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Neurodevelopmental Genomic Strategies in the Study of the Psychosis Spectrum

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Introduction

Precision medicine strives to provide customized health care that guides medical decisions and practices. Such an effort aims to tailor therapeutic interventions to an individual's characteristics and requires classifying individuals to subpopulations that differ in susceptibility to disease, underlying biology, prognosis, and response to treatment. The classification necessitates a scientific basis that builds on molecular biology technologies including genomics, proteomics, metabolomics, and transcriptomics. As knowledge accumulates, early identification of biomarkers of pathological processes associated with disease entities can lead to early intervention, which may ultimately result in prevention and better prognosis.

Complex brain disorders, such as schizophrenia spectrum disorders, pose special challenges including the heterogeneous clinical presentation, the impact on multiple cognitive and functional domains, the chronic course that requires a life-span perspective, and the lack of validated biomarkers. While these are major obstacles to aligning clinical neurosciences with a precision medicine approach, there has been a paradigm shift in research that is currently helping elucidate the underlying neurobiology of psychosis and building bridges essential for implementation of precision medicine (Insel & Cuthbert, 2015).

Recognizing that schizophrenia spectrum disorders are neurodevelopmental, a key focus has been on early signs of the emergence of psychosis and integration of clinical phenotypic measures with quantitative dimensional neurocognitive and neuroimaging parameters. Such efforts evaluate the presence of abnormalities before the emergence of psychosis that meets current diagnostic criteria, attempting to determine convergent brain-behavior aberrations indicative of progression of psychosis. Early identification with reliable measures can lead to early intervention that can help bend the developmental trajectory of youths at risk for psychosis and, hopefully, bring it closer to that of typically developing young people. This early identification may provide vulnerable individuals with yardsticks to measure and tools to achieve milestones that are critical in transition to adulthood and independent functioning. This paradigm shift requires complementary studies of populations at an early age before symptoms reach diagnostic criteria, and it is therefore important to study individuals who are

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at high clinical or genetic risk for psychosis in order to maximize the potential clinical relevance of findings.

This chapter will highlight complementary approaches to the study of the emergence of psychosis. First, progress in research efforts that examine neurocognitive and neuroimaging measures in help-seeking individuals at clinical risk for psychosis will be summarized. Second, findings from a community-based large sample, the Philadelphia Neurodevelopmental Cohort (PNC), will be highlighted. Third, an informative neurogenetic approach from the study of 22q11.2 deletion syndrome, which is associated with about 25 % risk of psychosis in late adolescence and early adulthood, will be presented. To conclude, the integration of these lines of research will be considered in the context of progress in genomics and implications for treatment.

The Course of Psychosis

Psychosis is a process that commonly emerges in adolescence and early adulthood, a pivotal period in brain maturation characterized predominantly by axonal myelination and neuronal pruning (Giedd et al., 1996; Huttenlocher, de Courten, Garey, & Van Der Loos, 1982; Jernigan & Tallal, 1990; Yakovlev & Lecours, 1967). This is also a dynamic time of development with added environmental stress from social, academic, and vocational expectations “to grow up.” The interplay of biology and environment makes this developmental epoch a critical period requiring careful dimensional dissection of the multitude of factors affecting maturation.

The standard clinical diagnostic approach is based on a constellation of reported and observed symptoms, their duration, severity, and impact on functioning (American Psychiatric Association, 2013). Such a symptom-based classification system is unlikely to contribute to elucidating effects of neural developmental processes on behavior as they relate to the emergence of symptoms. Commonly, by the time of clinical presentation and when diagnostic criteria are met, the underlying process has likely been in evolution with associated decline in functioning. Therefore, it is paramount to shift our attention to earlier phases of psychosis.

Early presentation of psychosis includes subtle changes in several domains (Miller et al., 2003), which are often attributed to developmental transitions to adolescence and young adulthood. Thus, initial detection of psychotic symptoms can be challenging as observable behaviors can be interpreted by family, friends, and professionals as difficulties encountered by young people who need to cope with increased complexities in diverse settings. For example, decreased concentration or motivation and problems in school or work performance may be evident; decreased social engagement and less interest in previous activities may be attributed to low mood or depression. Anxiety, misperception, and suspiciousness are associated with increased guardedness, and the adolescent may avoid discussing such symptoms with the family or others. Thus, the core features of psychosis — delusions, hallucinations, and disorganized thinking—are present but concealed or in a mild subthreshold form. They may increase in frequency and severity causing distress and

impairment, or in some individuals they may stay at the subthreshold level or diminish and even abate (Fusar-Poli, Bonoldi, et al., 2012).

Figure 1 provides a schematic illustration of the evolution of psychosis. In the psychosis continuum, the clinical risk stage, or prodromal phase, has become incorporated into the DSM-5 (Section III—Emerging Measures and Models) as attenuated psychosis syndrome, indicating that further study is required to determine whether it should be included as a diagnostic category in future revisions (Fusar-Poli, Carpenter, Woods, & McGlashan, 2014; Tsuang et al., 2013). Multiple considerations guided the decision not to include the attenuated presentation as part of schizophrenia spectrum disorders in the DSM-5. These include the lack of certainty of progression to schizophrenia and the stigma associated with the diagnosis.

With the growing interest of characterization of the early stages of psychosis, the study of brain and behavior in schizophrenia has moved from investigation of chronically ill individuals to those with shorter illness duration, first episode (Andreasen et al., 2011; Gur, Cowell, et al., 2000; Ho, Mala, & Andreasen, 2004; Gur, Turetsky, et al., 2000) and now prodromal (Fusar-Poli, Bonoldi, et al., 2012; Giuliano et al., 2012). The focus on early subthreshold signs of psychosis, while challenging clinically, provides a unique opportunity to address potential confounding effects of multiple factors in brain-behavior research. Such factors, including psychoactive medications and limited functioning and social isolation, common in patients with long duration of illness, are less likely to be present or prominent as the psychotic process emerges. Furthermore, as noted above, symptoms emerge during a dynamic period of brain maturation resulting in a fluid clinical presentation requiring longitudinal studies. Advances and availability of tools to examine brain and behavior have stimulated the integration of such measures into the study of clinical risk.

Brain Behavior Endophenotypes in the Study of Psychosis

Neurocognition

Neurocognitive deficits are a hallmark of schizophrenia (Barch & Ceaser, 2012; Kahn & Keefe, 2013; Saykin et al., 1991), and various neuropsychological tests have been applied in schizophrenia research to gauge the presence, pattern, and extent of deficits that have also been used in clinical risk studies as psychosis emerges.

An extensive literature has documented the nature and extent of neurobehavioral deficits in schizophrenia (Gur, Braff, et al., 2015; Gur, March, et al., 2015; Heinrichs & Zakzanis, 1998; Kahn & Keefe, 2013; Saykin et al., 1991). Against a background of diffuse impairment, some neurocognitive domains related to executive control, episodic verbal memory, and social cognition have shown greater vulnerability (Gur & Gur, 2013). Notably, as studies shifted to first-episode patients with schizophrenia, including neuroleptic naïve participants, it became evident that the pattern of cognitive deficits that was observed in chronic patients with schizophrenia (Saykin et al., 1991) was present early in the disease (Saykin et al., 1994). This consistency supports the application of quantitative measures in clinical risk samples as potential vulnerability markers. Furthermore, when such endophenotypic measures (Gottesman & Gould, 2003) are administered to family members,

they demonstrate heritability and intermediate impairment compared to healthy participants with no family history of psychosis (Calkins et al., 2010; Greenwood et al., 2007, 2013; Gur, Braff, et al., 2015; Gur, Loughead, et al., 2007; Gur, March, et al., 2015; Gur, Nimgaonkar, et al., 2007). Thus, with established paradigms that documented the nature and extent of brain abnormalities in schizophrenia, a growing literature examined individuals at clinical high risk during the prodromal phase of illness. The goal of such efforts is to evaluate whether the predictability of the future course of psychosis can be enhanced with multimodal brain-behavior measures. The initial literature summarized below is based on help-seeking people who are at clinical risk for psychosis.

The rapidly growing literature on individuals at risk for psychosis (Dickson, Laurens, Cullen, & Hodgins, 2012), while different in sample sizes, rigor of reporting inclusion and exclusion criteria, and tests administered, affords quantitative meta-analyses that examine neurocognitive domains. In a meta-analysis of 14 studies, 1214 individuals at risk for psychosis were compared to 851 healthy controls (Giuliano et al., 2012). Small to medium effect sizes of neurocognitive impairment in the psychosis risk group were observed. Significant deficits were noted in general cognitive abilities, attention, working memory, episodic memory, language functions, and visuospatial abilities. The only domain that did not differ between the groups was motor skills. Seven of these studies conducted longitudinal follow-up demonstrating that participants in the psychosis risk group, who transitioned to psychosis at follow-up, had medium to large effect sizes of neurocognitive deficits at baseline compared to healthy participants, supporting the utility of neurocognitive assessment.

Another meta-analysis (Fusar-Poli, Deste, et al., 2012) included 19 studies with a sample of 1188 participants at clinical risk and 1029 healthy comparison participants. The clinical risk group manifested lower general intelligence, and deficits in several domains were observed: executive functions, attention, working memory, verbal fluency, verbal and spatial memory, and social cognition. Processing speed did not distinguish between the groups. Transition to psychosis was examined in a subset of seven longitudinal studies with 19 months mean follow-up duration (Becker et al., 2010; Brewer et al., 2005; Koutsouleris et al., 2012; Pukrop et al., 2007; Riecher-Rossler et al., 2009; Seidman et al., 2010; Woodberry et al., 2010). Findings indicated that individuals who transitioned to schizophrenia, compared to those who did not develop psychosis at follow-up, were more impaired at baseline. They had lower general intelligence and poorer performance in verbal fluency, verbal and visual memory, and working memory.

Most studies on clinical risk for psychosis have examined “cold” cognition, and relatively few have focused on social cognition. Impaired social functioning has long been evident in people with schizophrenia, including premorbidly. Systematic studies evaluating affective processes have been more limited. The development of measures that relate to the perception, interpretation, and response to display of emotions is a relatively recent addition to the range of neurobehavioral probes available to evaluate this capacity. The first meta-analysis summarized above (Giuliano et al., 2012) included three studies that examined social cognition. Deficits in emotion processing and “theory of mind” tasks were noted in the group at clinical risk (Addington, Penn, Woods, Addington, & Perkins, 2008; Chung,

Kang, Shin, Yoo, & Kwon, 2008; Pinkham, Penn, Perkins, Graham, & Siegel, 2007). In the second meta-analysis (Fusar-Poli, Deste, et al., 2012), data from six studies, some overlapping, with measures of the social cognition, were included (Addington et al., 2008; An et al., 2010; Chung et al., 2008; Green et al., 2012; Szily & Keri, 2009; van Rijn et al., 2011). Significant impairment in clinical risk participants compared to healthy controls was noted. This literature is growing (Kohler et al., 2014) indicating that the domain of social cognition is important in transitioning to schizophrenia and is related to level of functioning.

Neuroimaging

Extensive research using magnetic resonance imaging (MRI) has documented aberrations in brain structure and function in schizophrenia, already evident in first-episode patients (Andreasen et al., 2011; Fusar-Poli et al., 2012c; Gur, Cowell, et al., 2000; Gur, Turetsky, et al., 2000). With the shift to study earlier stages in the psychosis process, this technology has been applied to people at risk for psychosis, enabling examination of brain integrity as psychosis unfolds. Measures obtained include structural parameters such as gray matter and white matter volumes, cortical thickness and diffusion tensor imaging (DTI) measures of structural connectivity, as well as functional parameters including functional connectivity and activation in response to neurobehavioral tasks designed to probe a specific circuitry. The neuroimaging literature on clinical risk for psychosis is growing, although it is still relatively limited in size of samples examined and follow-up (Fusar-Poli, Bonoldi, et al., 2012). The largest body of studies has evaluated structural MRI focusing on gray matter volume (Brent et al., 2013).

A meta-analysis of 14 voxel-based morphometry studies, most using a 1.5 T scanner, compared psychosis risk and first-episode schizophrenia patients to healthy controls (Fusar-Poli et al., 2012c). The clinical risk group had lower gray matter volume in several regions including the right temporal, limbic, and prefrontal cortex, whereas the first-episode group had lower volumes in the temporal insular cortex and cerebellum. Notably, the onset of psychosis was associated with decreased gray matter volume in temporal, anterior cingulate, cerebellar, and insular regions. These regions are implicated in cognitive and emotion processing functions that are aberrant in schizophrenia, and volume reduction in these regions has likewise been reported in multiple studies of schizophrenia.

There are several points to consider when evaluating the finding highlighted above, such as methodological limitations involved in MRI meta-analytic approaches and the cross-sectional nature of most studies. Indeed, the majority of participants at clinical risk did not yet transition to psychosis. Nonetheless, it is informative that brain regions that show volume reduction in schizophrenia also show abnormalities in those at risk for psychosis (Fusar-Poli et al., 2012c). Larger samples in a longitudinal design will be important to advance the understanding of underlying neuro-anatomical differences between those who transition to psychosis and those who do not. Integration of clinical phenotypic data and neurocognitive parameters with the neuroimaging data is important for elucidation of brain-behavior relationships.

Other brain parameters have been evaluated in fewer studies. Thus, white matter abnormalities have been reported in schizophrenia, early in the course of illness, as well as in individuals at risk for psychosis (Carletti et al., 2012; Fusar-Poli et al., 2011).

The resting blood oxygenation level-dependent (BOLD) signal in functional magnetic resonance imaging (fMRI) paradigms provides a measure of connectivity, reflecting "cross-talk" integration among brain regions. It examines the time-series correlations among brain regions, indicating which regions show synchronized activation. Aberrations in schizophrenia in frontotemporal connectivity have been reported and have also been seen in those at clinical risk (Crossley et al., 2009). This literature is preliminary and limited.

DTI quantifies restricted water diffusivity in white matter, enabling noninvasive detection of subtle white matter abnormalities and facilitating the understanding of complex large-scale brain networks. Abnormalities in DTI have been reported in schizophrenia, both in chronic patients and in first-episode presentation (Peters & Karlsgodt, 2014; Roalf et al., 2013), with reduced white matter integrity in fronto-temporal tracts. The literature on psychosis risk is limited to several cross-sectional studies, with differing findings such as reduced fractional anisotropy in frontal lobe (Bloemen et al., 2010) and in the superior longitudinal fasciculus (Borgwardt, McGuire, & Fusar-Poli, 2011). In a longitudinal study (Carletti et al., 2012), individuals at risk for psychosis ($n = 32$) were compared to healthy controls ($n = 32$) and first-episode patients with schizophrenia ($n = 15$), on a 1.5 T scanner. The psychosis risk and control participants were re-scanned after 28 months. At baseline, the first-episode group had decreased fractional anisotropy and increased diffusivity relative to controls, and the psychosis risk group was intermediate between the other two groups. At follow-up, further reduction in fractional anisotropy was evident in left frontal region only in those psychosis risk individuals ($n = 8$) who transitioned to psychosis. This suggests that progressive changes occur at disease onset, which has been reported before for gray matter (Andreasen et al., 2011; Borgwardt et al., 2007; Gur, Cowell, et al., 2000; Gur, Turetsky, et al., 2000; Smieskova et al., 2010). Again, however, the available data are preliminary and large-scale studies are needed.

fMRI has been applied to individuals at risk for psychosis, commonly in small samples with neurobehavioral probes that have shown differences between schizophrenia patients and controls. Neurobehavioral domains examined include working memory, using the n-back paradigm. Overall, psychosis risk groups show decreased activation in the BOLD response in dorsolateral and medial prefrontal regions (Fusar-Poli et al., 2012c). The pattern of activity is similar to that seen early in the course of schizophrenia, but less pronounced abnormalities are observed. To evaluate activation changes with disease progression, longitudinal designs are necessary. Such designs have been applied in several fMRI studies (Smieskova et al., 2010). This small literature suggests that individuals who transition to psychosis differ from those who do not, with the latter group showing normalization. Thus, the application of fMRI holds promise as a tool that may facilitate identifying brain circuitry dysfunction that may underlie the psychotic process.

Community-Based Psychosis Spectrum Approach

The studies on clinical high risk highlighted above included help-seeking individuals who present to specialty research centers that focus on early identification and intervention. These efforts have been complemented by population-based studies of non-help-seeking individuals. Consistent with psychosis as a continuum process, the rate of transition to psychosis of non-help-seeking persons (Kaymaz et al., 2012) is lower than help-seeking people (Fusar-Poli et al., 2014).

Identification of at-risk individuals through a community-based sampling strategy has limitations including costs relative to a potentially low yield of clinically relevant subsamples. However, there are advantages when understanding the full continuum of the psychosis process is desired. Such studies are essential for addressing questions related to the presence of neurocognitive and neuroimaging parameters prior to help seeking and in longitudinal studies to examine both vulnerability and resilience. The PNC is a community-based sample of youths that include individuals with psychotic spectrum symptoms proportionate to their presence in the population. The PNC participants were evaluated both clinically and neurocognitively, and, in a subsample, neuroimaging parameters were obtained. Longitudinal studies of the PNC are underway. Here, we will present the overall approach and focus on data pertinent to the subsample with psychosis spectrum features.

The Philadelphia Neurodevelopmental Cohort

The PNC sample includes about 9500 youths (ages 8–21) enrolled in a collaborative project between the University of Pennsylvania and Children's Hospital of Philadelphia. Participants were previously genotyped and were recontacted for phenotypic assessment. Medical information was also available in electronic medical records. Sample ascertainment and assessment procedures have been detailed (Calkins et al., 2015). Briefly, participants and collaterals were administered a comprehensive computerized structured interview by trained interviewers that included psychopathology assessment of major domains (e.g., anxiety, mood, psychosis, and externalizing behaviors).

Psychosis Spectrum Features

The presence of psychotic experiences was evaluated by three screening tools that assess positive sub-psychosis, positive psychosis, and negative/disorganized symptoms (Calkins et al., 2014). Individuals evidencing any of those symptoms with frequency and associated distress impacting functioning were classified as "psychosis spectrum." Among the total sample of 7054 participants ages 11–21, 21.0 % (N = 1482) met psychosis spectrum criteria. For medically healthy participants (N = 4848), 3.7 % reported threshold psychotic symptoms consisting of delusions and/or hallucinations. An additional 12.3 % reported significant subthreshold psychotic positive symptoms, with odd/unusual thoughts and auditory perceptions, followed by reality confusion, being the most discriminating and widely endorsed attenuated symptoms. A minority of youths (2.3 %) endorsed subclinical negative/disorganized symptoms in the absence of positive symptoms. The high frequency of psychosis spectrum symptoms is consistent with findings from population-based studies

conducted in other countries (Kelleher et al., 2012; Schimmelmann, Walger, & Schultze-Lutter, 2013). Significant predictors of psychosis spectrum status include being male, younger, and non-European American ethnicity.

Neurocognition and Psychosis Spectrum

Neurocognitive assessment of PNC participants included a computerized neurocognitive battery (CNB), adapted from functional neuroimaging studies (Gur et al., 2010; see RC Gur chapter in this volume), yielding performance measures of accuracy and speed (response time) across domains (Gur et al., 2012). The 1-h CNB examines executive functions (abstraction and mental flexibility, attention, working memory), episodic memory (words, faces, shapes), complex cognition (verbal reasoning, nonverbal reasoning, spatial processing), social cognition (emotion identification, emotion intensity differentiation, age differentiation), and sensorimotor speed. Developmental and sex difference effects (Gur et al., 2012; Roalf, Gur et al., 2014) and factor structure (Moore, Reise, Gur, Hakonarson, & Gur, 2015) have been documented. A novel approach examined the prediction of chronological age based on performance and demonstrated that psychosis spectrum youth lag behind typically developing people and those with other forms of psychopathology (Gur, Calkins et al., 2014; Gur, Braff, et al., 2015; Gur, March, et al., 2015).

Comparing psychosis spectrum to non-spectrum youths, covering for age, ethnicity, and parental education, showed decrease performance accuracy across domains in the psychosis spectrum group. Performance speed was also reduced for several measures: for executive functions (abstraction and mental flexibility, working memory), for episodic memory (verbal), for complex cognition (language, spatial processing), for social cognition (emotion identification, emotion intensity differentiation), and for sensorimotor (both motor and sensorimotor). Thus, the pattern of deficits is similar but milder than that reported for schizophrenia and is similar to that observed in help-seeking clinical risk for schizophrenia individuals (Fig. 2).

Neuroimaging Measures in Psychosis Spectrum

A randomly selected subsample of about 1500 PNC participants underwent multimodal imaging acquired at the Department of Radiology at Penn Medicine on a single Siemens 3T scanner. The 1-h MRI protocol has been described (Satterthwaite, Elliott, et al., 2014). Briefly, the protocol was comprised of scans designed to obtain information on brain structure, perfusion, structural connectivity, resting state functional connectivity, and fMRI during the performance of working memory (fractal *n*-back) and emotion identification tasks. Neuroradiological reading (Gur et al., 2013) and quality assurance were rigorously obtained (Satterthwaite et al., 2013; Satterthwaite, Elliott, et al., 2014; Satterthwaite, Vandekar, et al., 2015; Satterthwaite, Wolf, et al., 2015). We first established the patterns of brain structure and function in relation to development and sex differences in healthy participants (Ingalhalikar, Smith et al., 2014; Satterthwaite, Shinohara, et al., 2014; Satterthwaite, Vandekar, et al., 2014, 2015; Satterthwaite, Wolf, et al., 2015) demonstrating the sensitivity of the brain parameters examined. We then began to apply the same approach to psychosis spectrum youths, and recent findings are highlighted.

The task selected for the fMRI study has been associated with deficits in patients with schizophrenia. A large literature has demonstrated executive deficits and failure to fully activate the executive system when engaged in a working memory task (Minzenberg, Laird, Thelen, Carter, & Glahn, 2009). Similarly, impairment in social cognition is well established in schizophrenia, and a growing literature consistently shows deficits in emotion processing (Kohler et al., 2014) and other measures associated with social cognition in schizophrenia and CHR (Allott et al., 2014; Amminger et al., 2012; Gur, Braff, et al., 2015; Gur, March, et al., 2015; Irani, Seligman, Kamath, Kohler, & Gur, 2012; Meyer et al., 2014; Walther et al., 2015). Functional neuroimaging studies in schizophrenia reported abnormalities in recruitment of fronto-limbic regions, including abnormal hyperactivation of amygdala in response to fear-related facial stimuli (Gur, Loughead, et al., 2007; Gur, Nimgaonkar, et al., 2007).

In the fMRI study, psychosis spectrum youths (n = 260) were compared to typically developing participants (n = 220). In the working memory n-back task, the psychosis spectrum group had lower activation than the comparison group throughout the executive control circuitry, including dorsolateral prefrontal cortex. Activation in the dorsolateral prefrontal cortex in the psychosis spectrum group correlated with cognitive deficits, but no correlation was found with positive symptom severity. During the emotion identification task, psychosis spectrum participants had increased activation compared to controls in response to threatening facial expressions in amygdala, left fusiform cortex, and right middle frontal gyrus. The response in the amygdala correlated with positive symptom severity but not with cognitive deficits (Wolf et al., 2015). Figure 3 illustrates the pattern of activation.

Dysconnectivity with resting state fMRI has been demonstrated in people with schizophrenia in brain networks including the default mode and the cingulo-opercular circuitry. We investigated whether such deficits are present in youth with psychosis spectrum features (n = 188) and compared them to typically developing participants (n = 204). The psychosis spectrum group evidenced multifocal dysconnectivity, implicating the bilateral anterior cingulate, frontal pole, medial temporal lobe, opercular cortex, and right orbitofrontal cortex. These results were driven by hyper-connectivity among default mode regions and diminished connectivity among cingulo-opercular regions, as well as diminished coupling between frontal and default mode regions (Satterthwaite, Vandekar, et al., 2015; Satterthwaite, Wolf, et al., 2015, see Fig. 4). These results suggest functional dysconnectivity in psychosis spectrum youths, which show marked correspondence to abnormalities reported in adults with established psychotic disorders.

The community-based studies applying brain-behavior quantitative measures indicate that differences in youths are already present when subthreshold psychotic symptoms are emerging. The pattern of deficits is consistent with aberrations reported in adults with schizophrenia, supporting the hope that a dimensional approach to psychopathology, as envisioned by the RDoC initiative (see other chapters in this volume), will likely yield biomarkers that will be both informative of underlying mechanisms and clinically relevant for the purpose of diagnosis, prevention, and intervention.

Genetically Informative: 22q11.2 Deletion Syndrome

The 22q11.2 deletion syndrome is the most common copy number variation (CNV) occurring in approximately 1:2000–1:4000 live births (Botto et al., 2003). It is typically caused by a sporadic uneven recombination event resulting in hemizygous deletion of approximately 3 Mb on the long arm of chromosome 22. This deletion of approximately 50 genes results in heterogeneous medical and neuropsychiatric manifestations. In addition to craniofacial and cardiovascular abnormalities, there are cognitive delays, with mild-to-moderate intellectual disability. There is increased risk for several psychiatric disorders including anxiety, attention deficit hyperactivity, and autism spectrum in childhood, with depression and schizophrenia emerging in adolescence and early adulthood (Gothelf et al., 2013; Tang, Yi, Calkins, et al., 2014; Yi et al., 2015). Perhaps the most striking effect of the 22q11.2 deletion is about a 25-fold increased risk of schizophrenia relative to the general population (Bassett et al., 2003). Although the frequency of psychiatric disorders in 22q11.2 deletion syndrome is relatively high, the developmental patterns and phenotypes are similar to manifestations of major psychiatric disorders in the general population (Antshel et al., 2006; Green et al., 2009). Therefore, the 22q11.2 genetic variation may provide a unique window for elucidating mechanisms of schizophrenia spectrum disorders.

Psychosis Spectrum Features in 22q11.2 Deletion Syndrome

In collaboration with Children's Hospital of Philadelphia "22q and You Center," we conducted a series of studies that examined overall psychopathology, focusing on psychosis spectrum features and brain-behavior parameters in the disorder. We evaluated 112 individuals with the confirmed deletion ages 8–45 (Tang, Yi, Calkins, et al., 2014). A comprehensive clinical assessment with structured interviews determined threshold and subthreshold psychosis and other psychiatric disorders. Consistent with the literature, psychopathology was common in our sample, with 79 % of individuals meeting diagnostic criteria for a disorder. Diagnoses of psychosis were made in 11 % of participants, attenuated positive symptoms were present in 21, and 47 % experienced significant subthreshold psychotic symptoms. Peak occurrence of psychosis risk was during adolescence, noted in 62 % of those aged 12–17 years.

In a subsequent study, 157 individuals with 22q11.2 deletion syndrome, ages 8–25 years, were evaluated for subthreshold psychotic features with the structured interview for prodromal syndromes (SIPS; Miller et al., 2003). The SIPS is a well-validated instrument that has been applied in non-deleted populations for detecting clinical risk but has only recently been applied to 22q11.2 deletion syndrome. Subthreshold symptoms were common, with 85 % of participants endorsing one or more symptoms. Factor analysis of the 19 SIPS scales disclosed a three-factor solution with positive, negative, and disorganized components, as emerged in non-deleted samples of clinical risk for schizophrenia (Tang, Yi, Moore, et al., 2014). As is the case for at-risk non-deleted samples, the significance and predictive validity of subthreshold symptoms require future longitudinal follow-up.

Neurocognition in 22q11.2 Deletion Syndrome

Reduced intellectual abilities, nonverbal greater than verbal, have been observed in individuals with 22q11.2 deletion syndrome (Bearden et al., 2001; Duijff et al., 2012; Tang, Yi, Calkins, et al., 2014). Neuropsychological reports indicate impaired executive functions, attention, working memory, verbal and nonverbal memory, visuospatial processing, and visuomotor functioning (Bish, Ferrante, McDonald-McGinn, Zackai, & Simon, 2005; Henry et al., 2002; Majerus, Van der Linden, Braissand, & Eliez, 2007; Woodin et al., 2001). Notably, most studies examined relatively small samples, largely focused on children and on a limited number of cognitive domains and did not include age-matched comparison groups. Neuropsychological measures utilize a healthy comparison group to gauge performance, and demographic variables such as age and sex are considered. Given the phenotypic complexity of 22q11.2 deletion syndrome, the choice of an appropriate comparison group is important when examining neurocognitive functioning. To date, there have been no studies comparing performance of individuals with 22q11.2 deletion syndrome, commonly associated with developmental delay and medical comorbidities, to non-deleted youths with developmental delay, medical comorbidities, and no known genetic disorder. Such a comparison is needed to identify neurobehavioral features that can be uniquely attributable to the deletion rather than to nonspecific effects of developmental delay or medical sequelae.

Quantitative neurobehavioral measures linked to brain circuitry can help elucidate genetic mechanisms contributing to deficits. To establish the neurocognitive profile and neurocognitive “growth charts” (see RC Gur chapter in this volume), we compared cross-sectionally 137 individuals with 22q11.2 deletion syndrome ages 8–21 to 439 demographically matched non-deleted individuals with developmental delay and medical comorbidities and 443 typically developing participants. We administered a CNB that measures performance accuracy and speed in executive, episodic memory, complex cognition, social cognition, and sensorimotor domains. The accuracy performance profile of 22q11.2 deletion syndrome showed greater impairment than developmental delay, in patients who were impaired relative to typically developing. Deficits in 22q11.2 deletion syndrome were most pronounced for face memory and social cognition, followed by complex cognition. Performance speed was similar for 22q11.2 deletion syndrome and developmental delay, but 22q11.2 deletion syndrome individuals were differentially slower in face memory and emotion identification. The growth chart, comparing neurocognitive age based on performance relative to chronological age, indicated that 22q11.2 deletion syndrome participants lagged behind both groups from the earliest age assessed. The lag ranged from less than 1 year to over 3 years depending on chronological age and neurocognitive domain. The greatest developmental lag across the age range was for social cognition and complex cognition, with the smallest for episodic memory and sensorimotor speed, where lags were similar to developmental delay (Fig. 5). The results suggest that 22q11.2 microdeletion confers specific vulnerability that may underlie brain circuitry associated with deficits in several neuropsychiatric disorders and therefore help identify potential targets and developmental epochs optimal for intervention.

Quantitative neurobehavioral measures that are linked to brain circuitry can be useful in evaluating underlying genetic mechanisms of behavioral domains dimensionally, across

psychiatric disorders, and therefore advance translational research with animal models (Hiroi et al., 2013; Jonas, Montojo, & Bearden, 2014; Meechan, Maynard, Tucker, & LaMantia, 2011). In this regard, 22q11.2 deletion syndrome provides an inimitable opportunity for dissecting associated neurobehavioral deficits in a way that could eventually lead to a mechanistic account of psychiatric phenomenology.

Neuroimaging in 22q11DS

Neuroimaging studies demonstrate consistent anatomic differences between individuals with 22q11.2 deletion syndrome and typically developing individuals. Findings include globally decreased cerebral brain volumes, volumetric reductions in the parietal lobe, reduction of cortical thickness in the parietal lobes and orbitofrontal cortex, reduction in cerebellar vermis hemisphere size, abnormalities in gyral complexity, and white matter hyperintensities (Bearden et al., 2009; Eliez, Schmitt, White, & Reiss, 2000; Jalbrzikowski et al., 2013). Additionally, prior neuroimaging studies report increased prevalence of cavum septum pellucidum and cavum vergae in 22q11.2 deletion syndrome (Beaton et al., 2001; van Amelsvoort et al., 2001), an observation also noted in non-deleted people with schizophrenia (Galarza, Merlo, Ingratta, Albanese, & Albanese, 2004; Trzesniak et al., 2011).

In our neuroimaging study of 58 individuals with 22q11.2 deletion syndrome, the rate of incidental findings on clinical neuroradiological readings was significantly higher in cases compared to typically developing youths (Schmitt et al., 2014). High prevalence of cavum septum pellucidum (19.0 %) and white matter abnormalities (10.3 %) was associated with psychosis in 22q11.2 deletion syndrome. Notably, in a study of healthy non-deleted youths of the PNC with similar procedures, we reported that the 16 cases with the incidental finding of cavum septum pellucidum endorsed more psychotic symptoms than those with no incidental findings, matched for age and sex (Gur et al., 2013). The consistency of findings suggests that aberrations in early neurodevelopment are associated with psychosis spectrum features in young people with and without the deletion. This effect buttresses the utility of applying complementary approaches in the study of psychosis spectrum.

To examine cortical morphometry in 22q11.2 deletion syndrome, we compared 53 patients with the deletion, 30 of whom with psychotic symptoms, to demographically matched non-deleted youths: 53 with psychotic symptoms and 53 typically developing. MRI measures of cerebral volume, cortical thickness, and surface area and an index of local gyrification were compared between the groups (Schmitt et al., 2015, Fig. 6). We found that patients with 22q11.2 deletion syndrome had global increases in cortical thickness associated with reductions in surface area, reduced index of local gyrification, and lower cerebral volumes relative to typically developing controls. Regions implicated were primarily in the frontal lobe, in the superior parietal lobes, and in the paramedian cerebral cortex. Focally decreased thickness was seen in the superior temporal gyrus and posterior cingulate cortex in 22q11.2 deletion syndrome relative to non-deleted groups. Patterns between non-deleted participants with psychotic symptoms and 22q11.2 deletion syndrome were similar but with important differences in several regions implicated in schizophrenia. Post hoc analysis suggested that like the 22q11.2 deletion syndrome group, cortical thickness in non-deleted individuals with

psychotic symptoms differed from typically developing controls in the superior frontal gyrus and superior temporal gyrus, regions previously linked to schizophrenia.

The simultaneous examination of multiple measures of cerebral architecture demonstrates that differences in 22q11.2 deletion syndrome localize to regions of the frontal, superior parietal, superior temporal, and paramidline cerebral cortex. The overlapping patterns between non-deleted participants with psychotic symptoms and 22q11.2 deletion syndrome suggest partially shared neuroanatomic substrates.

Further Links to Genomics

Large-scale studies have investigated the genomic architecture of schizophrenia. These efforts have used the dichotomous clinical diagnostic approach of case-control definition. More recent efforts have expanded this line of research to include brain-behavior endophenotypes, which as continuous measures can be examined in samples that do not meet diagnostic criteria such as individuals at clinical risk and genetic risk.

The emerging literature indicates that schizophrenia, a highly heritable syndrome, is polygenic and multiple genes with small effects contribute to the etiology. Increased sample size has added power to detect genes with small effect sizes. In samples of over 20,000 cases and 20,000 controls, Ripke et al. (2013) reported on 13 risk alleles providing an estimate that about 6000–10,000 independent and largely common SNPs contribute to the heritability and etiology of schizophrenia. Subsequently, the study of the Schizophrenia Working Group of the Psychiatric Genomics Consortium identified 108 loci with small effects associated with schizophrenia (Fromer et al., 2014). This collaborative effort also reported on 128 established and novel loci (Schizophrenia Working Group of the Psychiatric Genomics Consortium, 2014). The growing literature indicates common variants between schizophrenia, bipolar disorder, autism spectrum disorders, and intellectual disability.

A dimensional approach, as envisioned in RDoC, is a complementary strategy of particular relevance for developmental studies examining early phases in the psychosis process. Clinical features are less distinct, and longitudinal studies are necessary to obtain data on developmental trajectories of dimensional endophenotypic parameters. Integration of genomic studies, which began with a dichotomous disease definition, and the more recent endophenotypic measures can be expanded to at-risk samples.

Linking genomics to neurocognitive measures requires a better understanding of the genetic architecture of cognitive abilities. Advancing the understanding on the magnitude of common genetic effects across and within neurocognitive domains, as well as patterns of shared and unique genetic influences, is necessary. In the PNC sample, Robinson et al. (2015) conducted a genome-wide complex trait analysis to estimate the SNP-based heritability of each neurocognitive domain of the Penn CNB as well as the genetic correlation between all domains. Several individual neurocognitive domains showed strong influence of common genetic variance. The genetic correlations highlighted neurocognitive domains that are candidates for joint interrogation in future genetic studies. Complex

reasoning, language, and spatial processing showed $r(g) > 0.7$. Future genomic investigation of complex traits and studies of at-risk youth can apply similar approaches.

As efforts at early identification with convergence of endophenotypic measures are underway, larger samples of individuals at clinical risk will become available for genomic studies. Applying to these samples, tools established in the large-scale schizophrenia consortium, such as the polygenic risk score (Purcell et al., 2014), will extend the approach to the full spectrum of psychosis. As clinical risk studies are collecting increasingly large samples with multiple endophenotypic measures, the utility of neurocognitive, neuroimaging, and neurophysiologic parameters can be examined in efforts to create gene networks explicating the underlying neurobiology of schizophrenia. Many genes implicated (e.g., GRM3, GRIN2A, SRR, GRIA1) are involved in glutamatergic neurotransmission and synaptic plasticity, corroborating a growing literature on underlying aberrations in schizophrenia. Both genome-wide association investigations of common variants and rare genetic variation studies converge in efforts to provide a mechanistic understanding of the etiology of schizophrenia while examining the psychosis continuum (Fromer et al., 2014; Gulsuner et al., 2013; Owen, Craddock, & O'Donovan, 2010).

The extension of genomic research to earlier phases of the psychotic process can also contribute to investigations of gene—environment interactions. Multiple environmental risk factors contribute to schizophrenia (Iyegbe, Desmond Campbell, Butler, Ajnakina, & Sham., 2014; van Os, Linscott, Myin-Germeys, Delespaul, & Krabbendam, 2009; Walker et al., 2013). The study of large samples of youths, in informative and integrated epidemiological, genomic, and endophenotypic paradigms, can advance the field and further help clarify the pathophysiology of psychosis. Such advances will facilitate the development of interventions that can affect the developmental trajectory of individuals as psychosis emerges.

Implications for the Study of Psychosis

The paradigm shift we are undergoing examines psychiatric disorders as a product of brain dysfunction at a system level, with a concomitant dimensional conceptualization of associated behaviors. Dissecting complex behaviors provides quantitative measures that can complement increasingly sensitive and sophisticated parameters of brain structure and function to inform genetic designs that apply genomic tools to elucidating the pathophysiology of psychosis. Several steps need to be considered to enable a productive endeavor.

Bridging the pediatrics and adult divide is essential for the study of neurodevelopmental disorders. To establish developmental trajectories, longitudinal efforts are critical and required for the vision of precision medicine. Thus, early identification of vulnerable youths will facilitate early interventions and building resilience. However, they need to be followed longitudinally to adulthood to know who progresses to clinical manifestations and who remains in a prodromal state or remits. Dissecting complex phenotypes requires multidimensional levels of analyses and advanced bioinformatics in a multidisciplinary

effort, where convergence of large samples with established common measures is prerequisite for integration with genomics.

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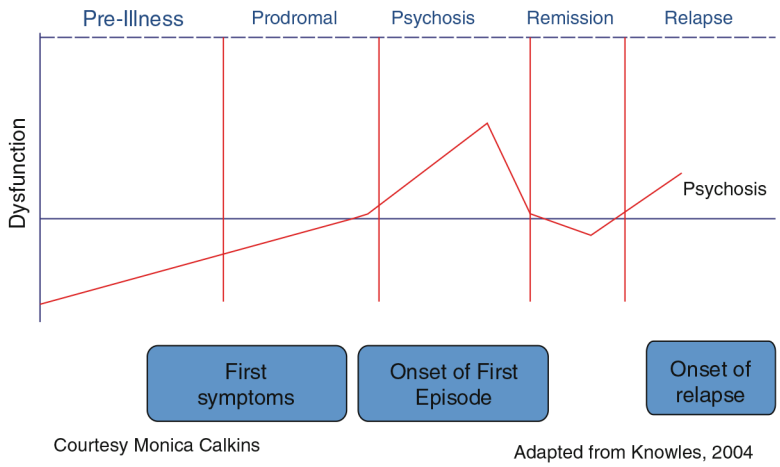

Fig. 1.
The course of psychosis (Adapted from Knowles et al., 2004)

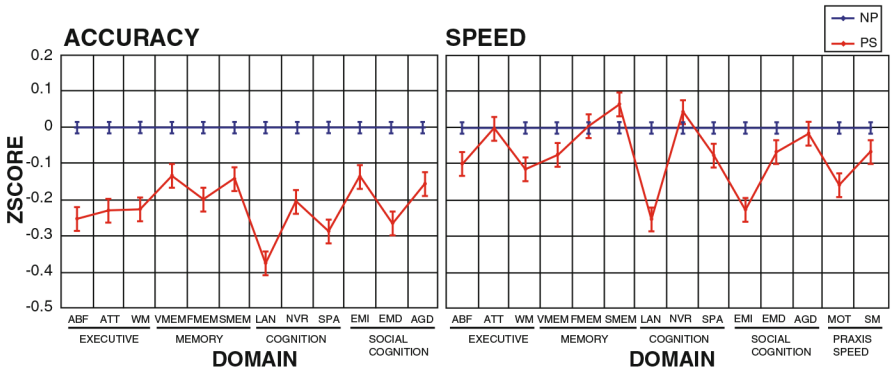

Fig. 2.

Performance on the Penn computerized neurocognitive battery (CNB) of psychosis spectrum (PS) compared to non-psychosis spectrum (NP) youths. Domains include *ABF* executive (abstraction and mental flexibility), *ATT* attention, *WM* working memory, *VMEM* episodic memory (verbal, *SMEM* facial (FMEM) spatial), *LAN* complex cognition (language), *NVR* nonverbal reasoning, *SPA* spatial processing, *EMI* emotion identification (social cognition), *EMD* emotion differentiation, *AGD* age differentiation, *MOT* praxis speed (motor), and *SM* sensorimotor. Adapted from Calkins et al. (2015)

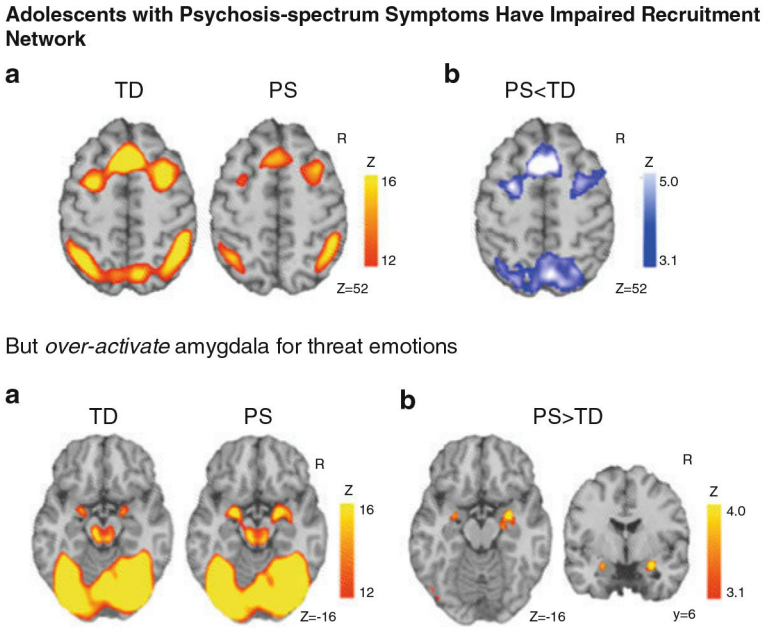

Fig. 3.

The pattern of brain activity in psychosis spectrum (PS) and typically developing (TD) youths for a working memory task (*top*) and an emotion identification task (*bottom*). The executive network shows greater activation in the TD than PS group for the working memory task. Greater activation in PS relative to TD is evident in the amygdala for the presentation of threat-related emotions. From Wolf et al. (2015)

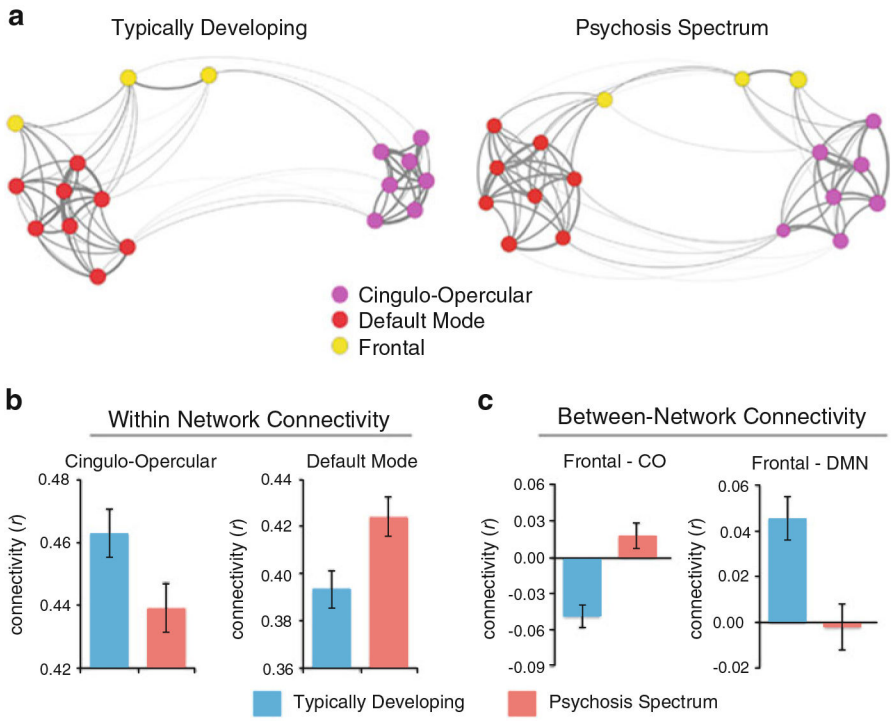

Fig. 4.

Resting BOLD connectivity in psychosis spectrum (PS) and typically developing (TD) youths. (**a**) Layout of mean connectivity within a network of nodes defined by connectome-wide association study (CWAS) and overlap of seed maps. (**b**) PS youth have diminished connectivity within the cingulo-opercular network (CO) but enhanced connectivity within the default mode network (DMN). (**c**) PS youth have enhanced connectivity between frontal regions and the CO network but diminished connectivity between default mode and frontal regions. From Satterthwaite, Vandekar, et al. (2015) and Satterthwaite, Wolf, et al. (2015)

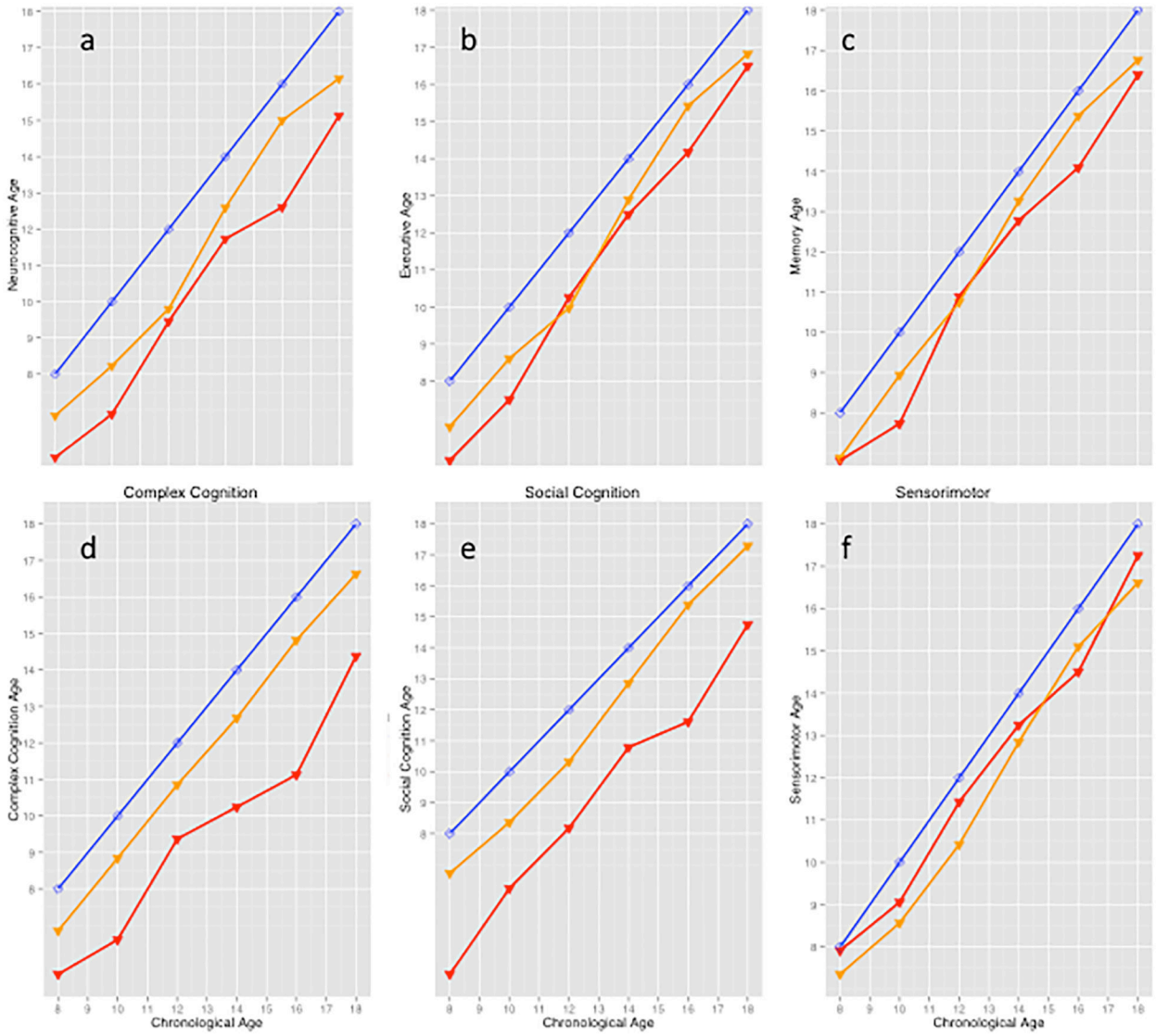

Fig. 5.

Chronological age compared with predicted neurocognitive age in years for typically developing (TD) participants (*blue line*), 22q11.2 deletion syndrome (22q11DS, *red line*), and developmental delay (DD) with medical comorbidities (*orange line*). Growth charts are provided for (**a**) predicted age based on all scores (all domains) and (**b** – **f**) predicted age based on tests grouped by each of the five domains. From Gur, Yi, et al. (2014)

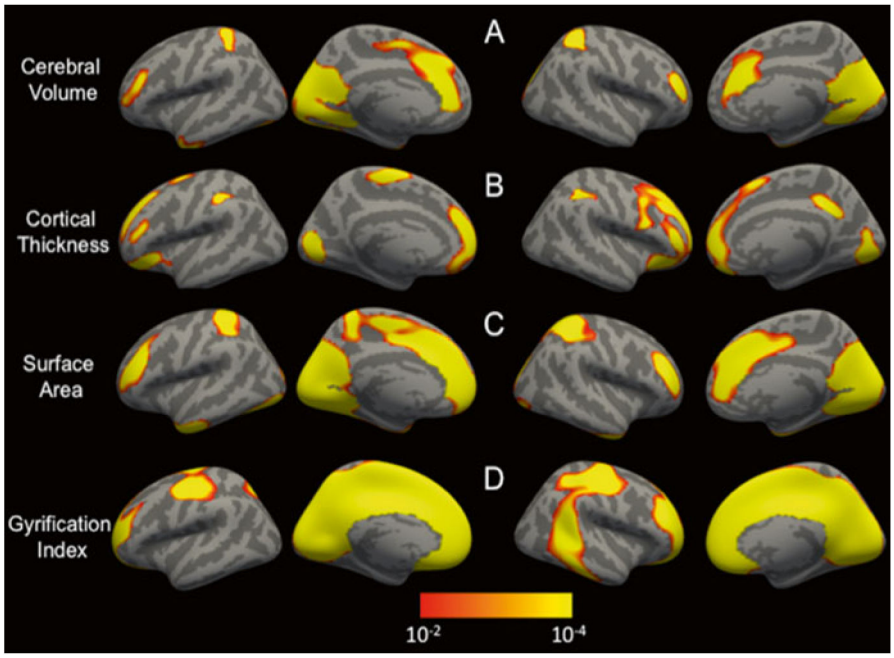

Fig. 6.

Group differences driving significant changes in cortical thickness. Pairwise probability maps depicting significant increases (*blue*) and decreases (*red*/*yellow*) in several morphological measures as compared with typically developing (ND-TD) and idiopathic psychotic symptom (ND-PS) groups. *ND* non-deleted, *PS* psychosis symptoms, *TD* typically developing. From Schmitt et al. (2015)