

Neuropsychological and Neuropsychiatric Features of Idiopathic and DYT1 Dystonia and the
Impact of Medical and Surgical treatment

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Introduction to Dystonia and its Classification

Dystonia is a hyperkinetic movement disorder. The latest expert classification defines dystonia as “a movement disorder characterized by sustained or intermittent muscle contractions causing abnormal, often repetitive, movements, postures, or both. Dystonic movements are typically patterned, twisting, and may be tremulous. Dystonia is often initiated or worsened by voluntary action and associated with overflow muscle activation.” (Albanese et al, 2103). After Parkinson’s disease and essential tremor, dystonia is the third most common movement disorder. It is estimated that around 75,000 people have Dystonia in Europe, and the annual period prevalence of primary dystonia was 152 per million (Epidemiological Study of Dystonia in Europe, 2000).

The expert review has proposed two major axes based on aetiology and clinical characteristics for the classification of dystonia (Albanese et al, 2013). Instead of the previous primary versus secondary distinction, the first axis based on etiology distinguishes dystonia associated with nervous system pathology, inherited or acquired, and idiopathic forms. The second axis involves classification in terms of clinical characteristics including age of onset (infancy: birth-2yrs, childhood: 3-12yrs, adolescence: 13-20yrs, early adulthood: 21-40yrs, late adulthood: >40yrs), body distribution (focal, multifocal, segmental, hemi-dystonia, generalized), temporal pattern (disease course: static or progressive, and variability: persistent, action-specific, diurnal or paroxysmal) and other associated features. The abnormal contractions can affect muscles of the eyes (blepharospasm), face and jaw (oromandibular dystonia), larynx (spasmodic dysphonia), neck (cervical dystonia,CD), hand during writing (writer’s cramp), hand, feet or trunk. The most common focal hand dystonia is writer’s cramp, but other types include typist’s, musician’s, and pianist’s cramps (Schmidt et al, 2009; Frucht, 2004). The age of onset of dystonia and the

particular body part first affected have prognostic implications. Early-onset dystonia, particularly in the legs, is likely to spread to other parts of the body and to become generalized. In contrast, late-onset dystonia, particularly in the upper parts of the body, is likely to remain focal or become segmental.

Pathophysiology of Dystonia

The cause of dystonia remains unknown. Dystonia is considered a movement disorder associated with dysfunction of the basal ganglia (Berardelli et al., 1998; Marsden, 1976), but cerebellar involvement in the disorder has also been documented (Argyelan, 2009; Delmaire et al, 2007; Jinnah & Hess, 2006; Neychev, Fan, Mitev, Hess, & Jinnah, 2008). Genetic studies have identified many genes causing various forms of dystonia in association with environmental factors (Nemeth, 2002; Fuchs and Ozelius, 2011).

Enlargement of putamina in CD or focal hand dystonia (Black, Ongur, & Perlmutter, 1998), increased gray matter volume in the internal segment of the globus pallidus (GPi) in CD (Draganski, Thun-Hohenstein, Bogdahn, Winkler, & May, 2003), and hyperechogenic basal ganglia lesions particularly in the lenticular nucleus in CD (75%) or focal hand dystonia (83%) (Becker et al, 1997) have been reported. Structural abnormality in the cerebellar cortex, particularly lobules V and VI, have been documented in writer's cramp (Delmaire et al., 2007) and CD (Draganski et al., 2003). Movement-related overactivity of the dorsolateral prefrontal cortex, the anterior cingulate, the supplementary motor area (SMA) and the lenticular nuclei, and underactivation of the primary motor cortex have been found in imaging studies (e.g., Ceballos-Baumann et al., 1995; Dresel, Haslinger, Castrop, Wohlschlaeger, & Ceballos-Baumann, 2006).

According to the classical De Long (1990) and Albin, Reiner, Anderson, Penney, and Young (1989) models, hyperkinetic movement disorders such as dystonia are associated with reduced inhibitory output from the GPi, which gives rise to increased thalamic and cortical activation. This model is supported by the hyperkinetic transgenic mice model of DYT1 dystonia (e.g., Chiken, Shashidharan, & Nambu, 2008) and neuronal recordings from the GPi of dystonia patients undergoing deep brain stimulation (DBS) surgery (e.g., Vitek et al, 1999). However, the improvement of dystonia with GPi-DBS, which reduces the activity of the GPi is not consistent with the De Long and Albin et al “rate” models.

Reduced cortico-cortical inhibition (Edwards, Huang, Wood, Rothwell, & Bhatia, 2003; Ridding, Sheean, Rothwell, Inzelberg, & Kujirai, 1995) and increased plasticity (e.g., Quartarone et al., 2003) have been demonstrated in dystonia, by employing different transcranial magnetic stimulation protocols. The loss of inhibition, particularly loss of ‘surround inhibition’, is considered responsible for loss of selectivity and overflow of activation to other muscles (Sohn & Hallett, 2003). Sensory abnormalities such as increased temporal and spatial discrimination thresholds (Bara-Jimenez, Shelton, & Hallett, 2000; Tinazzi et al, 2002) in dystonia have been related to reduced activity of inhibitory networks in the primary somatosensory cortex in the disorder (Rocchi et al, 2016; Antelmi et al, 2016).

Dystonia does not develop in all carriers of dystonia mutations, and some gene carriers remain asymptomatic. Task-specific dystonias such as writer’s cramp and musician’s dystonia have been associated with hours spent writing or practicing a musical instrument (Roze et al., 2009; Schmidt et al., 2009) and are often preceded by some specific trauma/insult (e.g., Defazio et al., 1998). These findings highlight the importance of environmental factors in the onset of dystonia in genetically predisposed and vulnerable individuals.

It has been proposed that the non-motor features of dystonia such as psychiatric problems, pain, sleep disturbance, executive dysfunction and sensory abnormalities may be explained by the loss of inhibition and increased plasticity that appear to be important in the pathophysiology of dystonia, which together with genetic susceptibility and environmental triggers such as physical or emotional trauma and repetitive actions result in manifestation of dystonia (Stamelou et al, 2012).

Cognitive Function in Dystonia

Cognitive deficits are not considered part of the initial clinical presentation and do not develop with disease progression in idiopathic or DYT1 dystonia. This clinical impression is largely confirmed by the handful of studies that have investigated cognitive function with neuropsychological tests in these types of dystonia (see Table 1).

Insert-Table 1 here -

Early studies focused on specific aspects of cognition in dystonia: intellectual ability, space perception and the effect of anticholinergic medication. Riklan, Cullinan and Cooper (1976) showed that children with dystonia were not intellectually impaired and in fact had higher IQs than controls. Although some reported normal perception of egocentric space (Anastopoulos et al., 1998), others documented significantly worse manipulation of personal space but not spatial perception (Hinse et al., 1996) or deficits in extrapersonal orientation in dystonia (Leplow & Stubinger, 1994). Finally, treatment of dystonia with high-dose anticholinergics was shown to

impair performance on a test of explicit memory and the Stroop task (Taylor, Lang, Saint-Cyr, Riley, & Ranaway, 1991).

Table 1 about here

Table 1 presents the more recent studies that have investigated cognition in idiopathic or DYT1 dystonia using relatively extensive batteries of standardized neuropsychological tests to assess various domains of cognition. A main focus across these studies has been on the assessment of executive function, a cognitive domain impaired in other basal ganglia disorders such as Parkinson's disease (Dirnberger & Jahanshahi, 2013). The Wisconsin Card Sorting test (WCST) has been used as a measure of executive function and specifically set-shifting ability in several studies. The results of the studies that administered the WCST to dystonia patients are inconsistent with some reporting that patients with dystonia performed worse than healthy controls (Bugalho et al, 2008; Aleman et al, 2009; Lange et al, 2016a), and others finding no such deficits (Taylor et al, 1991; Jahanshahi et al, 2003; Romano et al, 2014). Similarly, on the extradimensional set-shifting subtest of the Cambridge Neuropsychological Test Automated Battery (CANTAB) modelled on the WCST, one study found patients with dystonia to be impaired relative to normative data of the test (Scott et al, 2003), whereas a second study by the same group did not replicate this deficit (Balas et al, 2006). In light of this inconsistency in the literature, a recent meta-analysis of the six studies which had used various versions of the WCST to assess set-shifting in dystonia (Taylor et al, 1991; Jahanshahi et al, 2003; Bugalho et al, 2008; Aleman et al, 2009; Romano et al, 2014) including a computerized version (Lange et al, 2016a,b), revealed medium effect sizes for dystonia-related deficits on the WCST (Lange et al, 2016b). This suggests executive dysfunction and specifically set-shifting to be a feature of idiopathic and DYT1 dystonia. However, on the basis of the analysis of the pattern of errors and

the event-related potential recordings during the computerized version of the WCST in their own study, Lange et al (2016b) proposed that the deficits in dystonia are suggestive of deficits in rule inference rather than set-shifting. This is clearly an issue that needs to be addressed in future studies.

The neuropsychological studies listed in Table 1 allow a number of other main conclusions. First, global and main domains of cognition such as IQ, and with a few exceptions, language and memory, are not generally impaired in idiopathic and DYT1 dystonia. Second, specific aspects of cognition including semantic fluency and dual task performance (Jahanshahi et al, 2003), sustained attention (Allam et al, 2013), working memory (Romano et al, 2013), behavioural regulation and set-shifting (Foley et al, 2017) are reported to be impaired in these patients. Other studies have also documented greater susceptibility to retroactive interference during recall (Balas et al, 2006), reduced motor dexterity and complex movement planning and object recognition (Aleman et al, 2009).

Other specific aspects of cognitive function have been assessed by other investigators. Hoffland and colleagues (2011) found deficits in praxis in patients with CD relative to matched healthy controls: the patients made more errors and were slower in copying meaningless gestures but not in copying meaningful gestures. In patients with writer's cramp, Fiorio, Tinazzi, & Aglioti (2006) found slower mental rotation of the hands, but not feet relative to matched healthy controls. In CD, Ploner, Stenz, Fassdorf, & Arnold (2005) investigated egocentric and allocentric spatial memory and found no significant differences between patients and controls, but unlike controls, the patients seemed to use a single strategy in completing different spatial tasks.

Intentional sequence learning has been evaluated in dystonia in several studies, combined with functional imaging. Relative to healthy controls, Ghilardi and colleagues (2003) found that intentional sequence learning was significantly reduced in nonmanifesting (NMC) DYT1 gene. The impaired learning in the NMC group was associated with significant increased activation in the pre-SMA and the lateral cerebellum and reduced activation in the left cingulate gyrus relative to the controls. In a subsequent study by the same group, Carbon et al (2011) studied intentional sequence learning in manifesting carriers (MC) of the DYT1 gene as well as carriers of the DYT6 mutation. Although both the MC and NMC of the DYT1 gene showed similar deficits in sequence learning, DYT6 carriers had no such deficits. Furthermore, the MC of DYT1 gene showed significant increases in sequence learning-related activation of the lateral cerebellum and right premotor and inferior parietal areas. These results suggest that deficits in explicit sequence learning may be specific to the DYT1 genotype.

In general, most of the cognitive deficits documented in idiopathic and DYT1 dystonia can be considered as reflecting executive dysfunction mediated by the fronto-striatal circuits. However, in deciding whether these deficits in performance of cognitive tests reflect genuine cognitive impairment, as previously noted (Jahanshahi et al, 2003), the potential confounding effects of a number of factors need to be considered. First, It is likely that the patient's motor symptoms and their conscious attempts to control these during cognitive assessment interferes with performance on some cognitive tests and could contribute to some of the specific deficits for example dual task performance (Jahanshahi, Rowe, & Fuller, 2003) or manual dexterity and complex movement planning (Aleman et al, 2009) or completion of the Trail Making Test (Foley et al, 2017) documented in some studies. In support of this possibility, Allam, Frank, Pereira, & Tomaz (2007) found deficits on a test of sustained attention in patients with blepharospasm, which

improved following symptomatic improvement with botulinum toxin such that after treatment the patients did not differ from the controls. By contrast, cognition in blepharospasm was not related to the severity or duration of symptoms (Aleman et al, 2009) and a recent study failed to find any association between ratings of the severity of dystonia in CD or generalized dystonia and performance on cognitive tests (Foley et al, 2017). Furthermore, two recent studies also included patients with hemifacial spasm as disease control groups (Dias et al, 2009; Lange et al, 2016a). One did not find any deficits on the Mini Mental State Examination or the Frontal Assessment Battery in either group (Dias et al, 2009) and the other study (Lange et al, 2016a) found deficits on a computerized WCST for the patients with blepharospasm but not those with hemifacial spasm, suggesting that these deficits were not simply due to symptom-related distraction. A second potential confounding factor is the anticholinergic and benzodiazepine medication that many patients are taking for the treatment of their dystonia, which could independent of the dystonia have a negative impact on cognitive function (Taylor et al, 1991); Britt and Day, 2016; Lampela et al, 2015; Federico et al, 2017). Third, as discussed below, depression and anxiety and obsessive compulsive disorder (OCD) are common psychiatric co-morbidities in dystonia for which at least a proportion of the patients would have been taking psychoactive medication and these co-morbidities and their medical treatment could also independently influence cognition (Austin et al, 1992; Purcell et al, 1997; Vytal et al, 2013; Chamberlain et al, 2005). However, while an association between higher depression and greater executive dysfunction was found in dystonia (Jahanshahi et al, 2003), no association between depression, anxiety and apathy and scores on tests of cognitive function were reported in two recent studies (Lange et al, 2016a; Foley et al, 2017). This is an issue that clearly needs to be examined in future studies by comparing the cognitive performance of dystonia patients with or without significant mood disorder.

Psychiatric Features of Dystonia

The methods used for the assessment of psychiatric disorders in dystonia range from structured clinical interview combined with application of the criteria from various versions of the Diagnostic Statistical Manual (DSM) to employment of validated self-report measures such as the Beck Depression Inventory, the Beck Anxiety Inventory, and the Yale Brown Obsessive-Compulsive Scale (YBOCS). Some studies have included healthy participants or a disease control group. With notable exceptions (e.g., Dias et al, 2011), most studies fail to specify what percent of the samples were taking psychoactive medication for treatment of their dystonia or psychiatric disorders.

Cervical Dystonia

There is now a sizeable body of evidence establishing high rates of psychiatric disorder in CD. In one of the earliest studies, Patterson & Little (1943) reported psychiatric disorder in 21 of their 83 (25.3%) CD patients. A sample of 100 CD patients and a control group of 49 patients with cervical spondylosis (CS) were assessed by Jahanshahi & Marsden (1988a). They found that 27.1% of the CD and 26.5% of the CS patients had past or present psychiatric disorders, a difference that was not significant. In both groups, depression and anxiety were the most common psychiatric diagnoses (in 21 of 23 CD patients). The remaining two CD patients had OCD and personality disorder. Moderate to severe depression affected 29% of CD and 15% of CS patients, but the differences between the groups in trait anxiety and obsessionality were not significant. Later studies by the same investigators (Jahanshahi & Marsden, 1988b, 1990a) confirmed occurrence of moderate to severe depression in CD, with the cognitive elements of depression distinguishing the CD and CS groups. The difference in the item relating to body

image was the most striking, with 39% of the CD and only 4% of the CS response suggestive of a negative body image (Jahanshahi & Marsden, 1988b).

Thirty two patients with CD were assessed by Naber, Weinbergr, Bullinger, Polsby & Chase (1988), who found mild depression in 25% and anxiety in only one patient, previous history of depression in three, and current psychiatric disorder in two patients. In a sample of 44 CD patients, 66% fulfilled the criteria for at least one diagnosis of current or lifetime psychiatric disorder (Wenzel et al, 1998). Among 40 CD patients, 55% had at least one lifetime or current psychiatric disorder. 40% met the DSM-III-R criteria for anxiety and 37.5% met the criteria for major depressive disorder (MDD). In 42.5% of these patients, at least one lifetime diagnosis was made prior to the onset of their dystonia (Moraru et al 2002). In a study with a somewhat larger sample, Lencer et al (2009) assessed 70 patients with CD and 16 with blepharospasm. Compared to a population-based sample (N=3943), the dystonia patients had a 4.5-fold increased chance of a psychiatric disorder, and their lifetime prevalence of psychiatric or personality disorder was 70.9%; with rates of anxiety and major depression being high.

Gundel, Wolf, Xidara, Busch, & Ceballos-Baumann (2001) completed a study with a large sample of 116 CD patients. They found that both lifetime and current rates of mood and anxiety disorders were significantly elevated in CD relative to the data from the general population, with lifetime mood disorders in 53.5% and anxiety disorders in 83.6%. Rates of current social phobia had a 10-fold increase in CD, whereas current mood disorders were increased by 2.4 times, and all lifetime psychiatric morbidity was increased by 2.6 times in CD compared to the representative general population sample. In a further study, Gundel and colleagues (2003) compared psychiatric morbidity in 48 patients with CD and 48 patients with alopecia areata (AA),

which results in hair loss and changes in physical appearance. Compared to the German general population data, both CD and AA patients had significantly higher current and lifetime psychiatric morbidity. Mood disorders, anxiety disorders, and social phobia were the most common diagnoses in both groups. Most importantly, current psychiatric disorder was significantly higher in CD (77%) than in AA (42%), despite the two disorders sharing changes in physical appearance.

In addition to depression and anxiety, OCD is another psychiatric feature in most types of dystonia. Bugalho, Correa, Guimaraes, and Xavier (2006) reported two cases with Meige syndrome and CD and writer's cramp, both of whom fulfilled DSM-IV criteria for OCD. Cavallaro et al (2002) specifically investigated OCD in 76 patients with various types of idiopathic focal dystonia. Twenty percent of their sample met DSM-IV criteria for OCD, and 3.5% for obsessive-compulsive spectrum disorders, and 10.5% were diagnosed with subclinical OCD. In the study of Cavallaro et al (2002), the prevalence of OCD in dystonia patients was significantly higher than healthy controls, and the patients had a significantly higher family morbidity risk for OCD than in the general population. By contrast, while Fabbrini et al. (2010) found high rates (57%) of psychiatric diagnosis in 89 patients with various forms of focal dystonia compared to patients with hemifacial spasm (HFS) and healthy controls, the incidence of anxiety or OCD was comparable between the three groups.

Blepharospasm

Blepharospasm is frequently associated with depression and in some studies with OCD, although the latter is less consistently reported. Hall et al. (2005) assessed 159 patients with blepharospasm and found that compared to patients with HFS, they were more than two times more likely to

meet the criteria for generalized anxiety disorder, and had significantly higher depression scores, but the groups did not differ in terms of obsessive compulsive symptoms. Lencer et al's (2009) sample included patients with blepharospasm as well as CD and reported a 4.5-fold increased rate of psychiatric morbidity in dystonia relative to the general population. Similarly, Fabbrini et al.'s (2010) sample also included cases with blepharospasm and other forms of dystonia and found mood and anxiety disorders in 67.7%. A similar rate of 71% with a current or lifetime psychiatric diagnosis was reported by Wenzel et al. (1998), with depression and phobias being the most common diagnoses.

Patients with blepharospasm have been reported to have higher rates of OCD and self-reported depression relative to healthy controls (Bihari, Hill, & Murphy, 1992). However, while Brooks, Thiel, Angerstein, & Dressler (1998) found that none of the patients with blepharospasm met the diagnostic criteria for OCD, they had significantly higher scores on the Hamburg Obsession-Compulsion Inventory than an HFS control group. By contrast, Munhoz et al. (2005) found high rates of OCD in both patients with blepharospasm and those with HFS. In the study by Munhoz et al (2005) 67% of patients with blepharospasm and 70% of those with HFS met the DSM-IV criteria for OCD, and, although this difference was not significant, the severity of OCD was greater in patients with blepharospasm. Similarly, Mula et al. (2012) found equivalent rates of OCD in 26% of patients with focal dystonia (8 blepharospasm and 11 CD) and 28% of HFS, which were higher than in healthy controls; although, the rates of depression or anxiety did not differ from healthy controls. Furthermore, in their sample of 15 patients with CD, 15 with blepharospasm and 15 with writer's cramp, Bugalho et al. (2008) reported that only three fulfilled DSM-IV criteria for clinical OCD, but significantly more patients scored above the cut-off score on the YBOCS than healthy controls. In Fabbrini et al's (2010) sample, only 1 in the 28 cases

with blepharospasm (3.57%) had OCD, whereas 9.6% of the sample of Wenzel et al (1998) met DSM-III-R criteria for OCD. Cavallaro et al. (2002) reported OCD in 20% of their sample with various types of focal dystonia, including blepharospasm. In general, the evidence suggests that, although the rates of OCD in blepharospasm are significantly higher than healthy controls, they are similar to disease control groups such as patients with HFS. The differing rates ranging from none to 67% may partly result from the use of different assessment tools and criteria for diagnosis of OCD.

Spasmodic Dysphonia

Cannito (1991) compared patients with spasmodic dysphonia and matched healthy controls and found that 39% of the patients reported depression and anxiety on self-rating scales, which was significantly higher than for the controls. Whurr, Lorch, and Nye (1998) found a similar rate of 37% for mild to moderate depression in patients with spasmodic dysphonia. In a sample of 48 patients with spasmodic dysphonia assessed by Gundel, Busch, Ceballos-Baumann, & Seifert (2007) 42% met DSM-IV criteria for current psychiatric disorder, which was significantly higher than in a control group with vocal fold paralysis (20%). Fabbrini et al. (2010) also examined 16 patients with laryngeal dystonia and found mood disorders in 12.5%, anxiety disorders in 18.7%, and adjustment disorders in 18.7%, but no OCD. However, the frequency of these psychiatric disorders in patients with spasmodic dysphonia was not significantly different from healthy controls. As noted below, patients with laryngeal dystonia had significantly higher levels of anxiety and social anxiety than other types of adult-onset focal dystonia (Berman et al, 2017).

Focal Hand Dystonia and Writer's Cramp

Based on clinical observation, Bindman and Tibbetts (1977) reported that 9 of the 10 patients with writer's cramp displayed obsessive personalities. In another study, no significant differences

in anxiety were found between patients with writer's cramp and healthy controls and only 3 of the 22 patients (13.6%) had a general anxiety disorder (Harrington, Wieck, Marks, & Marsden, 1988). Kubota and colleagues (2001) compared 12 patients with writer's cramp and found significantly higher obsessive-compulsive symptoms in the patients compared to a group of individuals with writing impairments due to peripheral nerve lesions and compared to healthy controls. Grafman, Cohen, and Hallett (1991) studied 20 cases with focal hand dystonia using the MMPI, the State-Trait Anxiety Inventory (STAI) and the Beck Depression Inventory, and, other than mild depression in 20%, the scores on the personality scales were within the normal range and none of the patients had a remarkable psychiatric history. It was concluded that focal hand dystonia is not associated with psychopathology. By contrast, Voon and colleagues (2010) studied 39 patients with focal hand dystonia, and found that 13% of the patients met the criteria for OCD compared with 2% in the general population. Recurrent depression was present in 18% of the patients and current or previous depression in 33%, 41% of whom had a family history of depression. Anxiety disorders affected 26% of the sample. None of the 11 patients with arm dystonia assessed by Fabbrini et al. (2010) had mood or anxiety disorders, and only 1 patient had OCD, and another had adjustment disorder. These rates were not different from their healthy control group. As noted by Fabbrini et al. (2011), the differences from the rates reported by Voon and colleagues may relate to the fact that although all their cases with focal hand dystonia had writer's cramp, the Voon sample consisted of people with musician's dystonia. Thus, although it seems that musician's dystonia is associated with psychiatric morbidity (Voon et al., 2010), other forms of focal hand dystonia, particularly writer's cramp, are not (Harrington et al., 1988; Grafman et al., 1991; Fabbrini et al., 2010). A recent study showed that while acute stress did not have any direct impact on the motor control of musicians with focal dystonia, those who were characterized by perfectionist personalities had on average developed dystonia about ten years

earlier than others, suggesting that such personality traits may act at long-acting potential triggers and accelerate the onset of the dystonic symptoms (Iannou, Furuya & Altenmüller, 2016).

However, life satisfaction among 243 people with musician's dystonia did not differ from 57 musician's without dystonia, irrespective of the course of the disease and even change of profession (Lee et al, 2015).

Generalized Dystonia

In the sample of 329 community dwelling patients with dystonia of various presentations, studied by Lewis, Butler, & Jahanshahi (2008), 10.4% had generalized dystonia and 30% had moderate to severe depression. The extent of dystonia had a significant effect on depression scores, which was due to patients with focal dystonia having lower scores. Around 54% of the participants were critical of their appearance, and 25% felt that there were permanent (negative) changes in their appearance. The body part associated with the highest level of depression was the neck, and patients with CD had the highest depressive scores, whereas depression was lower in patients with generalized dystonia. These results suggest that since postural abnormality is most visible in patients with CD, it is associated with high levels of perceived stigma (Papathanasiou, MacDonald, Whurr, & Jahanshahi, 2001). Similarly since generalized dystonia is usually of early onset, patients are more likely to have adjusted better over time. In this sample, self-esteem, body concept, disfigurement, and quality of life were significant predictors of depression in patients with focal, segmental and generalized dystonia (Lewis et al, 2008)

There is evidence for the association of recurrent MDD with the DYT1 mutation. Heiman et al. (2004) studied a large group of patients with the DYT1 gene mutation and compared manifesting carriers (MC), nonmanifesting carriers (NMC), and noncarriers (NC). They found that the risk of

recurrent MDD was increased in both MC and NMC compared to NC. The prevalence of early-onset recurrent MDD was 12.5% in MC, 10% in NMC and 1.5% in NC group. The severity of dystonia was not associated with the risk of recurrent MDD. It was concluded that the psychiatric expression of DYT1 appears to be limited to recurrent early-onset MDD because carriers were not at increased risk for other affective disorders. Similarly, early-onset recurrent MDD was associated with the DYT1 mutation, and this association was independent of motor manifestations of dystonia. The same group (Heiman et al, 2007) subsequently investigated rates of OCD in their sample. There were no significant differences in OCD between the three groups, with the OCD rates of 3% in MC, 2% in NMC, and 5% in NC. Therefore, unlike early-onset MDD, which is associated with the DYT1 gene, no association was found with OCD.

Table 2 about here

Sleep problems in dystonia

Table 2 provides a summary of the studies that have used polysomnographic sleep recordings (Jankel et al, 1983; Sfroza et al, 1991; Fish 1991, Lobbezoo et al, 1996a) or self-report measures such as the Pittsburg Sleep Quality Rating Scale and the Epworth Daytime Sleepiness Scale (Avanzino et al 2010, Paus et al 2011, Eichenseer et al 2014; Yang et al, 2016) to assess sleep in various forms of dystonia. This evidence shows that sleep problems are common in focal and generalized dystonia and present in 44 to 72% of patients with CD and 46 to 75% of those with blepharospasm. In both CD and blepharospasm sleep quality and efficiency is affected, and in some patients with blepharospasm sleep latency and duration is also altered. By contrast, excessive daytime sleepiness seems to be rare and only reported in one study, possibly due to anticholinergic medication (Trotti et al, 2009), whereas others (Avanzino et al 2010, Paus et al

2011, Eichenseer et al 2014; Yang et al, 2016) did not find any evidence of excessive daytime sleepiness on the Epworth Sleepiness Scale in dystonia relative to healthy controls. Klingelhofer et al. (2014) assessed sleep in 102 patients with CD using the Non-motor Symptom Questionnaire developed for Parkinson's disease. Their results showed that 60% of the CD patients reported difficulties falling or staying asleep; 51% reported fatigue which limited daytime activities; 40% reported not feeling refreshed after sleep. They found a weak ($r=.23$) but significant correlation between the number of non-motor symptoms reported and the severity of dystonia.

A number of studies have used polysomnography (Jankel et al, 1983; Sforza et al, 1991; Fish et al, 1991a,b, Lobbezoo et al, 1996a). The results of these studies are inconsistent, with some suggesting that REM sleep is reduced, increased mini-arousals which disrupt sleep continuity, while others finding sleep EEG patterns to be normal in dystonia. Fish and colleagues completed a number of polysomnographic studies in primary and secondary generalized dystonia and control participants. They reported occasional occurrence of involuntary movements observed during wakefulness during stage one sleep or after awakening or lightening of sleep but not in the deeper stages of sleep (Fish et al, 1991a). They did not find any evidence of abnormal sleep spindles in primary torsion dystonia (Fish et al, 1990) and axial atonia was maintained during REM sleep in dystonia (Fish et al, 1991b). By contrast, an earlier study also using polysomnography reported abnormalities including overabundance of stage 2 sleep, a characteristic pattern or spindle activity, increased latency to sleep and reduced sleep efficiency in 25 cases from the literature and 4 cases examined by the investigators (Jankel et al, 1983). In 10 patients with blepharospasm or Meige syndrome, Sforza et al (1991) found reduced REM

sleep and increased arousals despite reduced involuntary movements during sleep. In their sample of 9 CD patients, Lobbezoo et al (1996a) found polysomnography to be normal.

Several potential mechanisms of sleep problems in dystonia can be envisaged. Sleep problems may be primary such that the same biological mechanism that causes dystonia also gives rise to sleep problems. By contrast, the sleep problems could be secondary to the severity of involuntary movements and pain, although these generally improve during sleep and dystonia disease severity has not been found to correlate with sleep problems in most studies and only Sforza et al (1991) found such an association. Alternatively, sleep problems could be side effects of anticholinergic or long term benzodiazepine use in dystonia. Sleep problems are frequent symptoms of depression and depression is common in dystonia. While the results of Paus et al (2011) suggest such an association between depression and sleep problems in dystonia, Eichenseer et al (2014) found group differences in sleep problems between dystonia patients and healthy controls even after controlling for depression, anxiety, age, gender and benzodiazepine use; suggesting that these factors are not solely responsible for development of sleep problems in dystonia. Two recent studies (Paus et al 2011 and Eichenseer et al 2014) have reported that sleep problems are not improved with botulinum toxin injections despite significant improvement of the dystonia and pain after such treatment.

Pain in dystonia

Pain is the presenting symptom in 10% of patients with CD (Lowenstein & Aminoff, 1988) and is a common experience in this type of dystonia, reported by 66% to 90% of CD (Lowenstein & Aminoff, 1988; Chan et al, 1991, Jankovic et al, 1991; Kutvonen et al, 1997; Paus et al, 2011; Charles et al, 2014). Charles et al (2014) conducted a multicenter study with 88 centres in the

US, on 1000 plus CD patients. 90% of the sample had pain and 10% did not. The patients with no pain were older, but the two groups did not differ in any other demographic variables. Those with pain were twice as likely to be unemployed and to have stopped working as a result of CD, clearly demonstrating the impact of pain on daily living. Pain is also experienced in other forms of dystonia. For example 62% of patients with blepharospasm report experiencing pain (Paus, et al, 2011) and 56% of 125 people with writer's cramp reported pain in the forearm while writing (Jhunjhunwala et al, 2015).

Evidence about pain thresholds in dystonia is inconsistent. Pain-pressure thresholds were found to be two times lower in dystonia compared with healthy controls (Lobbezoo et al., 1996b). However, in another study, reduced pain ratings and mechanical pain sensitivity and increased mechanical pain thresholds were reported in the affected side of patients with focal hand dystonia (Suttrup et al., 2011), but these results could be attributed to the beneficial effects of botulinum toxin treatment.

In a large scale (N=478) recent study, Berman et al (2017) addressed the question of whether the psychiatric manifestations of adult-onset focal dystonia differ according to the site of onset of dystonic symptoms and how these related to dystonia and pain severity. They found high levels of depression, anxiety and social anxiety in all groups with focal dystonia, although the severity of anxiety and social anxiety symptoms varied by onset site. The most pronounced differences reported were higher anxiety in cervical and laryngeal dystonia and lower anxiety in upper cranial dystonia and higher social anxiety in laryngeal dystonia. For all groups, increased pain was associated with worse neuropsychiatric symptoms. However, higher anxiety and social anxiety in laryngeal dystonia and lower anxiety in upper cranial dystonia persisted after

correcting for pain and dystonia severity. These results were interpreted as indicating that anxiety and social anxiety differ by the site of onset of the adult-onset focal dystonias, differences which are not simply accounted for by pain or dystonia severity. This raises questions about the potential aetiology of these psychiatric manifestations which we consider next.

Are Psychiatric Disorders in Dystonia Primary or Secondary?

A key question is whether psychiatric disorder in dystonia is primary, and has a biological basis, or if it is secondary to the onset and experience of living with dystonia? There is evidence supporting both these possibilities. A similar conclusion was reached from a review of evidence to examine the hypothesis that mood and anxiety disorders are intrinsic to the neurobiology of dystonia which also concluded that emotional reactivity, particularly in the context of pain secondary to dystonia also needs to be recognized as contributing to the psychiatric problems in dystonia (Zurowski et al, 2013)

In support of the primary nature of psychiatric disorder in dystonia, in a proportion of cases, the onset of psychiatric disorder precedes the development of dystonia (Lauterbach et al, 2004; Wenzel et al., 1998; Moraru et al., 2002). As many as 69% (Fabbrini et al, 2010) or 42% (Wenzel et al, 1998; Moraru et AL, 2002) of patients are reported to have had psychiatric disorders prior to the dystonia onset, and in another study, the mean age at which psychiatric disorder was identified preceded the average age of onset of dystonia (Lencer et al., 2009). Further evidence comes from a study that showed higher rates of recurrent MDD in both MC and NMC of the DYT1 gene than NC (Heiman et al., 2004). Furthermore, a longitudinal follow-up study

reported that in CD, psychiatric disorders remained stable over 5 years despite improvement of dystonia (Berardelli et al, 2015).

Dystonia is often a disfiguring and disabling. The muscle contractions can be painful and dystonia can make participation in simple daily activities difficult, and in the visible forms of dystonia the outward disfiguring nature of the condition can have a negative impact on various aspects of the patient's life, particularly social interaction and engagement. There is also evidence supporting the secondary nature of psychiatric disorders in dystonia. Some studies have found that depression and anxiety are significantly associated with dystonia severity (e.g., Naber et al., 1988; Lewis et al., 2008; Scheidt et al., 1996; Berman et al, 2017). Others have shown negative perceptions, coping strategies, social support, and life events to be key predictors of depression in CD (Jahanshahi & Marsden, 1990; Jahanshahi, 1991; Lewis et al., 2008; Gundel et al., 2001; 2003). Furthermore, a longitudinal study showed that changes in mood tracked changes in severity of CD (Jahanshahi & Marsden, 1990b). Elsewhere, significant improvement of depression and anxiety have been noted when dystonia improves with botulinum toxin injections (e.g., Jahanshahi & Marsden, 1992; Whurr et al., 1998; Murry, Cannito, & Woodson, 1994) or deep brain stimulation (DBS) (e.g., Halbig et al., 2005; Kiss, 2007).

Figure 1 about here

Based on our research findings, we formulated a model of reactive depression and social avoidance in dystonia (Jahanshahi, 2005; see Figure 1), particularly CD where the abnormal postures and movements of the head are very visible. This gives rise to a sense of disfigurement which in turn can be associated with a negative body concept and perceived stigma. These in

turn can be associated with low self-esteem and depression on the one hand and social embarrassment and social avoidance on the other hand. While this reactive model of depression and social disability put forward by Jahanshahi (2005) has some support from the empirical evidence and results of regression analyses (Jahanshahi & Marsden, 1990a,b; Jahanshahi, 1991; Page et al, 2007; Lewis et al, 2008; Papathanasiou et al, 1997; 2001), it is also important to note that with correlational data such as these the direction of causality cannot be determined. Nevertheless, the important point to note is that the patient's perceived disfigurement and the associated social embarrassment can be considered as 'hidden' symptoms of dystonia.

To summarize, a considerable proportion of patients with various forms of focal, segmental, or generalized dystonia experience psychiatric disorders, with depression, anxiety, and OCD being the most common. In fact, a 4.5-fold increase in psychiatric morbidity in CD and blepharospasm (Lencer et al., 2009) and a 10-fold increase in social phobia in CD (Gundel et al, 2001) relative to the general population make these psychiatric comorbidities pressing features for the clinical management of dystonia. This evidence highlights the importance of identifying and treating psychiatric disorder in dystonia

Quality of life (QoL) in dystonia

As part of the Epidemiological Study of Dystonia in Europe across 7 European countries, Camfield and colleagues (2003) had the generic measure of QoL the SF36 completed by 289 CD patients via a postal survey. They compared QoL for the CD patients with published data for the general population, and previous studies on patients with Parkinson's disease, stroke or multiple sclerosis. The CD patients scored much worse in all 8 domains of the SF36, particularly in energy/vitality, pain, physical and emotional role limitation than a cross-section of the general

population of a similar age. Compared to the patients with the other three types of chronic neurological disorder, the CD patients scored better for physical functioning but worst for mental health and emotional role limitation.

On the same sample of CD patients as the Camfield study, Ben-Shlomo et al (2002), used multiple regression analysis to identify the most important predictors of the physical health and the mental health components of QoL on the SF36. Duration of illness (longer duration better QoL), global severity (self-rated on 0-10 scale, more severe CD worse QoL) and anxiety and depression were the significant predictors of *physical* health in CD. Self-deprecation, being single, disease duration, global severity, anxiety and depression were the significant predictors of *mental* health. The association of longer duration of illness with better quality of life suggests development of successful coping strategies in the course of the illness.

With Donna Page and Ginger Butler (Page et al, 2007), we administered the generic QoL measure, the EuroQoL to the sample of 372 patients with all forms of focal, segmental, multifocal, generalized dystonia recruited from the Epidemiological Study of Dystonia in Northeast of England. As shown in Figure 2, a higher percentage of patients with dystonia reported problems in all the QoL domains indicative of worse QoL on all the subscales including mobility, self-care, usual activities, pain and anxiety and depression relative to the normative data from the general population. The most frequently reported problems were in the domains of pain, followed by usual activities and then anxiety and depression. The mean VAS rating of overall life satisfaction was 60.7 (SD=20.3) which differed from the scores for the general population for all age groups.

Figure 2 about here

Skogseid et al (2007) used the SF36 to assess QoL in 70 patients with CD before and after 5 years of treatment with botulinum toxin injections. At baseline, the patients had lower scores on the SF36 in all domains, and they differed from the normative data by 1 SD. There is a bias towards women and older age in the CD population, and both female gender and age are associated with lower QoL satisfaction in the general population. The rated severity of CD correlated with the SF36 scores, and together with depression on the Hospital Anxiety and Depression Scale were predictive of QoL scores.

In another study, seventy three patients with generalized, hemi, segmental or focal dystonia and a group of healthy controls completed the SF36, Spielberger State Trait Anxiety Inventory, the Beck Depression Inventory and the Visual Analogue Scale ratings of mood, energy and fatigue (Soeder et al, 2009). All domains of the SF36 were worse in dystonia than in healthy controls. The VAS rating of fatigue predicted both the physical and mental health components of QoL on the SF36 after controlling for age, gender, depression and severity of dystonia.

Werle et al (2014) administered the Craniocervical dystonia questionnaire CDQ-24, a disease specific QoL measure, which has stigma, emotional well-being, pain, activities of daily living, and social/family life subscales to 70 CD patients and also used assessed CD severity. Pain was present in 84% of the sample and was a source of disability in 41%. The most frequent complaints were difficulty in keeping up with professional and personal demands (74.3%), feeling uneasy in public (72.9%), hindered by pain (68.6%), annoyed or bitter (47.1%) lonely or isolated (32.9%). They concluded that the physical, social and emotional aspects are the most affected components of QoL in CD. QoL was related to the severity of CD and also to pain.

The above review of some of the studies of the impact of dystonia on QoL clearly demonstrates that this movement disorder and its accompanying non-motor features such as depression, anxiety, fatigue and pain have an adverse effect on QoL of the patients. Similar to Parkinson's disease (Schrug, Jahanshahi & Quinn, 2000), depression and anxiety are the strongest predictors of quality of life in CD (Ben-Sholmo Camfield, & Warner, 2002) and other forms of focal, segmental, and generalized dystonia (Page, Butler, & Jahanshahi, 2007).

Impact of Medical and Surgical Treatment of Dystonia on Cognition, Psychiatric Morbidity, and Quality of Life

Medication is the first and most common treatment of dystonia. This usually includes anticholinergics, GABA-derivatives or benzodiazepines. Symptomatic relief of dystonia for periods up to 3 months is achieved with botulinum toxin injections into the affected muscles to induce temporary paralysis. Surgical interventions such as deep brain stimulation (DBS) of the internal segment of the globus pallidus (GPi) or the subthalamic nucleus result in an average symptomatic improvement ranging from 55–73% (Tagliati et al, 2011).

The evidence on the impact of DBS treatment of dystonia on cognition, psychiatric morbidity, and quality of life was reviewed by Jahanshahi, Czernecki, and Zurowski (2011).

Cognition

The effect of high-dose anticholinergic medication on cognitive function in adults with dystonia was investigated by Taylor et al (1991). They found poorer performance on explicit memory and

worse performance on the Stroop in patients with dystonia compared to matched healthy controls after starting treatment with high dose anticholinergics.

As noted above, attempts to consciously control the symptoms may influence cognitive performance (Jahanshahi et al., 2003) and some support for this is provided by Allam et al. (2007) who found that sustained attention deficits relative to healthy controls improved substantially with the improvement of blepharospasm following administration of botulinum toxin injections. However, this effect requires further verification in future studies.

Five studies have specifically examined changes in cognition following bilateral DBS of GPi or STN in idiopathic or DYT1 dystonia using detailed neuropsychological assessment (Halbig et al, 2005; Pillon et al, 2006; Jahanshahi et al, 2014; Owen et al, 2015; Dinkelbach et al, 2015), and others present results on cognition as part of clinical investigations (Vidailhet et al., 2007; Kupsch et al., 2006; Hung et al., 2007; Valdeoriola et al., 2010; Kleiner-Fisman et al., 2007; Ostrem et al., 2011). These results indicate that DBS treatment of idiopathic or DYT1 dystonia is not associated with change in major domains of cognition, other than a deficit on a test of sustained attention (Jahanshahi et al, 2014) and decline in alternating category fluency (Dinkelbach et al, 2015). However, individual patients show postoperative decline on specific cognitive tests (e.g., Halbig et al., 2005; Kleiner-Fisman et al., 2007; Jahanshahi et al., 2014; Owen et al, 2015). Some studies have also reported improvement of aspects of cognitive function following DBS surgery (Halbig et al, 2005; Pillon et al, 2006; Owen et al, 2015). However, in the absence of unoperated control groups or a failure to use parallel versions of cognitive tests; practice effects, postsurgical reduction of anticholinergic medication, and

improved motor symptoms are potential confounding factors for such observation of better performance on some cognitive tests after surgery.

Psychiatric Morbidity

Symptomatic treatment of dystonia with botulinum toxin injections results in improvement of mood. Following such injections, improvements in depression and functional ability have been reported in CD (Jahanshahi & Marsden, 1992) and improvements in depression and anxiety in spasmodic dysphonia (e.g., Murry et al, 1994; Whurr et al, 1998).

Assessing patients' psychiatric status prior to surgery is essential. Since suitability for DBS requires exclusion of patients with major psychiatric disorders, the evidence on the impact of DBS surgery on psychiatric comorbidity may not be fully representative of the range or severity of psychiatric disorders associated with dystonia (Jahanshahi et al, 2011). Mild to moderate depression is significantly improved after GPi-DBS in dystonia (Halbig et al., 2005; Kupsch et al., 2006; Kiss 2007, Valderiorla et al., 2010). These same studies show that anxiety tends to remain stable after surgery, possibly due to post-surgical reduction of benzodiazepines with improvement of dystonia (see Jahanshahi et al., 2011 for review). Although OCD is another common psychiatric disorder in dystonia, to date, none of the studies have reported the impact of DBS surgery on OCD symptoms.

There has been one case report of migration of the implanted electrode to the region of the amygdala causing depression with delusions and severe apathy (Piacentini et al., 2008). The most serious psychiatric adverse effect of DBS surgery in primary dystonia has been suicide. Two of the 16 dystonia cases (12.5%) in the sample of Foncke et al (2006) committed suicide. A

multitude of factors influence suicidal behaviour, and it is not clear whether suicide following DBS is a result of the stimulation spreading to limbic circuits or reflects problems with readjustment to change following surgery. Suicide is a preventable adverse effect of DBS surgery, and careful pre-operative psychiatric screening and frequent postoperative follow-up can be valuable in this regard (Jahanshahi et al., 2011).

Table 3 about here

Quality of Life

Some of the studies examining the effect of treatment of dystonia with botulinum toxin on QoL are summarized in Table 3. With some minor exceptions, this evidence indicates that botulinum toxin treatment improves QoL in all forms of focal and non-focal dystonia. This improvement in QoL following botulinum toxin injections has been mainly in the pain-related as well as in the social, emotional and physical functioning domains (Brefel-Courbon et al, 2000, Hogikyan et al, 2001; Hilker et al, 2001).

QoL measures, usually the SF36 but also the EuroQoL, have been included as primary outcome measures in studies of DBS for dystonia. The majority of these studies report significant improvement in QoL following DBS surgery. The improvement ranges from 36% to 51% (Jahanshahi et al, 2011). Some studies report that QoL improved in all domains of the SF36 (Skogseid, 2008), whereas others reported improvement in specific domains (eg pain, physical functioning or general health (eg Vidailhet et al, 2007) or the mental component only (Kleiner-Fisman et al, 2007). An interesting finding which emerged from a qualitative analysis of post-surgical interviews with 14 dystonia patients who had GPi-DBS was the observation that the rapid physical change produced by the surgery was a challenge to the patients' identity. Some

referred to the dissociation between their new body with improved posture and feeling the same inside. This was exemplified by the statement from one patient that “Even though I have been given a new body, I haven’t been given a new mind. It’s like plastic surgery, you might change your nose but how you feel about yourself is still the same.” Thus, despite the significant improvement of their movement disorder, the patients found life post-DBS challenging and voiced a need for guidance and counselling to come to terms with the rapid physical changes brought about by the surgery (Hariz et al, 2011).

Conclusions and Future Directions

In idiopathic and DYT1 dystonia, most cognitive domains including IQ, memory, and language are intact and isolated deficits in executive function, set shifting, visuo-spatial processing, praxis, mental rotation, and sequence learning have been reported. Psychiatric disorders, particularly depression, anxiety, and OCD are common in dystonia. It is unclear whether psychiatric comorbidity in dystonia is a primary feature of the illness or a secondary reaction to the disabling and disfiguring movement disorder, and there is currently evidence supporting both possibilities. To address the question of whether psychiatric disorders in dystonia are primary or secondary, further studies examining associations between presence of specific dystonia genetic mutations and psychiatric disorders would be informative. Furthermore, the relation of the severity of the dystonia symptoms to psychiatric comorbidity has not been extensively examined and could be a topic for future investigation. This coupled with longitudinal studies of changes in dystonia symptoms and psychiatric comorbidity over time from the early stages of the illness, can clarify any synchrony or temporal dissociation between these various aspects of the disorder. Imaging studies comparing dystonia patients with or without cognitive executive deficits and psychiatric disorders would also help clarify the neural substrates of these non-motor symptoms.

The evidence reviewed here shows that, similar to Parkinson's disease, dystonia is also a movement disorder with prominent non-motor features including executive dysfunction, depression, anxiety, OCD, sleep problems, and pain. Furthermore, non-motor features such as depression and anxiety have been shown to have a major influence on the quality of life of patients with primary dystonia (Ben-Shlomo et al., 2002; Page et al., 2007), which suggests that they should also be the focus of clinical management in dystonia alongside the movement disorder.

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Author	N	Sample characteristics	Measures	Main findings
Jahanshahi 2003	10 12	Various (3 generalized, 5 cervical and 2 focal arm) Age and IQ matched controls	National Adult Reading Test, Stroop, Verbal fluency (phonemic, semantic, alternating categories), WCST, random number generation, Missing Digit test, Paced Visual Serial Addition Test, Self-ordered random number sequences; Visual conditional associative learning; Single and Dual task performance (tapping and pegboard) BDI	Poorer semantic word fluency and dual task performance relative to controls, but group differences not significant after Bonferroni correction. No deficits on other cognitive tests
Scott 2003	14	Various (11 generalized, 2 focal and 1 segmental)	CANTAB (ID/ED set shifting; reaction time; spatial working memory; spatial span; stockings of cambridge; rapid visual information processing test); Functional Limitations Profile; HADS; SF36	Greater deficits on attentional set shifting relative to normative data. No deficits on other cognitive tests.
Balas 2006	28 28	Generalized (20 manifesting and 8 non-manifesting DYT1 gene carriers) Education, gender, and IQ matched controls	CANTAB ID/ED set shifting; stockings of Cambridge; spatial working memory; spatial span; spatial span reverse; Judgment of line orientation; Purdue pegboard; Raven's matrices; RAVLT; Rey complex figure; STAI; Stroop; TMT; Verbal fluency (phonemic and semantic); Visual analogue scale; WAIS-III (digit span; similarities; symbol search);	Increased verbal memory retroactive interference in symptomatic DYT1 group relative to controls. No deficits on other cognitive tests.
Allam 2007	9 9	Blepharospasm Age and education matched controls	RAVLT; SAT; Stroop; Toulouse Pieron Test; WMS-R (digit and digit symbol subtests)	Deficits in sustained attention. No deficits in other cognitive tests.
Bugalho 2008	45 27	Various (15 Blepharospasm 15 Cervical dystonia 15 Writer's cramp) Age, gender, and education matched controls	Benton visual retention test; Stroop; WAIS-Block assembly test; WCST; Y-BOCS	More perseverative errors on WCST relative to controls. No deficit on other cognitive tests.

Aleman 2009	20	Blepharospasm	BAI; BDI; Digital recognition; Oral making trails; Purdue pegboard test; Raven's matrices; Tactile denomination; Tapping test; WAIS-I (five digits test, manual sequences); WCST; WMS (lists of words I and II Spatial location)	More impairments in complex movement planning, motor dexterity, visuospatial working memory, and tactile object recognition relative to controls. No deficits on other cognitive tests.
	17	Age, gender and education matched controls		
Romano 2013	17	Cervical dystonia	N-back test; TMT; WCST; WMS	Patients showed working memory deficits on <i>n</i> -back test, impairment of mental control and visual reproduction subtests of WMS, deficits on processing speed and set shifting on TMT. No deficit on the WCST.
	28	Blepharospasm		
	37	Age and gender matched controls		
Foley et al 2017	25	Cervical dystonia	National Adult Reading Test, WAIS-III, MMSE, Recognition Memory for Words and Faces, Graded Naming Test, Trail-Making Test, Stroop test, Phonemic verbal fluency, WCST, Hayling Sentence completion Test, Brixton Spatial Anticipation Test, Elevator Counting subtest of the Test of Every Attention, Silhouettes and Incomplete Letters subtests of Visual Object and Space Perception Battery, HADS	No significant differences on any measure between the two dystonia groups. The dystonia patients were impaired on the Trail making test relative to controls and deficits on the Stroop and Hayling were found in 2 and 6 patients respectively. The severity of dystonia and mood did not correlate with performance on the cognitive tests
	13	Generalized dystonia		
	50	Age-matched controls		

BAI: Beck Anxiety Inventory; BDI: Beck Depression Inventory; CANTAB: Cambridge Neuropsychological Test Automated Battery; FAB: Frontal Assessment Battery; HADS: Hospital Anxiety and Depression Scale; ID/ED: Intra/Extra dimensional; MMSE: Mini Mental State Examination; RAVLT: Rey Auditory Verbal Learning Test; RNG: Sustained Attention Test; SF-36: Short Form 36; STAI: Spielberger State and Trait Anxiety Inventory; TMT: Trial Making Test; WAIS: Wechsler Adult Intelligence Scale; WCST: Wisconsin Card Sorting Test; WMS: Wechsler Memory Test; Y-BOCS, Yale-Brown Obsessive Compulsive Scale.

Table 1. Studies investigating cognitive function in idiopathic or DYT1 dystonia.

Table 2: Studies of sleep in dystonia. Bleph: blepharospasm, CD:cervical dystonia, HC: healthy controls. PGD:primary generalized dystonia, SGD: secondary generalized dystonia.

Authors	N	Sample	Main Findings
Silvestri et al (1990)	31	Bleph., Meige, Tourette	impaired sleep efficiency, reduced REM, Increased awakenings, correlated with disease severity
Sforza et al (1991)	10	Bleph. Meige	reduced REM sleep, increased arousal, reduced invol. movements during sleep
Fish et al (1991)	14 10	PGD SGD	no abnormal sleep spindles, axial atonia maintained during REM sleep
Lobbezoo et al (1996a)	9 9	CD HC	normal polysomnography, larger variance in sleep latency
Avanzino et al (2010)	52 46	Bleph. CD	75% Bleph. & 72% CD reduced sleep efficiency. in bleph. also sleep duration & latency affected. no correlation with disease severity, depression key factor
Paus et al (2011)	110 111	CD Bleph. HC	46% Bleph. & 44% CD & 46% had sleep problems Related to female gender, restless leg syndrome, bruxism. Daytime sleepiness rare (6%). Sleep problems not improved by botulinum toxin.
Eichenseer et al (2014)	54 52	CD HC	65% of CD impaired sleep quality or latency, no differences in daytime sleepiness, sleep not improved by botulinum toxin injections
Yang et al (2016)	60 60 60	CD Bleph. HC	33 of blepharospasm (55 %) and 43 of CD (71.7%) had sleep problems. No differences from HCs n daytime sleepiness. No correlation between severity of dystonia and sleep problems.

Table 3: Studies of the effect of treatment of dystonia with botulinum toxin injections on quality of life. QoL: quality of life; CD: cervical dystonia; Bleph: blepharospasm; OMD: oromandibular dystonia; V-RQoL: voice related quality of life

Figure 1: The Jahanshahi (2005) Reactive Model of Depression and Social Disability in Dystonia

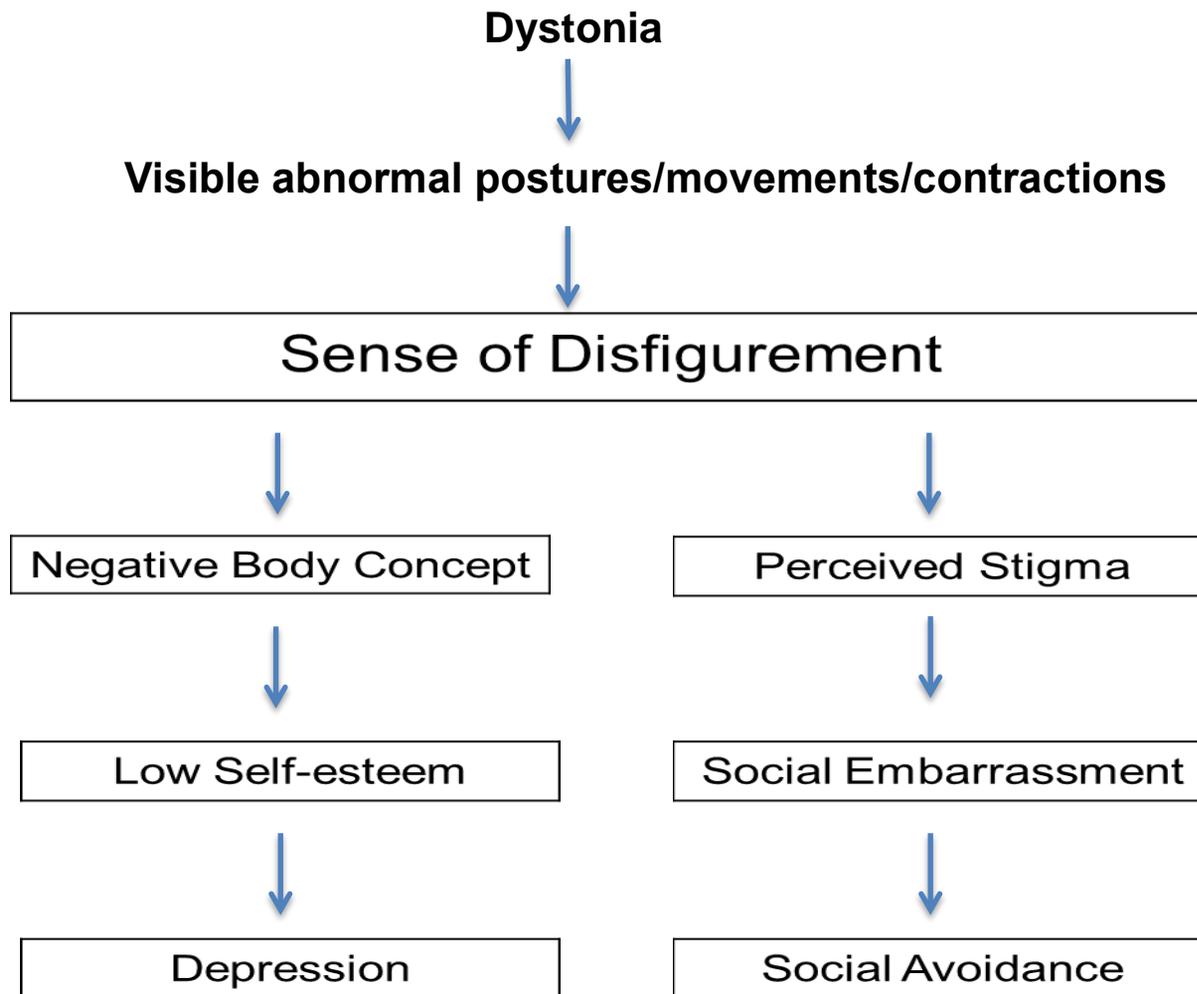


Figure 2: Scores on the five scales of quality of life on the EuroQoL in idiopathic focal, segmental and generalized dystonia relative to normative data from the general population. From Page, Butler, Jahanshahi (2007) with permission.

