to examine the relation that anxiety and depression and sleep quality in pregnant women.
Methods: 31 pregnant women were categorized 2 groups ; 8(25% higher ranking) subjects as being in the poor sleep health group, and 8 (25% lower ranking) subjects as being in the good sleep health group by the total score of each factor was calculated according to a sleep health risk index. These two groups were then compared with the Hospital Anxiety and Depression Scale (HADS).
Results: Compared with the good sleep group, the poor sleep group had significantly higher anxiety score ($P < 0.01$). Depression score was worse in the poor sleep group ($P < 0.10$). The anxiety and depression score and sleep health risk index had an important significant positive correlation (0.57, $P < 0.01$; 0.31, $P < 0.10$)
Conclusions: Anxiety and depression, in pregnant women, is closely related to Sleep quality.

OTHER - Poster Presentations

P-41-012
Insomnia and sleep-awake rythem in pregnant women

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Objectives: Sleep problems are common in pregnant women. However, there are limited data on pregnant women, and it is not clarified about the approach. The aim of this study was to examine the relation that sleep quality and the amounts of walking and physical activity in pregnant women.
Methods: A survey was conducted on 31 pregnant women (in week 19 to 38 of pregnancy; 31.4±4.0 years old of 22 primipara and 9 multiparous women; average age), for 7 to 8 days in which the subjects were asked to monitor their pregnancies using a check sheet in addition to measuring the amounts of walking and physical activity, recording waking and sleeping times, sleep time.
Results: There was a correlation between monitoring of the amount of walking and exercise and monitoring relating to sleep time and sleep status. The amount of daily activity during the day, abdominal distention and psychological state had an effect on sleeping. It turned out that it is checked that the activity rates of a person with good sleep are low around 14:00($P < 0.05$), and it is high around 18:00($P < 0.05$), and an active mass in the evening and sleep are related from an afternoon.
Conclusions: Preparing the regularity of sleep and the importance of the approach in consideration of activity in the daytime or the balance of rest were suggested to the improvement of the quality of sleep and awakening at the pregnancy.

P-41-013
Psychological experiences of family members about disable children

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P-41-014
Postpartum affective symptoms and its link to mother-infant bonding

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Objectives: To study the association between affective symptoms and mother-infant bonding in postpartum
Methods: One hundred spanish mothers attended in the Perinatal Psichiatry Program of the Hospital Clinic in Barcelona were evaluated at 6 weeks postpartum. Each participant completed a sociodemographic form and personal psychiatric history, the Edimburgh Postpartum Depression Scale (EPDS), the General Health Questionnaire (GHQ-12), the Postpartum Bonding Questionnaire (PDQ).
Results: Half of the sample were women aged between 18-34 years, 40% have university degree, 93%were married, 72% have satisfactory economic status, 72% were primiparous. EPSD (SD) 13.15 (7.85), GHQ-12(SD) 9.47(3.58). Bonding disorder 19%.
Conclusions: We did not find diferrences between PBQ and sociodemographic variables. Women with bonding disorder had a higher score of EPDS and GHQ-12.

P-41-015
Compare the gender types of employed Iranian women regarding their mental health and marital satisfaction

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Objectives: 1. There is a difference between the frequency of the three gender types (feminine, masculine and androgyny). 2. There is a difference between the employed women with different gender types regarding "mental health" and its components (somatic symptoms, anxiety, social dysfunction and depression) There is a difference between the employed women with different gender types regarding "marital satisfaction" and its components (patterns of social role, problem-solving and emotional relationship).
Methods: Participants were 824 women who married and had a diploma or higher education employed in offices. They were randomly selected. The Bem Sex-Role Inventory and GoldBerg's mental health questionnaire and Family Assessment Device-1 (FAD-1) was used.
Results: The results showed that: Androgyny gender type in employed Iranian women is significantly more than masculine and feminine gender types. And There is a significant difference among the three types of women regarding their mental health and marital satisfaction.
Conclusions: Based on the results of this study, after the androgynous gender type which was the most frequent type, the undifferentiated type, defined as weakness in both feminine and masculine gender types, was second. Based on Bem's (1975) theory and her followers, people with the undifferentiated gender type will have more mental and social problems. Therefore, the authorities and all people who are involved in the education of children and even young people have to spend more time and money on the of psychological-gender development of children, teenagers and young adults. Lack of attention to the stereotypic frames and traditional gender types is not equal to leaving them out entirely, but to flourish all the potentials related to masculine and feminine traits.

P-41-016
Comparison of sexual function and mental health between marriage well-adjusted and maladjusted women

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Objectives: The paper in this research is comparison of sexual function and marital adjustment of well-being and illness ladies referred to Tehran psychiatric and psychology clinics.
Methods: The statistical community under study were 180 person elected by random from among 18 to 50 years old ladies who were referred to Tehran psychiatric and psychology clinics during the months of April, May and June whose age average was 36 years old. In this research three questionnaires, FSFI, Rosen used for sexual operations, GHQ for public health and Spainer used for adjustability of the couple in connection with their sexual function and their components and also their marital adjustment ladies.
Results: ,The results show that sexual function and its components were significantly difference, but at sexual function-sexual desire-slipping-sexual excitation-orgasm and pain are not diffrent. Also, the quantity of T was calculated for marital adjustment at 5% statistical views revealed significant difference.
Conclusions: All in all, it revealed that the well-being ladies in comparison with illness ladies enjoyed better in sexual function and marital adjustment.

P-41-017
Prevalence and treatment of mood symptoms in patients with late-onset delusional disorder

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Objectives: Mood symptoms can be prominent in patients with late-onset delusional disorder (LODD).Whether these symptoms resolve with the treatment of the psychosis, or whether they require antidepressant medication remains controversial. We studied this issue in a prospective series of patients presenting with LODD.
Methods: Consecutive patients age 45 and older meeting DSM-IV TR diagnostic criteria for delusional disorder were studied prospectively. Patients with cognitive impairment or dementia were excluded. Assessments were performed at presentation, at 72 hours and bi-weekly thereafter using standardized rating scales. All patients were treated with low-dose antipsychotic medications at the discretion of the treating physician.
Results: 90 patients (56 female, 34 male) with an average age of 66.1 (range 45-90) were enrolled in the study. The mean admission BPRS score +/- SD was 48.1 +/- 9 (range 27-77), and the mean discharge BPRS score was 25.5 +/- 5 (range 5-38). 55 patients (61%) met criteria for a major depressive episode and had a HAM-D score of >17 at admission, with a mean score of 23.6. All patients scored positively on the core depressive features items 1-3 of the HAM-D. 15 patients (17%) had active suicidal ideation or had made a suicide attempt. 44/55 patients (80%) with a HAM-D score of >17 achieved complete remission of their depression (HAM-D <7) within 1 week with antipsychotic treatment alone. The remaining 11 patients had a >50% decrease in their HAM-D score.
Conclusions: (1) The prevalence of patients with LODD that meet criteria for a major depressive episode is high. (2) Patients with LODD and depressive symptoms respond quickly to treatment with antipsychotics alone, and most achieve complete remission of their depression within 1 week. (3) These findings have significant implications for the treatment of delusional disorder in the elderly, where addition of an anti-depressant can cause significant side effects and toxicity.

P-41-018
The Neuroimmunology of Neuroleptic Malignant Syndrome

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Objectives: Neuroleptic Malignant Syndrome (NMS) is an acute and life-threatening reaction to antipsychotic drugs with unknown pathophysiology. We have proposed an immunological mechanism for NMS based on our previous report of a decrease in serum iron in NMS patients, a key feature of the immunological cascade known as the acute phase response (APR). In this study we measured serum iron in a series of patients with NMS as well as acute phase reactants over the course of illness in a case of NMS.
Methods: We prospectively measured serum iron in 33 patients presenting with NMS. We determined levels of acute phase reactants including alpha-1 antichymotrypsin, fibrinogen, ESR, interleuken-6, CRP, serum iron, and albumin in a case of NMS. Reactants were measured on day 1, 2, 3, 4, 6, and 14 of illness.
Results: Serum iron was low in 32 of the 33 cases of NMS with a mean of 5.38 SI and standard deviation of 2.78 (normal range = 13-32 SI). In all cases, serum iron returned to normal with resolution of the syndrome. In the remaining case, the levels were at the lowest limit of normal and returned to high normal range with recovery. In an individual case of NMS, positive acute phase reactants peaked within 72 hours and returned to normal by day 14, and negative acute phase reactants were low during the acute phase of illness and returned to normal with clinical improvement. The temporal profile of the acute phase reactants paralleled changes in vital signs, CPK and clinical course of the syndrome.
Conclusions: The finding of low serum iron and changes in acute phase reactants in NMS supports an immunological mechanism for this drug toxicity.

P-41-019
Psychoneuroimmunology aspect of gynecological pathology

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Objectives: to study of psychoneuroimmunology aspect of gynecological pathology.
Methods: psychopathological, immune, functional investigation of vegetative nervous system. Examined 50 women of reproductive age (mean age - 28,4±5,2 years), under treatment at a gynecologic hospital. Results were processed with standard kit of programs Statistica for Windows 2000 Version 6.0.
Results: In all examined we have revealed depressive symptoms (12,4±3,2 scores according to Hamilton scale). Anxiety and depression in examined patients were comorbid. In clinical picture of borderline neuro-mental disorders in these contingent symptoms of anxiety dominated above manifestations of depression. We have registered high level of all compounds of anxiety (21,3±3,9 scores according to scale by Hamilton). Investigation of variability of heat rate in female patients has demonstrated decrease of current functional state, excessive activation of simpatico-adrenal system and reduction of activity (tone) of parasympathic system of self-regulation. During carrying out of functional cardio-rhythmographic probes also registered a significant decrease of adaptive reserves of the organism of examined. This alteration is a pathogenetic base of development of reactions of disadaptation which clinically manifest in examined women through syndrome of vegetative dysfunction. Changes of reaction of system of immunity at patients with gynecological diseases are unidirectional and are shown disregulastion of intercellular cooperation leukocytes of peripheral blood. Obtained in the research lead by data testify about expressed disbalance production Th1- and Th2-cytokines. Mechanisms of change of intercellular cooperation cells are interfaced to the expressed infringement of production cytokines (IL2, IL4, INFγ).
Conclusions: Raliable correlation interrelations between psychopathological characteristics and key factors of immunopathogenesis reflect the psychoneuroimmune nature of gynecological pathology. Investigation has been performed within Presidential Grant of Russian Federation for state support of young Russian scientist (№ of Grant МК-3743.2008.7).

P-41-020
Work inability as psychic reaction to recurrent breast cancer – a clinical case

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P-50
Other / Obsessive-Compulsive Disorders / Personality Disorders

P-50-001
Checking behaviours in obsessive-compulsive disorder don't compensate for working memory deficits

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Objectives: Checking represents the most observed symptom in Obsessive-Compulsive Disorder (OCD). Neuropsychological studies suggest that checking may be a compensatory mechanism of working memory (WM) deficit (Cha, 2007). However, no consistent evidence has been established. The objective of this study is to test for WM deficit in OCD with an innovative paradigm.

Methods: 40 OCD (27 checkers and 13 non-checkers; Y-BOCS checklist) and 40 healthy subjects were included. Each participant performed 2 tasks: 1) The "comparison task". It is a delayed matching to sample task where subjects were required to match two sequentially presented pictures ('true' or 'false'). After each choice, a feedback informed subject's response accuracy. 2) The "checking task" (Rotgé, 2008). This task starts as the "comparison task". However, once the choice has been made, the subjects were given the choice to check or to validate their response. In the "check" case, the same paired pictures are proposed allowing the subjects to update their choice. In the "validate" case, subjects had directly access to their response accuracy.
Results: In the comparison task, all participants performed equally in terms of response accuracy and response time. In the checking task, OCD checkers performed equally but check significantly more frequently (0.71) as compared to non-checkers and controls (0.36). They were also slower to validate their choice (703ms vs 585ms).
Conclusions: OCD check more than controls but their performances are not impaired when they have no checking possibility. This suggests that memory processing preceding checking is not impaired in OCD, therefore not favouring the WM deficit hypothesis. Further analyses are in progress to clarify the processes implied in checking.

P-50-002
Piercing/ Tattoo and underlying psychopathologies

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Objectives: Over the last decade, tattooing and body piercing have become the most common forms of permanent body modification (BM) and it has recently begun to receive more systematic attention from clinical researchers. (1) Many studies on adolescents showed some sort of correlation between piercing and risk taking behaviour.(3)(4) (5) Tattooing has also been associated with a presumption of underlying psychopathology. (6) In the scenario above stated of the persisting uncertainties regarding the association of BMs with deviant or psychopathological traits, it was considered necessary to investigate the correlation of piercing/tattoo with the presence of potential underlying psychopathologies.
Methods: Our study involved 120 volunteers with body modifications (piercing or tattoo) (age and sex matched). All subjects were evaluated using the following tests: the Psychological General Well Being Index (PGWBI), the Self Harm Inventory (SHI), the Borderline Syndrome Index (BSI), Dissociative Experience Scale (DES II), Toronto Alexithymia Scale (TAS-20).
Results: The one-way ANOVA for the every assigned test data was performed in order to statistically confirm the correlation of piercing/tattoo with the presence of multiple psychopathologies. The TAS-20 means showed body modifications to be associated with a border line personality. The same correlation is even more evident looking to the SELF-HARM test data. The DES-II results showed that, even if all groups are still in the normal range, the body modifications samples have the means close to the dissociation thresholds. The same data distribution describes a strong association of body modification with the border-line BSI even the values are still under the threshold limits. The PGWBI results highlighted a general minor psychological wellness for the body modifications samples.
Conclusions:
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2. MayoClinProc2002;77:29–34.
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4. Pediatrics2002;109:1021–1027.
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P-50-003
Morningness-eveningness personality traits and melatonin levels

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Objectives: The search for biological markers of personality traits has produced controversial results. Melatonin (MLT), the main hormonal product of the pineal gland, has been used as a biological marker of neuroticism, introversion-extroversion and morningness-eveningness. The aim of this research consist of studying whether MLT level is related to the trait of morningness-eveningness in a sample of healthy subjects.
Methods: 51 healthy subjects participated in the study. Evening-morningness trait was evaluated with the Composite Scale of Morningness (CSM). Following the recommendations of Adan et al (3), the sample was divided according their CMS scores in two groups. With the 10th and 90th percentiles as cut-off scores, scorers were classified as evening types and morning types. Blood samples were drawn at 09:00, 12:00 and 24:00 hours. The study was carried out during one week-end. Subjects remained in a supine position one hour before blood extraction in order to avoid the postural effect on MLT levels. Serum MLT was measured by ELISA techniques. The analyst was blind with respect to the samples pertaining to the 09:00, 12:00 or 24:00 hour extractions.
Results: Both groups, percentile 10th (evening type) and percentile 90th (morning type) are formed by six subjects. MLT level comparisons were as follows: At 09:00 Evening type 7.9±1.33, Morning type 3.3±1.70 ($p< 0.0001$), at 12:00 Evening type 2.9±1.60, Morning type 1.7±0.63 ($p=0.107$) and at 24:00 hours, Evening type 34.3±14.71, and Morning type 23.2±11.41 $p=0.219$). In general, evening type scorers had higher MLT levels than morning types. This difference was statistically significant for the MLT levels at 09:00 hours and there was a trend towards significance in the 12:00 hours MLT levels.
Conclusions: Daytime melatonin levels may be used as a peripheral biological marker that discriminates between morningness and eveningness chronotypes.

P-50-004
Headache perception in the mental illness

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Objectives: The analysis of the relation between the symptoms reported and the perception of patients' emotional and behavioral functioning.
Methods: Measures of physical and mental disorders in a small pool of patients with headache.
Results: In the majority of our patients (70%) there is the evidence of overlap of symptoms, diagnostic criteria and clinical diagnoses. Mood disorders are the most representative sub-group.
Conclusions: Headache is the most common neurological condition presented to general practitioners and to neurologists worldwide. Pain perception is correlated to circumstantial mental parameters, such as feelings of depression or state anxiety and to innate characteristics as trait anxiety and the tendency to express discomfort through somatic symptoms (somatization). On the other hand a variety of compounds have been used in the preventative and/or acute treatment of various types of headache in the past for the treatment of refractory and severe headache such the phenothiazine antipsychotics prochlorperazine and chlorpromazine. Recent reports associate neuropathic pain and psychoaffective disorders that seem to share an anatomophysiological common background at the Brodmann Area 25 of the anterior cingulated gyrus. Differences in patients perceptions and a better understanding of the relation between mental illness and headache may be important for the management and maybe suggesting the necessity of new multidisciplinary approaches to the ill.

P-50-005
Munchhausen syndrome

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Objectives: Little is currently known about the etiology and the psychopathology of factitious disorders with physical or psychological symptoms. Besides the difficulties involving the diagnosis, reluctance of those patients to undergone psychological testing and heterogeneity in details of cases published in literature are at the origin of this situation. No epidemiological data on factitious disorder are available in the Greek population. In the international literature Bhugra found that only 0.5% factitious disorder among patients successively admitted in a psychiatric hospital. Munchhausen syndrome characterized by the intentional production of physical symptoms to gain the sick role, more frequently be reported in the recent years but most health care providers are still not sufficiently aware of that factitious disorders are common. A 30 years old housewife in her interview at the emergencies, revealed a long history of seeking treatment at numerous hospitals and doctors during the last three years due to "dramatic" history of "stomach pains". There was no clinical evidence of internal bleeding and physical examination, laboratory and radiological tests were negative. No neurological signs were found and our patient meets the ICD 10 criteria for factitious psychological disorder.
Methods: Clinical examination, laboratory tests, neuroimaging and bibliographic research.
Results: The clinician's suspicion remains the most important part of the diagnosis of factitious disorders. The primary treatment for Munchausen syndrome is still today psychotherapy though no medication is shown to be universally efficacious. Treatment will focus on changing the thinking and behavior of the individual (cognitive-behavioral therapy). Family therapy also might be helpful in teaching family members not to reward or reinforce the behavior of the person with the disorder. At the present time selective serotonin reuptake inhibitors (SSRIs) may be used to treat any related illness, such as depression, anxiety or a personality disorder.
Conclusions: The Munchhausen syndrome is a condition that must be included in the common clinical investigation and differential diagnosis even without a clear evidence of illness.

P-50-006
Psychosis and stroke

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Objectives: Stroke represents a major public health problem, but relatively little work has been directed towards and about the treatment of common neuropsychiatric disorders after stroke. Mood disorders are the most common neuropsychiatric disorders occurring after a cerebrovascular accident with a prevalence of depression among the patients that remains between 30 and 40% for the first 2 years. In the past years studies have emphasized the association between schizophrenia and right hemisphere parietal-temporal-occipital lesions. However, the prevalence of psychotic symptoms following stroke is unknown. On the other hand the greater 10-year mortality associated with incident post-stroke psychosis spotlights the importance of the psychiatric evaluation of any stroke patient.
Methods: Bibliographic research.
Results: None of the antipsichotics at the present time have a clear indication for the post stroke psychosis therefore the choice of the treatment is governed by the drug safety profile. Risperidone with a beginning dose 0.25 titrate slowly upwards is the most used drug but in our clinical experience haloperidol with doses between 5 and 10 mg is a low cost alternative with few side effects and a clear improvement, not only for the psychiatric ill but in the total quality of life.
Conclusions: Rapid diagnosis and pharmacological treatment of post-stroke psychotic spectrum disease are crucial as the motor rehabilitative efforts in the months following a stroke. Patients who have poststroke psychosis appear to have less ability to participate in their rehabilitation, and a worsened long-term functional outcome. The scientific community must reconsiderate the role of the psychiatric assistance in this category of patients.

P-50-007
Serotonin reuptake inhibitors unresponsiveness, hormonal endophenotypes and serotonergic polymorphisms in obsessive compulsive disorder

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Objectives: (1) investigate frequencies of polymorphisms of serotonergic system genes, OCD and response to SRIs; (2) investigate the relationship among polymorphisms and endocrine response to citalopram in non-responders (NR), responders (RP) and healthy volunteers (HV).
Methods: Patients were classified in RP (Y-BOCS<9, n=30) and NR (≤ 25% reduction in Y-BOCS after ≥ 3 trials, n=32) to SRIs. Thirty HV were included. Plasma cortisol, prolactin and GH were determined by immunoradiometric assays. Serotonin concentration in platelet rich plasma was measured through liquid chromatography. Investigated polymorphisms were: G861C (rs6296) of serotonin receptor 1D β (5HT1Dβ) gene, T102C (rs6113) and C516T (rs6305) of serotonin receptor subtype 2A (5HT2A) gene.
Results: Genotypic distributions of 5HT2A T102C in the case group were not in Hardy-Weinberg Equilibrium(p=0.00001). A lower frequency for CC genotype of 5-HT2A T102C in the case group (p<0.001) and a higher frequency for CC genotype of both 5-HT2A C516T and 5-HT1Dβ G681C among NR versus RP (p<0.01 and p=0.018) were observed. An interaction between serotonin and 5-HT1Dβ G681C was observed with the highest serotonin level observed among CC-control subgroup and the lowest among CC-NR subgroup. Prolactin response was higher in HV (p=0.017). CC homozygotus for G681C 5-HT1Dβ showed a higher prolactin response (p<0.01). HV-CC subgroup showed the highest prolactin response (p<0.001). Peak secretion of cortisol was lower in NR than RP (p=0.015). A higher cortisol response was observed in CC 5HT1Dβ G681C homozygotus (p=0.011). HV-CC subgroup showed the highest cortisol response (p=0.003).
Conclusions: (1) CC homozygosis of 5-HT2A T102C was more frequent among OCD patients than in HV; (2) CC homozygosis of 5HT2A C516T was more frequent among NR than in RP; (3) CC homozygosis of 5-HT1Dβ G681C was associated with higher cortisol and prolactin responses and higher serotonin concentration among HV but not among NR.

P-50-008
Riskful decision making and delayed discounting procedure in patients with antisocial and borderline personality disorder

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Objectives: Antisocial Personality Disorder (ASPD) and Borderline Personality Disorder (BPD) are associated with abysmal clinical and social problems. However, little is known about the underlying psychopathology of these disorders. In riskful decision-making, individuals try to choose the best possible options in facing an ambiguous decision-making dilemma. This process has been linked to the VentroMedial Prefrontal Cortex (VMPFC), as its lesion leads to abnormal decision-making and impulsive-psychopathic behavior. Moreover it has been hypothesized that decrease in value of rewards because of delaying, is the reason for people to choose options which has instant reward in the cost of giving up greater delayed rewards. This process is assessed by Delayed Discounting Task (DDT).We compared the performance of patients with ASPD and BPD on GT and DDT with normal controls.
Methods: Twenty-four participants with ASPD and 28 with BPD were recruited applying SCID II and were compared with 25 normal controls. Mean score of Gambling Task was calculated by the differences of choices from advantageous and disadvantageous cards. The hyperbolic Delay-Discounting model was used where the κ coefficient indicated how much participants discounted delayed rewards, served as a parametric value operationalizing impulsivity. One way ANOVA compare the three groups.

Results: The Δcoefficient was significantly different in participants with ASPD and BPD, compared to normal controls. In the GT, participants with ASPD and BPD both tended to choose disadvantageous cards that offered them appealing immediate rewards but incurred long-term loss. Normal controls, on the other hand, tended to choose advantageous cards that brought small immediate rewards but provided an ultimate net benefit.
Conclusions: The impulsivity commonly seen in the behavior of patients with ASPD and BPD may result from short-span of decisions and tendency to focus on immediate gratification rather than long-term benefit. The impaired riskful decision-making might indicate VMPFC dysfunction in these patients.

P-50-009
Comorbid axis II and axis I disorders in psychiatric inpatients in western Quebec

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Objectives: The Diagnostic Comorbidity of Axis II and Axis I Disorders (DCAAD) have received surprisingly little attention in inpatient populations. The purpose of this naturalistic study was then to determine the first admission rates for Personality Disorders (PDs) and to estimate the DCAAD pattern in a Quebec clinical population.
Methods: In this cross-sectional study, data was taken from discharge summaries of all 4506 adult first admissions to a regional psychiatric hospital from 1980 to 2007. Beside a correlation analysis for linear trend in proportions, the DCAAD were examined using Relative Risk (RR) statistics.
Results: Over the study period, the treated prevalence rate of PDs was 29% (Clusters B = 12%, C = 3% and A = 3%) among first admitted subjects. Borderline PDs with a rate of 8% was the most prevalent subtype. PDs were significantly correlated to younger age, male gender, higher drug abuse rates and shorter length of stay. PDs rates have changed from 26% in 1980-81 to 32% in 2006-07, a stable trend (p = 0.208). Positive and significant associations were observed between PDs and adjustment disorders, substance use disorders, dysthymic and anxiety disorders (RR = 2.33, 2.28 and 1.81). Major mood disorders and schizophrenia related disorders were significantly and negatively associated with PDs (RR = 0.86 and 0.37).
Conclusions: The DCAAD appear to have a heterogeneous pattern in this inpatient population. However, our results arise some controversy. The adjustment disorders not mood disorders, seems to be the most prevalent Axis I comorbid diagnosis with PD. In contrast to available literature, we found that PDs rates were greater for men than for women and the length of stay was shorter for inpatients with comorbidities.

P-50-010
Obsessive-compulsive disorder and exhibitionism. Due to a clinical case

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lia litvan Shaw

Objectives: To review the relationship between exhibitionism as a paraphilic behaviour and obsessive-compulsive disorder (OCD).
Methods: Due to a patient diagnosed as OCD with psychotic symptoms and exhibitionism and temporary meeting criteria for pathologic gambling and alcohol abuse, we reviewed the relationship between obsessive-compulsive disorder (OCD) and paraphilia, specifically exhibitionism.
Results: Depending on the social conventionalism of the behaviour there is a first distinction between paraphilic and paraphilic-related disorders, also named compulsive-sexual disorder, hyperphilia, sexual addiction or sexual impulsivity. The studies reviewed do not permit to differentiate on psychopathology, comorbidity and psychological and social impairment between the two groups. There are two published studies evaluating the comorbidity with OCD that included few patients and mixed in the same group paraphilia and paraphilia-related disorders. The results showed a 12-14% of comorbidity between compulsive sexual behaviour and OCD. As for exhibitionism comorbidities, we only found one study with twenty-five patients. The results were: 36% major depressive disorder, 20% alcohol dependency, and 28% compulsive sexual disorder. Its comorbidity with OCD was about 8%.
Conclusions: Our revision pointed out that the studies are scarce and were done with few patients. The results show an infrequent relationship between OCD and paraphilic behaviour. However, there is a group of patients with OCD who also have compulsive sexual behaviour. According to literature, it seems that distinguishing between paraphilic and non-paraphilic behaviour is not relevant. The reviewed articles show a comorbidity with impulse control disorders that are also found in our patient. We think that this case is an example of the Hollander obsessive spectrum, which puts together different disorders in a continuum from compulsive to impulsive behaviour, including sexual behaviour disorders.

P-50-011
Adding pregabalin to a patient with obsessive compulsive disorder resistant to Selective Serotonin Reuptake Inhibitors (SSRIS). A case study

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Objectives: Introduction – Purpose: Pregabalin is an anticonvulsant that also has indication for one of the anxiety disorders, Generalized Anxiety Disorder. The purpose of this presentation is to demonstrate the effect of pregabalin to another major anxiety disorder, Obsessive Compulsive Disorder.
Methods: Material: The case of a 31 year-old female, married with two children, diagnosed with OCD (according to DSM-IV criteria) is described. The symptoms were present for the past five years but she had never taken any medication prior to her visit to the outpatient clinic of the Psychiatric Hospital of Petra Olympus. She was treated initially with sertraline (to the maximum dosage and duration) followed by paroxetine, with no change in her condition. The patient agreed to receive pregabalin (in addition to paroxetine, 60mg/day). Pregabalin was initiated at 150 mg/day for one week and then the dosage was increased to 300 mg/day.
Results: Results: 3 weeks after the co-administration of pregabalin the patient showed remarkable improvement. She has been under the medication for six months and has not presented any side-effects.
Conclusions: Conclusions: In accordance with other international references this presentation shows that pregabalin can be effective in the treatment of resistant to SSRIS OCD.

P-50-012
Psychogenic polydipsia. A case report

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Objectives: Psychogenic Polydipsia is an uncommon clinical disorder characterized by excessive water drinking (more than 3 liters/day). It frequently occurs among chronic psychiatric patients, particularly those with schizophrenia. Other psychiatric conditions that have also been associated with polydipsia are mental retardation, affective disorders, personality disorders and psychosis with onset during childhood.
Methods: A 65-year-old chronic schizophrenic male was admitted to the Acute Ward of the Psychiatric Hospital of Petra Olympus (P.H.P.O). His admittance had to do mostly with psycho-social problems, as he was homeless and had no relatives interested in him. From the very first day the nursing staff observed that he was consuming large amounts of water (almost 6 liters/day). His serum sodium was 130 mEq/L and his urine specific gravity was 1.005 (both below normal values). Urea, creatinine, and blood glucose were normal. He was transferred to the Internal-Medicine-Ward of the local public General Hospital for further testing, where he was admitted for evaluation of diabetes insipidus. His abdomen ultra sound and his cella turcica CT showed no abnormalities. Furthermore, a water restriction test was conducted indicating primary polydipsia. (Urine specific gravity increased to 1.015 and serum sodium increased to 135mEq/L.)
Results: He was discharged with diagnosis psychogenic polydipsia and was brought back to the Acute Psychiatric Ward. He received medication with risperidone 3 mg/day, haloperidol 10 mg/day and was placed on controlled water uptake, observed by the nursing staff.

Conclusions: One month later, giving his consent, he was transferred to a hostel of the Network of the Community-based-Psychiatric- Services of the P.H.P.O. for permanent residency, aiming both at his rehabilitation and in an effort to create the best possible environment for a controlled water uptake. Six months later, his lab tests were still in normal range (serum sodium 140,3mEq/L, urea 38mg/dl, and urine specific gravity 1.010).

P-50-013

Treatment of tourette's disorder in an adolescent with the administration of aripiprazole. A case study

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Objectives: Tourette's disorder is a rather uncommon disorder that appears during childhood or early adolescence and is characterized by the presence of multiple motor and one or more vocal tics. The therapeutic approach consists of administration of small dosages antipsychotics (mostly first generation ones) together with behavioral therapy. The aim of this presentation is to demonstrate the effect of aripiprazole to an adolescent suffering from Tourette's disorder.
Methods: A sixteen-year-old girl visited the Child-Adolescent Department of the Community Mental Health Center of Katerini. She presented a vocal tic (a hiccup-like sound which was produced 4-6 times each minute) and two motor tics: quick blinking of the eyes and rapid shoulder movement. She had received – prior to her visit – treatment with pimozide with no response and later with risperidone (2mg/day), but presented hyperprolactinaemia and medication was stopped. Her lab results and EEG were normal. She was diagnosed with Tourette's disorder and began treatment with aripiprazole.
Results: Aripiprazole was initiated at 2mg/day (oral solution) and dosage was gradually titrated to 7.5mg/day (during a period of three weeks). At the same time she had frequent sessions with her psychologist. Five weeks after the beginning of aripiprazole administration the patient showed marked improvement. The vocal tic was literally eliminated (produced only once during a whole session) and frequency and intensity of the shoulder movement were considerably decreased. Aripiprazole was well tolerated by the patient.
Conclusions: In accordance with other international references this presentation shows that aripiprazole, a second generation antipsychotic agent which has a mild side-effect profile can be proven useful in the treatment of Tourette's disorder in children and adolescents.

P-50-014

"Been there, done that": Scent marking behavior in the rabbit as a possible model for understanding the neural control of stereotyped and repetitive behavioral patterns

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Objectives: An understanding of the neural control of adaptive behaviors that are normally expressed in a repetitive manner could provide an improved understanding of the pathophysiology of OCD. The rabbit displays a scent marking behavior called "chinning", in which it rubs its chin repetitively against objects in its environment. Chinning, like ambulation, is acutely stimulated after being placed in an open field arena containing markable objects (e.g., bricks), and thereafter declines ("habituates"). We are investigating the neural control of this behavior.
Methods: Rabbits were placed in an open field arena containing bricks for 30 min, during which time chinning and ambulation were initially stimulated, and subsequently declined. The rabbit was then returned to its home cage for 5 min, and a specific change (or no change) was made in the open field arena or in the markable objects. The rabbit was then returned to the open field arena, and chinning and ambulation were quantified across the next 30 min. In a second set of experiments, we tested the effect of 8 OH-DPAT [a 5-HT(1A) agonist], ketanserin, ritanserin [5-HT(2A/2C) antagonists] and cis-(Z)-flupenthixol (a D1/D2 antagonist) on the acute expression of this behavior.
Results: We found that replacing the objects within the arena with visually novel ones stimulated a new bout of chinning (but not ambulation), whereas changing the location of the arena stimulated ambulation (but not chinning). 8 OH-DPAT (100 µg/kg) dramatically inhibited chinning, while not affecting ambulation. The other drugs had no effect on either behavior.
Conclusions: These results indicate that chinning is acutely stimulated by object novelty, but not by spatial or olfactory novelty. Neither D1/D2 or 5-HT(2A/2C) receptors appear to mediate the acute expression of this behavior, but the inhibitory effect of 8 OH-DPAT suggests that 5-HT(1A) receptors could be involved in the habituation response.

P-50-015

The neuropharmacology of "just right": Nest building behaviour as a possible model for understanding the pathophysiology of obsessive compulsive disorder (OCD)

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Objectives: An understanding of neurochemical processes underlying the perception of task completion, and the subsequent inhibition of the corresponding goal-directed behavior, could provide an improved understanding of the pathophysiology of OCD. When a pregnant female laboratory rabbit is given access to straw, she immediately begins to construct a maternal nest by repeatedly collecting the straw in her mouth, carrying it into a wooden nest box inside her cage, and depositing it there until the nest is finished ("straw carrying"); thereafter, this stereotyped behavior is inhibited for several hours, even if the finished nest is removed. We are using pharmacological techniques as a first step toward defining neurochemical processes underlying the acute onset and inhibition of this behavior.
Methods: Pregnant female rabbits were given the following sc injections: 1) saline or DMSO vehicle; 2) 8-OH DPAT, 150 µg/kg; 3) ritanserin, 0.5 mg/kg; 4) ketanserin, 1 mg/kg; or 5) cis-(Z)-flupenthixol, 200 µg/kg. Straw was placed into the cage 10 - 60 min later, and the female's behavior was observed for the next 3 hrs. At 3 hr, all straw was removed from the nest box and weighed (as a quantitative measure of straw carrying), and the empty nest box was returned to the cage. More straw was placed inside the cage, and at 6 hr the straw inside the nest box was again weighed.
Results: The 5-HT(1A) agonist 8 OH-DPAT significantly reduced straw carrying across the first 3 hours, while the D1/D2 antagonist cis-(Z)-flupenthixol nearly eliminated this behavior. The 5-HT(2A/2C) antagonists ketanserin and ritanserin had no effect. None of these drugs significantly altered general activity (ambulation) in open field.
Conclusions: These results suggest that D1/D2 receptor stimulation underlies the acute stimulation of this stereotyped behavioral pattern, while the 5-HT(1A)receptor could participate in its inhibition once the nest is perceived as "finished".

P-50-016

The comparison of defense style and mental disorder between military students and unmilitary students

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Objectives: Aim: the objective of This study was comparing defense style and mental disorder in military students and unmilitary and also finding the relation between defense mechanism and mental disorder.
Methods: Measurement: DSQ-40 (Andrews,1993) MMPI-1 Sample:89 military students(MS) who graduated in army university (M=23/57,SD:2/33),100 unmilitary students(UMS) (M=21/76,SD:2/55) participated in this study.
Results: Results: finding showed there was significant difference between MS and UMS in MMPI scale and defense style. In MMPI test UMS show higher number in this scale than MS: F, ,HS, D, HY, PD,PA,PT,MA, and SC and MS in K and L have higher numbers. Also UMS used neurotic and immature defense style more than MS. Finding showed there was significant relation between defense style and mental disorder.

Conclusions: This study suggested there are a relation between some personality traits and defense mechanism, also abnormal personality traits can be relate to nurotic and immature defense style.

P-50-017
Clinical characteristics of obsessive compulsive disorder with Schizophrenia

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Objectives: We investigated the prevalence of obsessive compulsive disorder (OCD) among patients with schizophrenia. We also investigated the differences in the psychotic symptoms and suicidality between patients with schizophrenia who did or did not have OC symptoms.
Methods: Seventy-one subjects with the DSM-IV diagnosis of schizophrenia were evaluated by the Structured Clinical Interview for DSM-IV Axis I disorders, the Yale-Brown Obsessive-compulsive Scale and the Positive and Negative Syndrome Scale.
Results: The OCD patients with schizophrenia were 20 (28.2%) among 71 subjects. The 20 subjects with OCD had significantly more severe negative and total psychotic symptoms evaluated with PANSS than subjects without OCD. The schizophrenia with OCD had significant higher recent suicidal attempt rate than the subjects without OCD.
Conclusions: The results of this study suggest the possibility that OCD symptoms in schizophrenia may be related to negative symptoms and the OC symptoms may be related to the impulsivity expressed as suicidal attempts.

P-50-018
Non-verbal memory dysfunction in checking type obsessive-compulsive disorder

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Objectives: The purpose of this study is to examine the role of memory dysfunction in obsessive-compulsive disorder(OCD). Especially we tested the memory function of checking type of obsessive compulsive disorder compare to that of cleaning type and that of normal controls.
Methods: Subjects were 67 patients aged 18-45 years who met the diagnostic criteria of obsessive compulsive disorder and 28 normal controls. Informed consent was done. OCD patients was divided into two groups, 'checking' type and 'cleaning' type patients by evaluation of Yale-Brown Obsessive compulsive scale and Maudsley Obsessive compulsive inventory. All patients were tested memory functions by Rey-Osterrich comlex figure test(RCFT) for non-verbal memory function, Hopkins verbal learning test(HVLT) for verbal memory function, Wisconsin card sorting test(WCST) and evaluated depression and anxiety by Beck Depression Inventory(BDI) and Taylor Anxiety scale.
Results:
1. The Reyimmediate and Reydelayed memory test scores were significantly lower($P<0.05$) in checking types than in cleaning types and normal controls(student t-test).
2. There were no significant differences of Reycopy test scores, and verbal memory test(HVLT) scores, BDI and Taylor Anxiety scale scores in checking, cleaning type groups and normal controls.

Conclusions: The non-verbal memory function of checking type OCD patients were significantly decreased than other OCD patients and normal controls. This non-verbal memory dysfunction is not related to depression and anxiety. This results suggest that checking symptoms development of OCD is related to non-verbal memory dysfunctions.

P-50-019
Neurocognitive impairment as predictors of cognitive behavioral therapy outcome in obsessive-compulsive disorder

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Objectives: This study was conducted to evaluate whether neurocognitive task performance at baseline predicts treatment response in obsessive-compulsive disorder (OCD).
Methods: A total of 25 patients diagnosed with OCD underwent cognitive-behavioral therapy (CBT). Self-reported symptom questionnaires (Yale-Brown Obsessive Compulsive Scale: Y-BOCS, Beck Depression Inventory: BDI, Beck Anxiety Inventory: BAI, Anxiety Sensitivity Inventory) and neurocognitive assessment were administered individually prior to CBT and shortly after the treatment. The neurocognitive tasks included Rey-Osterrieth Complex Figure Test, Object Alternation Test, Controlled Oral Word Association, Wisconsin Card Sorting Test (WCST), and Trail Making Test A/B.
Results: Nine patients showed a reduction of more than 35% on the Y-BOCS score, who were classified as responder group. Responders showed significantly higher scores on BDI and BAI than non-responders before CBT. But two groups did not significantly differ on any of the neurocognitive tasks except for the number of trials on WCST (responders made more trials on the WCST). There was a significant main effect of time (pre-post CBT) on the scores of Y-BOCS, MOCI, BDI and BAI, but not an interaction effect (group by time).
Conclusions: The patients participated in CBT showed a significant symptom reduction including OC symptoms as well as depression and anxiety. But the overall treatment response rate in the present study was 36%, which is lower than that of previous research. Considering that responders were more depressive and anxious than non-responder at baseline assessment, patients experienced more subjective distresses are likely to have stronger drive to treatment. The present study failed to find any significant neuorpsyhcolocial differences between responder and non-responder. In conclusion, OCD patients with neurocognitive impairment can similarly benefit from CBT similar to those without such deficit.

P-50-020
An examination of delusional thinking in Body Dysmorphic Disorder

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Objectives: Body Dysmorphic Disorder (BDD) is characterized by a severe dislike in ones appearance, resulting in a belief about an 'imagined' or minor defect. Previous research has suggested that BDD patients' beliefs can be classified as delusional or non-delusional, with this distinction being represented by two separate disorders on the DSMIV. The current authors argue against this dichotomy and argue that delusional thinking should be considered on a continuum. The aim of the current study is to examine the severity, frequency and phenomenology of delusional thinking in BDD.
Methods: 14 BDD patients and 14 healthy controls were administered the Peters Delusional Inventory (PDI). The PDI examined the number of delusional beliefs endorsed, and levels of preoccupation, distress and conviction.
Results: As a group BDD patients endorsed three times as many delusional beliefs as healthy controls. However, an examination of the normal distribution of the two groups established that the BDD patients' delusional ideas were indeed on a continuum: with some patients endorsing no or few delusional ideas and others up to 13 different delusional beliefs. There were not two discrete groups. The most commonly endorsed delusion was delusion of reference. BDD patients were more preoccupied and distressed by their delusional ideas. This pattern of findings was similar to the profile reported in schizophrenia.
Conclusions: This data demonstrates that BDD should not be dichotomized on the DSM on the basis of delusional thinking. Further that BDD should perhaps be reclassified as a psychotic condition.

P-50-021
Correlation relationships between steroid and thyroid hormones and motivational features in patients with neurotic, stress-related and somatoform disorders

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Objectives: Objectives: Study of hormonal parameters and features of motivations in patients with neurotic, stress-related and somatoform disorders and mentally healthy persons.
Methods: Methods: 1 group - 35 patients with dissociative (conversion) disorders (ICD-10, F44), 2 group - 29 patients with adjustment disorders (ICD-10, F43.2) and control - mentally healthy persons (27 persons) were investigated. Immunoenzyme analysis for definition of concentration of steroid and thyroid hormones was carried out. Requirement for achievement and motivation of approval in groups of patients and control were investigated with questionnaires.
Results: Results: We have observed a statistically significant increased level of cortizol and thyrotrophin and a lowered maintenance of dehydroepiandrosterone sulfate in group 2 as compared with control and group 1 ($p<0,05$). The statistically significant increased level of triiodthyroninum and free thyroxinum is characteristic for patients from the first group as compared with control and group 2 ($p<0,05$). Low values of requirement for achievement is characteristic for persons from group 2, tendency to decreased values with the years by scale of motivation of achievement is characteristic for control and group 1. Tendency to increased values over years according to scale of motivation of approval is characteristic for control and patients of both groups. Correlation analysis has shown that in group 2 authentic correlation relationships are revealed between dehydroepiandrosterone sulfate and thyroid hormones and motivation of approval. In group 1 statistically significant correlation relationships are revealed between steroid and thyroid hormones, motivation of achievement and approval.
Conclusions: Conclusions: Adjustment disorders are characterised by individual correlation relationships between motivational features and dehydroepiandrosterone sulfate. Dissociative (conversion) disorders differ according to numerous interrelationships between steroid and thyroid hormones and motivations of achievement and approval.

P-50-022
Cannabinoid CB2 receptor mediated regulation of impulsive – like behaviors in mice

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Objectives: The recent identification of CB2 receptors in brain areas of rats and mice has awaked the interest to characterize its functions and potential therapeutic applications in neuropsychiatric disorders. The aim of this study was to identify if the acute administration of a cannabinoid CB2 receptor agonist (JWH133) or antagonist (AM630) modulate some behavioral aspects of impulsiveness.
Methods: The effects of JWH133 (1 mg/kg, i.p.) and AM630 (1 mg/kg, i.p.) on motor activity (open field), exploration (head-dipping on the hole board), novelty-seeking (object preference on the hole board) and pre-attention (prepulse inhibition) were studied in DBA/2J mice presenting a highly impulsive behavioral endophenotype.
Results: The travelled distance in the center of the open field increased 203% after the administration of AM630 and 167% after JWH133. In the hole board, no differences were detected in the exploratory level since the number of head introductions was similar between treatment groups. The administration of AM 630 blocked the novelty seeking behavior showed by DBA/2J mice whereas JWH 133 was without effects. In the prepulse inhibition paradigm, the administration of AM 630 at 90dB prepulse significantly improved the pre-attentional level (control mean = 5.35%, AM 630 mean = 35.7%, $p = 0.017$). Indeed, the % of prepulse inhibition in the AM 630 group was always significantly higher than in the JWH 133 group. However, the administration of JWH 133 markedly impaired the pre-attentional level of DBA/2J at 74dB prepulse.
Conclusions: Taken together, these results strongly suggest that the functional manipulation of the cannabinoid CB2 receptor modulates impulsive and anxiety-like behaviors, novelty seeking and pre-attention, and may show potential benefit as a new therapeutic target in the treatment of impulsivity-related disorders.

P-51
Other II

P-51-001
The aggressive and potentially patient

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Objectives: It has been estimated that over half of healtcare professionals will be assaulted by a patient some time in their career,probably reflecting the increase in aggression and violence in society. Nurses are especially at risk because they are often the ones working wiht patients most closely. Historically ,nurses working with psychiatric patients have been taught to be alert to and manage violent ,assaultive behavior; however ,now nurses working in emergency deparments, general hospitals,clinics,and nursing homes must be prepared to deal with it (). Thoght studies linking violence and mental ilness are inconsistent, Previous violent behavior and a history of psychiatric illness, particularly schizophrenia,paranoia,bo rdeline personality disorder,personality disorders,and posttraumatic stres disorder remain the most frequent risk factors associated with predicting an aggressive outburst
Methods: research review
Results: Etiology Aggresive ,violent behavior has many causes. Biologic studies include genetic,Which link cromosomal abmormalities to aggressive behavior ,hormone imbalance, particularly testosterone ,and neurotransmitter irregularities,specifically the abnormal secretions of the dopamine and seratonin. Psychologic studies on aggression are related to a person's view of the world as a source of anxiety. Social learning theory views aggression as a learned behavior. Sociacultural studies look at an aggressive individaul's poor interpersonel skills. Nursing Management Risk for violence, directed to others; Help patient to verbalize angry feeling by reflecting and by clarifying your understanding of feelings. Communicate your interest by appropriate eye contact,restating what patient has said, and asking questions. If needed ,alow patient to release tension physically on inanimate objects such as pillows and prescribed exercise ,as appropriate. Do not ignore aggressive behavior in hopes that it will go away. It needs to be addressed. Minimizition of behavior and ineffective limit setting are the most frequent factors contributing to escalation.

P-51-002
Neurobiology of aggression

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Objectives: The main objective of this work is to establish greater understanding and deepen the various factors and neurobiological mechanisms involved in aggressive behavior.
Methods: It has been a literature review conducted by the search page data "pubmed", with articles published in the last 10 years, entering keywords such as "aggressiveness, violence, neurobiology, antisocial behavior." Conducting a review of the data currently available on this subject and the interaction of different variables.
Results: The evidence found in the various studies for the understanding of this emotional state has identified the importance of involvement of many phylogenetically primitive structures such as the hypothalamus, the thalamus, the midbrain, the hippocampus and nucleus tonsillar Despite the importance of this issue when it has tried to study in depth, in therapy, researchers have encountered many difficulties such as lack of drugs specifically indicated in the approach to aggressiveness, the difficulty of tests designed to assess violent behavior and behaviour variations after administration of a drug.

Conclusions: The genetic, neurochemical, and neurophysiologic findings obtained in different studies, open a new path of hope for understanding and reasoning about the neurobiological aspects involved in such behavior. Individual antisocial behavior is the result of the balance of biological, social and emotional factors

P-51-003
The dynamics of violent and non-violent mortality as indicator of societal crisis

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Objectives: The purpose of the study was to evaluate the correlations of the dynamics of violent (suicides and homicides) mortality rates as indicators of societal crisis and non-violent mortality from the diseases of circulatory system, gastric/duodenal ulcer and malignant neoplasms in male and female population in young and middle (15-55 yrs) ages in 1990-2002.
Methods: Correlative analysis of the statistical data for mortality (age-sex specific death rates per 100 000 population) derived from WHO Statistical Information System and the State Statistical Committee for 1990-2002 years.
Results: The results have shown strong agreement for the dynamics of suicides and homicides causes of death for males (25-54 age group) and females (15-45) ($p<0.05$). For suicides and disorders of circulatory system the dynamics of mortality rates was in a very strong agreement in males (15-44) and in females (25-34) groups. The similar strong agreement of the dynamics of rates of homicides and disorders of circulatory system mortality for males (25-54) and females (15-54) revealed. For suicides/homicides and gastric/duodenal ulcer strong agreement of dynamics of mortality rates was for males (25-54 and 35-44). None significant correlations of the dynamics of both violent caused and neoplasms mortality rates revealed.
Conclusions: The results of the study have confirmed the distress-related hypothesis of the rapid growth of mortality from different causes of death in young and middle age groups of population of the Russian Federation.

P-51-004
KINA in psychoneuroimmunology

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Objectives: We try with this revision work to call the attention of the International Psychiatric Community that many of the disorders of our speciality are medical inflammatory diseases of the CNS, specially depression and schizophrenia.
Methods: Review of MEDLINE from 1988 to 2008 to look for the findings of immunological mechanism of inflammation contributing to the pathogenesis of depression or schizophrenia, and personality.
Results: We found in 1970 - 1972, an increase of immunoglobulins in spinal fluid and blood and also antibrain antibodies. From 1988 to date has been found in high concentrations KINA which explains Psychotic symptoms and cognitive dysfunction in schizophrenia. In addition depressive symptoms and cognitive dysfunction in depression. The imbalance of T Helper I and II Helper T in schizophrenia inhibits the enzyme indoleamin dioxigenase (IDO), degrading Triptophan into Kinurenine and from there to Quinolinic Acid. In Depression increase of T Helper I cytokines increase IDO and decreases Triptophan Hydroxilase (TH), degrading Triptophan to Kineurine and from there to Quinolinic Acid with the resulting decrease of Serotonin in the CNS.
Conclusions: The theory of KINA explain psychotic symptoms in schizophrenia and depressive symptoms in depression, besides the cognitive dysfunction in both.

P-51-005
Karolinska Interpersonal Violence rating, a new tool in biological psychiatric research

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Objectives: Assessment of lifetime exposure to violence and expression of violent behaviour is important in clinical psychiatry. Psychiatric patients score higher in exposure and expression in different studies. The aim was to create a new rating measuring exposure and expression of violence for clincal use.
Methods: Rating was administered as structured interview for 160 suicide attempters and a large group of healthy volunteers.
Results: Suicide attempters had significantly higher scores in three subscales compared to controls. In both patients and controls childhood exposure to violence predicted expression of violent behaviour in childhood and as an adult as well as re-exposure to violence as an adult. Preliminary results show differences in serotonergic system in exposed patients.
Conclusions: The rating has good predictive ability and seems suitable in biologic psychiatric research as a new tool to measure both exposure and expression of violence.

P-51-006
Kleine - Levin Syndrome and Neuroleptic Malignant Syndrome

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Objectives: Kleine - Levin Syndrome (KLS) is a rare, underdiagnosed disorder that usually affects young males. It is characterised by periodic episodes of hypersomnia, hyperphagia, abnormal sexual behaviour and emotional disturbances. Neuroleptic Malignant Syndrome (NMS) is a serious side - effect of treatment with antipsychotic medication. It is characterised by autonomic dysfunction, altered consciousness, extrapyramidal symptoms and fever. We present the first case of NMS in a female patient suffering from KLS.
Methods: Case report.
Results: A 27-year-old woman presented with recurrent episodes of depression since the age of 13. Later on, she additionally presented with prolonged sleep, compulsive hyperphagia, impulsive behaviours, hypersexuality and irritability. The episodes lasted from a few days to a few weeks with almost complete remission under treatment with fluoxetine, valproic acid and haloperidol. SPECT scans showed hypoperfusion in the right median temporal lobe and right thalamus. During the last episode, she was receiving carbamazepine (400mg/day) and ziprasidone (80mg/day) without remission. She started receiving haloperidol up to 40mg/day due to persistent behaviour disturbances. She became confused and developed rigidity, tachycardia, fever (37.7 0C) and CPK elevation (755 U/L). She was diagnosed as suffering from NMS. Antipsychotic medication was stopped and NMS symptoms disappeared over the next 10 days. One year later she was receiving clozapine 50mg/day. She was free of KLS symptoms or side - effects.
Conclusions: This case report demonstrates the possible relationship between KLS and mood disorders as well as the association between KLS and organic brain dysfunction. Given that NMS is a potentially lethal side - effect of antipsychotic treatment, physicians should be aware of the potentially increased vulnerability of KLS patients to NMS.

P-51-007
Behavioural analysis of sexuality in relation to HIV/AIDS: Commitment in sexual behaviour

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Objectives: To assess how often HIV/AIDS & sexualitytalks are involved into household conversations, and assessment of HIV/sexuality attitudes in rural background.
Methods: In order to assess the impact of /awareness programs/counseling about HIV-screening among seropositive couples, our 10 years old NGO devised feedback questionnaire. It given to all psychiatrists of rural tribal area of Dhule-city for analysis. subjects agegroup range 16-40, having an active sexual live and living together as couples for >2 years.
Results: n=35, 68% allopathic, 20% Ayurvedic & 12% traditional healers. Among couples screened 21% reported to often talk about HIV/AIDS affection in their intimate conversations with partners. Yet 79% kept silence about their affection for various reasons. However 78% of them agree to be screened after counseling. Among them only 11% were couple seropositives. Out of these seropositive couples 21% were both seropositives and 2 serodifferents. Only 8% however agreed to break the silence about their affection by informing their partners.
Conclusions: HIV/AIDS affection often comes into private conversations of many couples [68%]. Although considerable number of consultants show positive approach, a great number (79%) remain silence about their affection only to reveal it too much late. We need to apply strong efforts through permanent sensitization and education and adequate counselling. Lessons learned: HIV/AIDS & sexuality disorders in Rural/tribal population is iceberg. We need to share knowledge & commitment for better action to achieve good results in prevention and fighting against HIV/AIDS in rural areas of developing countries. We need to shift our focus form urban to rural areas where AIDS epidemic is silently spreading its tentacles. We NGO psychologists from resource poor developing nations need platform like 9th World congress of biological psychiatry to interact with experts from Europe to work on this issue.

P-51-008
Combating psycho-social stigma & discrimination associated with sexual disorders: Efforts by faith based community model of Indian NGO

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Objectives: NGO's from resource-poor nations notice stigma/discrimination suffered by HIV-patients. stigma/discrimination reduces patient-compliance to ARV-drug-administration. We devised community model with four community-volunteers & two traditional-faith-healers to overcome this hurdle. Our Interventions reduces stigma, therefore crucial for improving QOL, emotional-health of PLWHA. [people-living-with-HIV/AIDS]. Our NGO-team trains traditional-faith-healers who are backbone of tribal/rural healthcare-system in developing-nations. They incorporates messages of love/compassion.
Methods: This NGO initiative was trial-project. Project components with two traditional-faith-healers [TFH]. We work in 21 villages with 23 patients enrolled. TFH advocated awareness raising/spiritual health/ community support. Social/community efforts reduces stigmatization/discrimination.
Results: In 7 workshops, 48 responses analyzed. It shows positive outcome in >74% subjects. Negative attitude of PLWHA towards health-care providers analyzed. Among 11 who underwent full course, 60% reported positive outcome/mind-frame. Incidences of forced sex is 32%; physical abuse is 57%; verbal abuse 84%; & threat to job 36% communicated to appropriate higher authorities for action. **Conclusions:** Stigma/discrimination changes attitudes of PLWHA towards ARV-therapy & reduces compliance. Involvement of local/respected faith-based leaders for AIDS control and creation of environment where faith plays important role. **Conclusions:** NGO's play vital role for sensitization of general-population/health-care-workers towards sex workers/PLWHA. study results demonstrated that multi-sectoral and multi-disciplinary approach by NGO's with community participation will improve ARV-treatment outcome & overall QOL. Our model seeks to explore power faith approach in promoting love, compassion and support to HIV positive community. 9th world-congress of biological-psychiatry-2009 must be platform to show needs/concerns of NGO workers from resource-poor-nation working in HIV control field.

P-51-009
Homicide and roots of homicidal behavior

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P-51-010
Sleep and circadian disturbances in depression

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Objectives: Desynchronisation of normal circadian rhythms, including the sleep–wake rhythm, is common in depression.The association between sleep disturbances and depression has long been recognised. The aim of this paper is to review the nature in sleep disturbances in depression and the physiological and neurobiological alterations that characterize depression during sleep.
Methods: All available resources(electronic and non electronic) were searched and combined with the experince from everyday practice.
Results: Insomnia is the difficulty to fall or stay asleep despite adequate opportunity for sleep, and is reported by as many as 90% of depressed patients (e.g.,Tsuno et al., 2005). Hypersomnia, which is prolonged sleep duration extended by more than 1 hour over habitual total sleep time, is reported from between 6% and 36% of depressed persons, but more commonly endorsed by younger depressed people and in patients with seasonal, bipolar, and atypical depressive disorders (Posternak & Zimmerman, 2001 ; Roberts et al., 2000). Of note, fatigue and low energy are endorsed by the vast majority of depressed patients, regardless of whether they experience insomnia or hypersomnia (e.g., Maurice-Tison et al.,1994;Tylee et al., 1999). Depressed people often report other sleep disturbances, including nightmares, nocturnal panic attacks, and excessive daytime sleepiness (Ohayon et al.,1997).
Conclusions: A number of investigators have suggested that sleep disturbance is more than an epiphenomenon resulting from depression and may instead be involved in its genesis. Support for this notion comes from the observation that several manipulations of sleep (total or partial sleep deprivation or REM sleep deprivation) represent potent (although time consuming and not always practical) treatments for depression. The effects of antidepressants on sleep are briefly summarized, and we conclude with recommendations for adjunctive pharmacological and non-pharmacological treatments that specifically target sleep disturbances in depressed patients.

P-51-011
Treatment of bipolar disorders

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Objectives: Bipolar disorder(also known as manic depression) is a treatable brain disorder that causes changes in person's mood, thought, energy and behaviour. It can affect anyone, regardless of age, ethnic background or social status.

Methods: All available resources(electronic and non electronic) were searched and combined with the experince from everyday practice and this is a rewiev of the various treatments that are currently available for the treatment of bipolar disorders.
Results: Medications known as "mood stabilizers" usually are prescribed to help control bipolar disorder. Other medications are added when necessary, typically for shorter periods, to treat episodes of mania or depression that break through despite the mood stabilizer. In situations where medication, psychosocial treatment, and the combination of these interventions prove ineffective, or work too slowly to relieve severe symptoms such as psychosis or suicidality, Electroconvulsive therapy (ECT), Transcranial Magnetic Stimulation (TMS), Vagus Nerve Stimulation (VNS), Magnetic Stimulation Therapy (MST) and even herbal or natural supplements may be considered.
Conclusions: Lithium,the first mood-stabilizing medication is often very effective in controlling mania and preventing the recurrence of both manic and depressive episodes. Anticonvulsant medications, such as valproate or carbamazepine, also can have mood-stabilizing effects and may be especially useful for difficult-to-treat bipolar episodes. Newer anticonvulsant medications, including lamotrigine, gabapentin,and topiramate,are also very effective in stabilizing mood cycles.Anticonvulsant medications may be combined with lithium, or with each other, for maximum effect. Atypical antipsychotic medications, including clozapine,olanzapine,risperidone,quetiapine, and ziprasidone, are are also used for bipolar disorder treatment. If insomnia is a problem, a high-potency benzodiazepine medication such as clonazepam or lorazepam may be helpful to promote better sleep.However, since these medications may be habit-forming, they are best prescribed on a short-term basis. Other types of sedative medications, such as zolpidem, are sometimes used instead.

P-51-012
Burnout-related emotional and physical exhaustion, but not depressive symptoms, is related to sleep complaints in a non-clinical sample

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Objectives: Burnout is considered a work-related emotional and physical exhaustion, and previous studies showed that independently of gender and age, high burnout scores were related to increased sleep complaints. By contrast, people with optimistic attitude seem to be less vulnerable to stress and burnout. Therefore, assessing a non-clinical sample, the present study aimed at investigating the relation between burnout, depressive symptoms, satisfaction with life, and sleep complaints in parallel.
Methods: A total of 2231 participants (age [years]: M = 40.77; SD = 10.30; 1183 females and 1048 males) took part in an internet-based study. Participants completed a series of questionnaires such as the Tedium Measure (TM; Pines, Aronson, & Kafry; 1983), the Insomnia Severity Index (ISI; Bastien et al., 2001) and the Satisfaction with Life-questionnaire (SWL; Diener et al., 1985). For statistical analyses, first, factor analyses split the TM in the dimension Depressive symptoms, Emotional and physical exhaustion, and Pessimism. Afterwards, to analyse all questionnaires in parallel, a Structural Equation Model (SEM) was applied.
Results: Pessimism, emotional and physical exhaustion, depressive symptoms, and low satisfaction with life were highly inter-related. Emotional and physical exhaustion was highly related to sleep complaints, whereas sleep complaints were not related to depressive symptoms, satisfaction with life, and pessimism.
Conclusions: Results suggest that among burnout symptoms the emotional and physical exhaustion is strongly related to sleep complaints and not depressive symptoms in this non-clinical sample. This is in line with the hypothesis that sleep disturbances may play a role in the development from non clinical burnout to depression, by increasing emotional and physical exhaustion.

P-51-013
Polysomnographic profiles of patients suffering from restless legs syndrome, depressive symptoms, and major depression are not gender-related

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Objectives: Amongst the variety of disorders affecting sleep, depressive disorders and Restless Legs Syndrome demand particular attention. Sleepiness, daytime fatigue, cognitive deficits, and loss of interest are symptoms attributable to both depressive disorder and RLS. Moreover, beside the overlap of symptoms, a high co-morbidity rate is observed. However, onset of RLS seems to precede onset of depressive symptoms. Surprisingly, no study so far has addressed this issue using sleep-EEG. Moreover, there is evidence that females are at increased risk for developing sleep disorders in general, and RLS in particular.
Methods: We compared retrospectively polysomnographic recordings of outpatients with RLS (n = 25; age 53.32 ± 16.23), RLS and depressive symptoms (n = 38; age 50.20 ± 14.42), and inpatients suffering from major depressive disorders (n = 15; age 51.47 ± 8.04).
Results: Results showed that both groups with RSL had lower sleep efficiency, compared to the group with major depressive disorder. Most disturbed sleep continuity was observed in the group with RLS and depressive symptoms, as a possible additive effect. Furthermore, RLS not only seems to precede onset of depressive symptoms, but because of overlap of symptoms, RLS also may lead to unfavorable overmedication: outpatients with RLS and depressive symptoms were twenty times more likely to be pre-treated with antidepressants, before being diagnosed as RLS. No gender-related sleep patterns could be observed.
Conclusions: Overall, the impact of RLS seems to be underestimated in community health care, and primary care physicians should be instructed to explore RLS. Moreover, applying objective sleep-EEG measurements, no gender-related gap could be observed.

P-51-014
REM-sleep increases transfer of executive knowledge after metacognitive learning

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Objectives: Sleep is crucial for memory consolidation and memory enhancement. Findings emphasize that both NREM-sleep and REM-sleep are important for specific memory consolidation; NREM-sleep rich sleep seems to particularly consolidate declarative memory; REM-sleep rich sleep seems to particularly consolidate non-declarative memory such as executive knowledge. However, the impact of sleep and sleep stages on transfer of executive knowledge is not known so far. Therefore, the present study aimed at exploring the impact of sleep on transfer of executive knowledge after metacognitive stimulation.
Methods: Ten female, young adults (mean age: 19.25) took part in the study. After an adaption night with sleep-EEG registration, the procedure was scheduled as follows: For the learning phase, participants learned to solve the Tower of Hanoi problem (ToH; three to five disks) with or without metacognitive stimulation; then, the second sleep-EEG registration followed. The post-sleep transfer phase consisted of a proximal (ToH with six disks) and two distal (Missionary and Cannibal problem; Katona's card problem) transfer tasks.
Results: For the learning tasks, metacognitive stimulation lead to an increased acquisition of executive knowledge: metacognitively stimulated participants needed less moves to solve the ToH compared to controls. For the transfer tasks, compared to controls, the metacognitive group solved the proximal transfer task in less moves and less time. Moreover, they improved their executive knowledge for the distal transfer tasks. With regard to sleep, compared to the control group, the metacognitive group displayed decreased Stage 4 and SWS, but highly increased REM-sleep.

Conclusions: Increased REM-sleep enhance transfer skills of complex executive knowledge after metacognitive skill acquisition ("knowing how") in young healthy women compared to age- and gender-matched controls. Most importantly, increased REM-sleep-dependent transfer effects were observed for proximal and distal transfer tasks, suggesting that increased REM-sleep may be involved in consolidating non-declarative executive knowledge.

P-51-015
The role and importance of nutrition in treatment of psychiatric diseases

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P-51-016
The use of neuropsychopharmacs in forensic patients and their self-esteem and self-perception of quality of life

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Objectives: Forensic psychiatric patients are mostly seriously ill, long-term hospitalized, socially retracted persons frequently having almost no life and reality outdoor the psychiatric hospital, i.e. persons out of society. Aim: Evaluation of the self-esteem and the self-perception of quality of life in forensic patients and some variables which influence it such as the type of the disease, treatment, the type of the crime and particularly used drugs, the duration of the treatment, social adoption within/outdoor of institution, psychiatric comorbidity etc.
Methods: This research included 50 patients treated on Department of Forensic Psychiatry of Psychiatric Hospital Rab, Croatia. They were mostly male gender, 20-60 years of age, suffering mostly of schizophrenia, many of them with psychiatric comorbidity. Basic methods of work was questionnaires Rosenberg's Self-esteem Scale and Short Form 36 Health Survey (SF-36) to access patients' self-esteem and self-perception of health i.e. quality of life, as well as evaluation of medical records and interviews. Main statistical analysis was made by correlations and regressive analyses.
Results: Preliminary results of this pilot study point on positive influence of good regulated therapy particularly biological one of psychiatric disease and balanced social contacts and integration; as well as negative influence of duration of the hospitalization and comorbidity on the subjects' self-esteem and perception of quality of life.
Conclusions: The nature of the illness, its treatment and particularly use of neuropsychopharmacs has an important influence to the self-esteem and self-perception of quality of life of the long-term socialy isolated patients.

P-51-017
The use of psychopharmacs in schizophrenic patients with and without committed criminal offence

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Objectives: It is well known that some shizophrenic persons could committ various kinds of criminal offences, and some others not. The reasons are complex and still not understanded enough. The main aim of this study was to establish if there were some differences in biological psychiatric treatment of schizophrenic patients with and without committed criminal act.
Methods: In 100 schizophrenic patients (both gender, 20-60 years of age) treated in last 5 years at Psychiatric Hospital Rab, Croatia, we evaluated complete therapy from the begining of their disease. A half of them were forensic patients, and a half were not. The evaluation was made retrospectively, by analysis of the data from the medical records of the patients.
Results: It was not found statistical differences between the type of used neuroleptics and the duration of the treatment between patients of control and tested group of examinees.
Conclusions: The answers of the questions: «Why do some schizophrenic persons committ a criminal act and some others do not?» and «Could we predict and control agression of some shizophrenic patients by using drugs?» are complex and we need to try to find them in integrative analysis of many factors.

P-51-018
"Oh, Baby, please don't cry!" Cortisol secretion in infants suffering from infantile colic is related to sleep, crying duration, and to family strain and depressive symptoms in mothers

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Objectives: Infantile colic (IC) affects 8 – 40% of infants, and causes distress both to the child and to parents. Generally, a lack of etiology and consensus of treatment is observed. Moreover, nothing is known about the neuroendocrine activity and sleep in infants suffering from infantile colic, as well as the impact of infants' suffering on family strain and mother's psychological functioning.
Methods: A total of 16 infants (mean age: 8 weeks; range: 2-12 weeks) were prospectively enrolled in the study. First, all infants underwent a thorough medical check, and IC was diagnosed. Afterwards, salivary cortisol was assessed in the morning. Moreover, mothers completed a series of questionnaires regarding the infant's crying and sleeping patterns, as well as regarding their own psychological functioning and sleep. Infants' sleep was assessed with actimeters. Then, mothers received medical and psychological counseling. After four weeks, infants and mothers were assessed once again.
Results: For infants, morning cortisol secretion was related to the daily duration of crying (r= .74**) and to the sleep duration (r= -.60*), both at the beginning and at the end of the study. Moreover, increased cortisol secretion at the beginning of the study was related to increased depressive symptoms and to deteriorated sleep in mothers (r's > .55*) and to increased family strain (r = .56*). At the end of the study, even if crying intensity and crying intensity may have decreased, mother's psychological functioning and sleep remained affected.
Conclusions: Infantile colic causes distress both to the infant and to the family system. Moreover, in infants, sleep patterns and cortisol secretion were related, an association observed so far only in preschoolers or adults. Then, the pattern of results suggests an early intervention to protect mothers for developing depressive symptoms and severe sleep complaints.

P-51-019
Children suffering from separation anxiety disorders (SAD) show increased HPA axis activity compared to healthy controls

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Objectives: The peak onset for many psychiatric disorders is adolescence, a time of remarkable physical and behavioural changes, but evidence for the beginning of psychiatric disorders already in childhood is given for ADHD, phobias, anxiety, and separation anxiety. With regard to separation anxiety disorders (SAD), little is known about the interplay between SAD and the neuroendocrine functioning. Therefore, the present study aimed at investigating the association between SAD and HPA-axis-activity in children suffering from separation anxiety compared to healthy controls.
Methods: A total of 31 children with diagnosed SAD (mean age: 8.45; 17 females, 14 males) and 25 healthy controls (HC; mean age: 9.74; 12 females, 13 males) took part in the study. All participants underwent several psychological and physiological tests lasting about two hours in the afternoon. Six saliva samples to assess HPA-axis-related cortisol secretion were gathered in parallel.

Results: Compared to healthy controls, children with SAD showed a highly increased HPA-axis-activity, as reflected by an increased cortisol secretion (always in nmol/l): AUC basal: SA: 1117.55, HC: 262.74; w(30.58) = 2.87, p = .007; AUC total: SA: 1390.85, HC: 180.14; w(30.10) = 2.93, p = .006; AUC netto: SA: 273.30, HC: -82.59; w(30.51) = 1.96, p = .06.
Conclusions: Separation anxiety disorders in children are reflected by highly increased HPA axis activity. Most importantly, compared to healthy controls, children with SAD showed increased basal cortisol values already at the beginning of and throughout the entire investigation. We hold that children suffering from SAD seem to be continuously under psychophysiological tension, which may lead to strain for social and academic performance.

P-51-020
Experience in long-term meditation reduces the hypothalamic-pituitary-adrenocortical (HPA) axis activity

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Objectives: There is an increasing effort in research to uncover the underlying changes in biological processes that are associated with reported changes in mental and physical health in response to meditation. Moreover, there is evidence that meditation decreases anxiety and increases positive affect. However, the impact of short- and long-term meditation on the HPA axis activity has been poorly investigated so far. To investigate the HPA axis activity is particularly important because aberrant cortisol secretion is associated with depressive disorders. The aim of the pilot study was to associate the HPA axis activity-dependent cortisol secretion with the duration of meditation in people with long-term expertise, and to compare patterns of cortisol secretion before and after training of novices in meditation.
Methods: Eighteen people took part in the study. Nine of them (age (years): M = 49.8, SD = 7.50) had long-term expertise in meditation (duration (months): M = 264; SD = 95.5), and nine were novices (age: M = 40.2, SD = 11.44). Saliva samples to analyze cortisol secretion were gathered before and after the first and the last training session of an 8 week behavioral intervention termed Mindfulness Based Stress Reduction (MBSR) which includes daily meditation practice.
Results: In people with long-term expertise, duration of meditation highly correlated with decreased cortisol secretion before (r = -.69, p = .04; controlling for age: r = -.72, p = .045) and after training (r = -.74, p = .02; controlling for age: r = -.68, p = .06). In novices, no statistically significant differences in mean cortisol secretions before and after the intervention could be observed, although there was a general decrease.
Conclusions: Results suggest that long-term experience in meditation has a favorable impact on the HPA axis activity. This result may in part explain why MBSR has a favorable impact on depressive symptoms.

P-51-021
Long-term treatment of Restless Legs syndrome does not improve satisfaction with life and sleep compared to healthy controls

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Objectives: Amongst the variety of disorders affecting sleep, the Restless Legs Syndrome (RLS) demands particular attention, because of its high clinical overlap with depressive symptoms. In RLS, sleep is considered to be disrupted "mechanically"; that is to say, sensorimotor activity leads to repeated physical arousal and awakenings. Typically, patients suffering from RLS complain about sleepiness, daytime fatigue, loss of interest, and low satisfaction with life. However, little is known about the long-term treatment outcome of patients suffering from RLS.
Methods: Of 63 patients with diagnosed RLS, 38 (60%) could be followed-up after 34 months. An age- and gender-matched control group (HC: healthy controls) was recruited in parallel. Participants completed a series of questionnaires related to sleep, satisfaction with life, and psychological functioning. Moreover, they completed a daily sleep-log for seven consecutive days and nights.
Results: First, results of patients with RLS did not differ with respect to age, gender, duration of disorder, and medication. Second, compared to HC, patients with RLS showed highly increased depressive symptoms, social withdrawal, and low perceived social support. Moreover, those patients with both diagnosed RLS and depressive symptoms showed higher scores of external locus of control and rumination, compared to HC and to patients with RLS. With respect to sleep, again compared to HC, patients with RLS reported a prolonged sleep onset latency, an increased sleep fragmentation, and affected mood and sleep quality.
Conclusions: Results suggest that irrespective of age, gender, medication, and duration of treatment, compared to healthy controls, patients with RLS complain both about unfavourable satisfaction with life and psychological functioning, and sleep even 34 months after onset of treatment. Thus, results may evidence the need to treat patients with RLS both with medication and psychotherapy.

P-51-022
Anxiety and aggression – contradiction or transmission and reciprocity? Personal and family level

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Objectives: This study explores the phenomenon of violence in the three generations of families of depressive, panic, generalized anxious and paranoid subjects. We investigated transgenerational patterns of violence and mental disorders in the form of the phenomenon of suicide, homicide and alcoholism. Consideration of dynamics of anxiety and aggression it has through temperament dimensions, particularly in relation to the traits as is multimer trait HA (Harm Avoidance) and trait Impulsivity (Multimer trait Novelty Seeking). Sample makes 160 subjects who were divided into two groups – experimental and Control.
Methods: Method is comparative. Instruments: Standardized family-psychiatric interview, genogram and genogramic interview,TCI. Statistical analysis: The results of investigation we measured with the central tendency –arithmetic mean and with measure variability of the sample-standard deviation. The statistical significance of differences we counted with unifactorial analysis of variance Fisher's linear discriminative function and with logistic regression. We also used factors analysis of data.
Results: This research shows high prevalence of violence in primary families of all four psychopathological groups. High percentage of committed suicides appears in the families of depressive, panic, and paranoid subjects. Homicides occur in the group where is the highest percentage of suicide –family of paranoid subjects. In group of generalized anxious no suicide or homicide but in this group is the highest percentage of alcoholism. This transentithetic appearance of auto and heteroaggression we considered as a problem of impulse control High prevalence of this trait of temperament with low cooperativeness which is distributed in all four groups indicate personality disorders with high probability. Details will be discussed in the paper.
Conclusions: Violence, anxiety and aggression are related categories, and they are multifactorial caused. Their expression is connected with influence of family transmission patterns, biological substrate of personality that epigenetic mechanisms gets specific phenotypic expression. This biopsychosocial connection is argued with distribution of personality disorders in experimental group.

Satellite Symposia

SA-01
Treating depression – from neurobiology to clinical practice

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SA-01-001
The serotonergic system: the link to therapeutic efficacy?

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Abstract: The monoamine hypothesis proposes that depression is caused by a decrease in brain monoaminergic function. This hypothesis stimulated the development of most classes of antidepressants available today. While there have been important advances in the safety and tolerability of the second generation antidepressants, a substantial proportion of depressed patients do not respond adequately to such drugs. This implies that the monoamine hypothesis needs to be reassessed in the light of recent neuroscience research. Thus, it is now accepted that acute changes initiated by antidepressants (e.g., selective serotonin reuptake inhibitors, SSRIs) produce secondary neoplastic changes that initiate transcriptional and translational alterations in cellular plasticity. For example, the serotonin 5-HT1B receptor, that modulates presynaptic serotonin release, interacts with a calcium binding protein, p11. This protein is decreased in the cingulated cortex of depressed suicide victims. Effective treatment of depressed patients with SSRIs results in an increase in cortical p11 protein. This is now considered to be an important mechanism whereby the antidepressant-induced increase in serotonergic function initiates intracellular changes downstream from the serotonin receptor, thereby resulting in the antidepressant response. How such cellular changes are linked to the clinical efficacy of antidepressants is uncertain. However, from comparative studies of the efficacy of citalopram versus escitalopram, the presence of an allosteric binding site on the serotonin transporter appears to extend additional molecular potency that is reflected in the enhanced therapeutic efficacy of escitalopram. Perhaps this is not surprising as there is considerable clinical evidence that, in therapy resistant depression, drug combinations that enhance serotonergic function (for example, lithium + SSRIs) also increase the therapeutic response. In conclusion, despite the limitations of the monoamine hypothesis, it is evident that the serotonergic system plays an important role as a trigger for the cascade of intracellular events that improve the mood state of a depressed patient.

SA-01-002
Optimising pharmacological treatment of depression in elderly patients

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Abstract: If all forms of depression are included, the prevalence of depression is as high as 12-15% in people beyond 65 years of age. Depression in older people is often undertreated or not treated at all. A recent systematic review has shown that, though older people are as likely as their middle-aged counterparts to respond to acute treatment of their depression, they are significantly more likely to suffer relapse.(Mitchell & Subramaniam. Am J Psychiatry 2005;162:1588-1601) Reducing risk of relapse should, therefore, be a particularly important element of the management plan for older depressed patients. The guidelines for the management of late-life depression in primary care concluded that "both tricyclic antidepressants and some selective serotonin reuptake inhibitors (SSRIs) are efficacious in the prevention of relapse and recurrence over periods of 1-3 years".(Baldwin et al. Int J Geriatr Psychiatry 2003;18:829-838) The evidence base underlying this recommendation will be reviewed. Placebo-controlled clinical trials of relapse prevention have demonstrated conflicting results in elderly depressed patients. There are relatively few placebo-controlled trials of SSRIs in this context. Gorwood et al. (2007) have recently concluded that escitalopram was effective in preventing relapse of major depressive disorder in older patients and was well tolerated as continuation treatment.(Gorwood et al. Am J Geriatr Psychiatry 2007;15:581-593)

SA-01-003
Optimising treatment outcome – keeping the patient in focus

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Abstract: Epidemiological and clinical studies indicate that individuals with major depressive disorder are differentially affected by several 'stress-sensitive' medical disorders - notably circulatory disorders, obesity, and diabetes mellitus. Research vistas are attempting to elucidate directions of causality and mediators/moderators of this syndromal overlap. Individuals with mood disorders cluster traditional and emerging (e.g., immuno-inflammatory activation) risk factors that contribute to the increased likelihood of somatic health issues. Iatrogenic factors and insufficient access to primary, preventative, and integrated healthcare systems are also contributory. Medical comorbidity in individuals with major depression has important implications for affective illness classification, individualising treatment selection, and patient management. Unfortunately, most systems of healthcare delivery are not ideally configured to adequately detect, diagnose, treat, and manage medical comorbidity in the mood disorder population. Despite efforts to characterise and uncover pathoaetiological factors subserving comorbidity in major depressive disorder, the evidence base informing therapeutic decisions in the comorbid major depressive disorder patient remains woefully inadequate. This deficiency is in part the consequence of the routine exclusion of patients with major depressive disorder and comorbidity from pivotal randomised clinical trials for all phases of major depressive disorder. Despite intensified research efforts to unravel pathophysiological factors subserving medical comorbidity in the mood disorder population, somatic health issues are ubiquitous, under-recognised and suboptimally treated. Facile screening for risk factors and laboratory abnormalities, along with behavioural modification for reducing medical comorbidity, are warranted.

SA-02
Pharmacological intervention in slow-wave sleep (SWS): a novel approach to the management of insomnia?

supported by an unrestricted educational grant from Sanofi-Aventis.

SA-02-001
Neurochemical aspects of sleep regulation with specific focus on slow-wave sleep

P.H. Luppi
France

SA-02-002
Understanding slow-wave sleep through neuro-imaging

P. Maquet
Belgium

SA-02-003
Slow-wave sleep and the formation of memory

Jan Born
Lübeck, Germany

SA-02-004
Slow-wave sleep deficiency and enhancement: implications for insomnia and its management

D.J. Dijk
Guilford, United Kingdom

SA-03
Agomelatine: A new therapeutic option for depressed patients

supported by an unrestricted educational grant of Servier.

SA-03-001
Molecular mechanisms regulating the endogenous circadian clock

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Abstract: Daily cycles of physiology and behaviour, including cognitive function and mood, are co-ordinated by an intrinsic circadian pacemaker, the suprachiasmatic nuclei of the hypothalamus (SCN), first identified in the 1970s. Molecular genetic studies, first in fruit flies in the 1980s and then in mammals in the 1990s have shown that the circadian timing mechanism of the SCN neuron consists of an auto-regulatory, transcriptional/ post-translational negative feedback loop. The cycle is initiated when the transcription factors Clock and Bmal1 stimulate expression of the Period and Cryptochrome genes. After several hours the accumulation of Per and Cry proteins suppresses this activation. The cycle can only start again once Per and Cry proteins are degraded from the nucleus. Recent studies have shown how the period of the circadian clock is determined, therefore, by factors that set the rates of synthesis and degradation of Per and Cry proteins, as evidenced by several heritable sleep disorders in humans. A critical observation of recent times is that this molecular oscillator is also present in neurons across the brain and in peripheral tissues. Circadian co-ordination relies, therefore, upon a spatially and temporally complex system of inter-cellular and inter-tissue signalling. Perturbation of this internal synchrony, as seen in rotational shift work, is associated with pronounced mood and metabolic disorders. Moreover, disturbances of the circadian sleep/ wake cycle are the principal cause for institutionalisation in neurodegenerative diseases. This new understanding of the molecular genetic and cellular bases to circadian pacemaking therefore provides an opportunity to revisit the mechanistic basis of longstanding but unresolved observations regarding the interplay between mood and cognitive disorders, sleep and circadian function. Moreover, knowledge of the clock's genetics and biochemistry now support the rational development of therapies to address these disorders by managing circadian structure.

SA-03-002
A pharmacological breakthrough in the treatment of depression: the melatonergic approach

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Abstract: Despite extensive investigations, the exact processes leading to depression and the mechanisms responsible for the therapeutic effects of antidepressants are not fully understood. Selective inhibitors of serotonin reuptake (SSRIs) or norepinephrine reuptake (NRIs) or of both processes (SNRIs), extensively used as effective antidepressants since 25 years, are still endowed with major limitations because of the delay before the response, and because of the high percentage of insufficient improvement. Furthermore, these antidepressants produce side effects leading patients to drop out of treatment. Rather than continuing efforts within the « monoaminergic hypothesis », another direction had therefore to be taken to make a real breakthrough in the treatment of depression. Special attention was devoted to the fact that depression is most often characterized by disturbed circadian rhythms, suggesting that the human circadian system is a key player in the etiology and the treatment of depression. This led to the synthesis of agomelatine, the first melatonergic antidepressant, with agonist properties at cloned human melatonergic MT1 and MT2 receptors and antagonist properties at 5-HT2C receptors, but devoid of impact on monoamine uptake and extracellular levels of serotonin. Studies in rodents showed the ability of agomelatine to re-synchronize circadian rhythms such as locomotor activity or body temperature, under free-running conditions or after abrupt phase shift of light-dark cycle. Moreover, agomelatine exhibited potent antidepressant-like effects in several validated animal models of depression, including the forced-swimming test, the learned helplessness model, the chronic-mild stress paradigm, the genetic model of helpless mice. Several studies suggested that the robust antidepressant action of agomelatine involves synergistic effects at its three targets, MT1, MT2 and 5-HT2C receptors. The unique pharmacological profile of agomelatine explains both its antidepressant efficacy not only in these models but also in patients with major depressive disorders and its good tolerability, as shown by several clinical trials.

SA-03-003
Agomelatine: Evidence-based antidepressant efficacy

Pierre-Marie Llorca
France

Abstract: The innovative first melatonergic antidepressant agomelatine is a potent agonist at MT1 and MT2 melatonergic receptors and an antagonist at 5-HT2C receptors, differing therefore from existing antidepressants. Several clinical studies versus placebo and comparators, in the short and long term, have demonstrated its efficacy and safety for the treatment of major depressive disorders: - Pooled data from 3 short-term, placebo-controlled studies confirmed the antidepressant efficacy of agomelatine in the total population (HAM-D total score and core symptoms) as well as in the most severe patients. - After 1 week, agomelatine improved better than venlafaxine the getting to sleep and quality of sleep, daytime alertness and feeling good. This translated in improved antidepressant efficacy when using the CGI scale - At week 2 the responder rate was significantly greater with agomelatine than with sertraline (20.0% versus 10.9%, respectively; P = 0.027). After 6 weeks of treatment, agomelatine decreased significantly more than sertraline the HAM-D total score from baseline (P=0.031) and the anxiety symptoms in depressed patients (P=0.016). These data confirm the antidepressant efficacy of agomelatine in relieving depressive symptoms, representing therefore a very reasonable option for all depressed patients.

SA-03-004
Management of depression with agomelatine

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Abstract: Agomelatine is an innovative therapeutic agent agonist at melatonergic MT1 and MT2 receptors and antagonist at 5-HT2C receptors. The efficacy of agomelatine in treating major depressive disorder (MDD) in both the acute and maintenance phases of treatment was assessed using the data of three long-term studies. A 6-week, randomized, double-blind study comparing agomelatine (25-50 mg/d) and venlafaxine (75-150 mg/d), followed by a treatment extension period of 18 weeks; a second study versus sertraline (50-100 mg/d) with the same design and finally, a 10-month trial assessing the prevention of relapse versus placebo. As soon as week 1, agomelatine improved daytime alertness, feeling good, getting to sleep, and quality of sleep. CGI-I scores were significantly more improved with agomelatine than with venlafaxine as was the rate of responders. The comparison with sertraline showed a superiority of agomelatine in the rest/activity cycle at week 1 and in the responder rate at week 2. After 6 weeks of treatment, the significant differences in favor of agomelatine versus venlafaxine (CGI-I) and the superiority to sertraline (HAM-D CGI-I and CGI-S total scores) were maintained. After 6 months, agomelatine resulted in superior global improvement as defined by the CGI-I when compared with venlafaxine and HAM-D responders when compared with sertraline. Agomelatine reduced the risk of relapse by 56.3% compared with placebo (P<0.0001), after 6 and 10 months of treatment. Altogether, these results show that agomelatine provides fast and sustained relief of depression and is therefore efficacious in the management of MDD in both the acute and maintenance phases of treatment.

SA-04
Shedding light on the signal of darkness: Melatonin in sleep and CNS disorders

supported by an unrestricted educational grant from H. Lundbeck A/S.

SA-04-001
Melatonin as a timekeeper

Anna Wirz-Justice
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Abstract: The duration of the endogenous melatonin surge acts as a clock (biological night), and also as a calendar (seasons). Exogenous melatonin functions as a zeitgeber and has direct soporific effects through thermoregulation

SA-04-002
Melatonin rhythm in CNS disorders

Dieter Kunz
Germany

Abstract: There are several CNS disorders that have characteristic changes in the melatonin rhythm, such as ADHD, Alzheimer's disease, and Parkinson's disease. This may be due to a neurodegenerative dysfunction that also affects the Circadian Timing System, evidence suggests that this may account for the sleep/wake disturbances often encountered in these disorders.

SA-04-003
Melatonin, sleep and the elderly

Raymond Cluydts
Belgium

Abstract: Melatonin tends to decline with age, and elderly patients with insomnia have even lower levels of melatonin than healthy age-matched controls. This may reflect a general dysfunction of the Circadian Timing System, whereby normal zeitgebers are inadequate to regulate the CTS. However, as external melatonin acts as a strong zeitgeber, regulating many other components of the CTS, this may explain the effect of melatonin in insomnia. Circadin® is a prescription-only melatonin, with a prolonged-release formulation that mimics the natural melatonin signal. Circadin® has been shown in controlled clinical trials to be efficacious in treating insomnia in the over-55's.

SA-05
Long term treatment in schizophrenia – strategies to help maximise individual patient outcomes

Satellite Symposium sponsored by Eli Lilly and Company.

SA-05-001
A decade of experience with oral atypical antipsychotics

John Davis
University of Illinois, at Chicago, USA

Abstract: Whilst controversy remains around which therapies are most effective in a disease with such diverse presentations, there has been a renaissance in the pharmacological treatment of schizophrenia especially in the last decade. Many studies lead to perhaps a better understanding of appropriate treatment paradigms. Although it was hypothesized that the greater tolerability of atypical antipsychotics might improve adherence as compared with that for typical oral antipsychotics, approximately 40% of patients with schizophrenia are poorly adherent, with nonadherence tending to increase over time. Reviewing the history of antipsychotic medications, for both oral and depot formulations can generate significant knowledge about what may be the optimal long-term treatment regimen for treatment of schizophrenia.

SA-05-002
Current barriers to successful patient outcomes: Is change possible?

Joseph Peuskens
University Psychiatric Centre, Katholieke Universiteit Leuven, Belgium

Abstract: Patient adherence especially in the long term treatment of schizophrenia remains a clinical challenge. Schizophrenia remains one of the most debilitating and devastating psychiatric conditions, with concomitantly high rates of morbidity and mortality. This symposium will review studies with a focus on first episode schizophrenia all the way through to chronicity. Discussion of the therapeutic advantages of psychotropic medications but particularly the atypical antipsychotics in the long term management of schizophrenia.

SA-05-003
Can novel atypical depots make a difference?

Luis San
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Abstract: Schizophrenia is a serious chronic illness that requires lifelong medications. Since the development of first-generation antipsychotic long-acting depot treatments in the 1960s, their advantages in the relapse prevention of schizophrenia have been demonstrated in several studies yielding both diminished rates and reduced durations of rehospitalisation. Depot antipsychotics may help patients adhere to treatment because they are administered by injection every two to four weeks, thus eliminating the need for daily dosing. Although the delivery system itself does not prevent nonadherence, it gives healthcare providers an opportunity to readily identify nonadherence and thereby provide early and effective follow-up efforts. As a result, treatment guidelines for schizophrenia recommend clinicians strongly consider depot medication for patients who may be nonadherent to antipsychotic treatment regimens. Newly developed is an intramuscular depot formulation of olanzapine, the oral form of which was commercialised in 1996. Olanzapine long-acting injection has been demonstrated to be efficacious in symptomatic patients and also in the maintenance of antipsychotic response without the need for additional oral antipsychotic supplementation. It can be administered at 2- or 4-week dosing intervals, and does not need to be refrigerated. The safety profile is similar to oral olanzapine. Additional risks of olanzapine long-acting injection include injection site adverse events and the possibility of post injection syndrome events. This post injection syndrome has been noted in association with 0.07% of injections (approximately 1.4% of patients) in clinical trials and usually starts approximately 60 minutes after injection. Most patients experiencing a post injection syndrome event have developed symptoms of sedation and/or delirium. All patients have fully recovered from post injection syndrome events with no lingering or apparent permanent sequelae, and the time to recovery has ranged from 1.5 to 72 hours. Because of the risk of post injection syndrome events, an observation period and additional precautions are necessary. Treatment with olanzapine long-acting injection appears efficacious in symptomatic patients and also in the maintenance of response, at 2- or 4-week dosing options, without the need for routine oral antipsychotic supplementation.

SA-06
Improving health, cognition and response in schizophrenia

supported by an unrestricted educational grant from H. Lundbeck A/S.

SA-06-001
Strategies for improving cognition in schizophrenia

Philip D. Harvey
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Abstract: Cognitive dysfunction is a central feature of schizophrenia, present in the majority of patients, preceding the onset of other symptoms, and persisting after other symptoms have been treated. Multiple cognitive domains are affected, with the greatest deficits in processing speed, working memory, executive functioning, and episodic memory. Despite the importance of cognitive dysfunction in schizophrenia, there are no current pharmacological treatments for this condition. Conventional antipsychotics have minimal benefits for cognition and even second-generation antipsychotics (SGAs) have had inconsistent results to date. One of the major neurochemical candidates for causal influence on cognitive impairments is the NMDA system. In an animal model for cognitive impairment in schizophrenia, the NMDA antagonist, PCP, induced impaired performance in rats. Subsequent treatment with sertindole reversed this deficit; risperidone, olanzapine and clozapine induced a weak/non-significant reversal, while haloperidol demonstrated no effect.(Rodefer et al., 2005) In human studies, the beneficial effects over conventional antipsychotics shown by sertindole were not due to lower occurrence of EPS, and were especially marked in the parameters of working memory and perseveration.(Gallhofer et al., 2007) There is some evidence that certain subsets of people with schizophrenia have greater improvements in cognitive performance and indicators of disability with SGA treatment; these include patients who are clinically responsive and adherent to treatment. The need for adjunctive treatment specifically targeting cognitive dysfunction is gaining acceptance. Pharmacological strategies and cognitive remediation have both been applied. Cognitive remediation efforts have lead to substantial effects on real-world outcomes, with people with schizophrenia improving more than 10-fold in their income after receiving cognitive remediation compared to comparison subjects.(McGurk et al., 2005) This effect has proven durable at 36-month follow-ups,(McGurk et al., 2007) suggesting that cognitive enhancement can have a marked benefit on real-world outcomes.

SA-06-002
Long-term health considerations when using antipsychotics

Marc De Hert
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Abstract: Patients with schizophrenia present a greater vulnerability to co-morbid physical diseases than the general population.(Casey 2005; Marder et al., 2004) A number of these co-morbidities may be due to the lifestyle of patients with schizophrenia, and are, therefore, potentially preventable. Bad diet, low physical activity levels, and smoking compound the risk of various disease states such as type II diabetes mellitus, metabolic syndrome, and cardiovascular disease. A recent European Physical Health Survey in schizophrenia showed that 84% of psychiatrists were concerned about the physical health of their patients.(Saravane et al., 2007) It is likely that certain characteristics of schizophrenia, particularly the negative symptoms, the sedative effects of some medications, as well as socioeconomic status will affect patients' general motivation to prepare meals properly and exercise. To some extent, physical co-morbidities may be attributable to antipsychotic treatment. Metabolic variables are not consistently studied in schizophrenia studies, despite the historical association. The Sertindole Cohort Prospective (SCoP) study protocol was amended to include metabolic assessments in a small subset of patients. Treatment with either sertindole or risperidone did not appear to be associated with an increased risk of developing metabolic syndrome. The metabolic effects of sertindole and risperidone were broadly similar - neither was associated with clinically relevant changes in blood pressure, triglycerides, total cholesterol, HDL-cholesterol, LDL-cholesterol, or plasma glucose. Monitoring of physical health throughout treatment is core to a holistic approach to therapy in schizophrenia. Guidelines from the American Psychiatric Association recommend that metabolic screening should be more frequent during the first 6 months of treatment given the potential reversibility of metabolic complications with early withdrawal and a switch to an atypical antipsychotic with a safer metabolic profile.(De Hert et al, 2006) If ignored, poor physical health may prompt medication non-adherence, which could eventually adversely affect the patient's mental health.(Weiden & Buckley, 2007)

SA-06-003
Implications of early response & non-response in schizophrenia

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Abstract: A central question in any treatment is: how fast does it act? This is of obvious interest to the patient and doctor; furthermore speed of onset is critical for the design of optimal clinical algorithms and for understanding the mechanism of action of antipsychotic medications. For decades, it was held that the onset of action for antipsychotic drugs was delayed, and that any early response represented nonspecific behavioural effects.(Kapur et al., 2005) Schizophrenia guidelines are based on these hypotheses, and recommend waiting several weeks before implementing major changes in treatment.(Leucht et al., 2007) Recent data suggest that the onset of antipsychotic action is early, within the first week, even the first day, the effect is distinguishable from sedation, specific to antipsychotic drugs, and seen with typical and atypical antipsychotics, and with oral and parenteral preparations.(Agid et al., 2006; Kapur et al., 2005) What does this mean for individual treatment? Individual decisions require not just statistical associations, but, predictive power. It has now been convincingly shown that lack of an early response (i.e., early non-response) reliably predicts long-term non-response with the same medication in patients with schizophrenia. The majority (80%) of non-responders by 3 months were correctly classified as early non-responders at 2 weeks (high specificity), and 84% of early non-responders at 2 weeks were subsequent non-responders by 3 months (high negative predictive value).(Kinon et al., 2008) Early non-responders attained less symptom improvement, were more likely to discontinue treatment, and incurred higher healthcare costs.(Ascher-Svanum et al., 2008; Kinon et al., 2008) Identification of early non-responders may minimise prolonged exposure to suboptimal treatment strategies.(Ascher-Svanum et al., 2008) Evaluating patients as early as 2 weeks may help identify non-responders who may benefit from an alternative therapeutic approach.(Kinon et al., 2008) These data represent the first systematic exploration of 'early response' and its implications.

SA-07
Bipolar Disorder: New Approaches and New Priorities

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SA-07-001
Acute Treatment of Bipolar Disorder

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Bipolar disorder is a devastating psychiatric illness with a highly variable course characterized by manic, depressive, or mixed episodes. When treating acute manic or mixed episodes, the goal is to alleviate symptoms (eg, aggression, agitation, psychosis, poor judgment, and social or occupational dysfunction), permitting a return to acceptable psychosocial functioning while simultaneously ensuring the safety of the patient and others. The choice of treatment is influenced by numerous factors, including characteristics of the manic episode, the need for rapid resolution, the presence of rapid cycling or psychotic symptoms, the patient's medication history, and the presence of comorbidities, as well the patient's willingness to accept therapy. There are several drug classes with proven efficacy in acute mania, including mood stabilizers (eg, lithium, valproate, carbamazepine), typical antipsychotics (eg, haloperidol, chlorpromazine), and atypical antipsychotics (eg, quetiapine, olanzapine, risperidone, ziprasidone, aripiprazole). Although many drugs have been studied as monotherapy, in the naturalistic setting, the majority of patients are treated with combination therapy, often with adjunctive benzodiazepines for anxiety. Lithium demonstrates at least moderate improvement in 2 to 3 weeks in 40-80% of patients but is more effective in classic mania, with poor response rates in patients with mixed states or rapid cycling. Lithium is poorly tolerated, especially at higher doses, and does not have a quick onset of action. Unlike lithium, valproate has a rapid onset of action (within 1 week) and is effective in treating mixed episodes, but it may induce weight gain. Typical antipsychotics have rapid-onset antimanic properties but are limited by extrapyramidal symptoms (EPS) and tardive dyskinesia and the propensity to induce depression. Atypical antipsychotics have been extensively studied in mania, as monotherapy and as adjunctive medications with mood stabilizers, with evidence for efficacy in mixed states, rapid cycling, and psychotic features. EPS is less common with atypical antipsychotics, but some have increased levels of somnolence and metabolic disturbances. The clinician-patient therapeutic alliance must take into account the risk-benefit ratio when choosing an agent that is efficacious, safe, and well tolerated. The treatment of bipolar disorder requires an integrative management approach, which must consider urgent and acute issues while maintaining a long-term perspective for functional outcome.

SA-07-002
New Priorities in the Treatment of Bipolar Disorder: Management of Depression

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Bipolar disorder is a biphasic, chronic disorder that includes symptoms of mania, depression, and often anxiety. For the majority of patients with bipolar disorder, depressive episodes represent the most debilitating and difficult-to-treat dimension of the illness. Furthermore, patients spend significantly more time in this phase than in the manic or hypomanic phase and attempt suicide more frequently around this illness phase. Yet, the availability of effective treatments remains limited. Lithium is the cornerstone of treatment for bipolar depression and may be associated with an anti-suicide effect independent of symptom relief. However, lithium has been associated with lower response rates in naturalistic studies and may be of less benefit to patients with rapid cycling or comorbidities. Second-generation antiepileptic drugs (AEDs) (ie, divalproex, carbamazepine) have modest antidepressant efficacy, whereas the third-generation AED lamotrigine is effective for the prophylactic treatment of bipolar depression. Importantly, lamotrigine is not known to be associated with the weight gain and somnolence inherent with some second-generation AEDs. The second-generation antipsychotics, quetiapine and the combination of olanzapine/fluoxetine, are the only antipsychotics so far that have shown benefit in large, randomized, controlled clinical trials for the treatment of bipolar depression.

Several atypical antipsychotics are associated with clinically significant weight gain and new-onset metabolic syndrome. This is important, as treatment-induced comorbidities can exacerbate existing conditions such as cardiovascular disease and may increase suicidality, which are significant hazards in this patient population. The use of antidepressants is controversial and can induce manic episodes or rapid cycling and exacerbate suicidality in susceptible patients. Although pharmacotherapy forms the cornerstone of management, treatments such as psychotherapy, which emphasize cognitive and interpersonal coping strategies, have stronger effects on depression. The incorporation of psychotherapy into chronic care algorithms is necessary for the optimal management of patients with bipolar depression. The availability of more effective therapeutics for managing depressive episodes arguably remains the greatest unmet need in bipolar disorder.

SA-07-003
Long-term Maintenance: Achieving the Optimal Response

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Although patients with bipolar disorder may experience a resolution of symptoms with acute treatment, many will continue to experience impaired functioning because of the episodic, chronic, and progressive nature of the illness. Maintenance therapy is needed for a variety of reasons, including preventing relapse, reducing sub-threshold symptoms, decreasing the risk of suicide, and reducing the frequency of rapid cycling and mood instability. Although long-term therapy is usually required to maintain or improve functioning and quality of life, it has been a significant challenge to identify clinically effective treatments for long-term management. Few available, well-tolerated treatment options are effective in all phases of bipolar disorder and prevent the recurrence of manic and/or depressive episodes. Mood stabilizers such as lithium remain the cornerstone of maintenance therapy for bipolar disorder, but lamotrigine also has been shown to be effective in the long-term prevention of depressive episodes. Additionally, monotherapy and adjunctive therapy with atypical antipsychotic drugs have shown efficacy in the maintenance of recovery. For example, olanzapine monotherapy has positive long-term data, and quetiapine in combination with lithium or divalproex has been shown to be more effective than lithium or divalproex alone in delaying the time to recurrence of mania and depression. Recently, ziprasidone demonstrated efficacy for the long-term maintenance treatment of bipolar mania. Ziprasidone in combination with lithium or divalproex was more effective than either lithium or divalproex alone in time to intervention for a mood episode. Monotherapy with aripiprazole was found to be effective in preventing relapse in patients previously stabilized on aripiprazole for 6 consecutive weeks. Moreover, long-acting injectable risperidone increased the time to relapse in highly recurring bipolar patients. Adverse effects of medications for bipolar disorder, such as weight gain and metabolic abnormalities associated with some atypical antipsychotics and rash and other side effects associated with some mood stabilizers, may need to be considered when using these agents long-term. In addition to pharmacotherapy, the patient's history, symptomatology, and lifestyle factors are important to consider when designing and implementing a long-term treatment plan. For these reasons, psychoeducation has emerged as a crucial tool in the long-term management of bipolar disorder.

SA-07-004
Controversies Surrounding Bipolar Disorder

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In the treatment of bipolar disorder, clinicians and patients are confronted with the task of choosing the appropriate pharmacotherapy, weighing sufficient efficacy against safety and tolerability, with remission as the treatment goal. In clinical practice, this task is often encumbered by other challenges, such as the presence of comorbid psychiatric and medical diseases, including, among others, the onset and severity of bipolar depression, the prevalence of substance abuse, and the presence of subsyndromal mood symptoms, all of which must be considered when making treatment decisions. Bipolar depression remains one of the most challenging conditions to accurately diagnose and effectively treat.
Although many effective drugs are available for the treatment of mania, treatment options for the depressive component are limited. The use of antidepressants is controversial, and the body of evidence suggests limited benefit; while their use may be effective in some individuals with bipolar disorder, they can precipitate treatment-emergent mania or rapid cycling and can exacerbate suicidality in susceptible patients. Substance abuse is often comorbid with bipolar depression. Comorbidities can complicate the initial diagnosis, change the bipolar course of illness, and affect the patient's response to treatment. In addition, in the presence of comorbid disease, the clinician may be faced with the difficult decision of when to begin treating symptoms of bipolar disorder in relation to symptoms of substance dependency. Subsyndromal symptoms are common during maintenance treatment for bipolar disorder and are associated with impaired function and quality of life. Subsyndromal symptoms are also clinically significant, as they are associated with relapse of the same polarity. Most patients experience symptoms before intervention, highlighting the need for more awareness and aggressive management of subsyndromal symptoms. Many challenges are associated with the treatment of bipolar disorder, but careful evaluation of various factors and open patient-physician communication may improve the overall treatment of this disorder and patients' outcomes.

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