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REVIEW ARTICLE

The non-motor syndrome of primary dystonia: clinical and pathophysiological implications

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Dystonia is typically considered a movement disorder characterized by motor manifestations, primarily involuntary muscle contractions causing twisting movements and abnormal postures. However, growing evidence indicates an important non-motor component to primary dystonia, including abnormalities in sensory and perceptual functions, as well as neuropsychiatric, cognitive and sleep domains. Here, we review this evidence and discuss its clinical and pathophysiological implications.

Keywords: primary dystonia; non-motor; sensory; depression; endophenotypes; pathophysiology; quality of life

Abbreviations: GABA = γ-aminobutyric acid

Introduction

Dystonia is a movement disorder characterized by involuntary muscle contractions resulting in twisting movements and abnormal postures. These impair both the quality and speed of voluntary movement (van der Kamp *et al.*, 1989; Agostino *et al.*, 1992; Inzelberg *et al.*, 1995; Curra *et al.*, 2000; Gregori *et al.*, 2008). Primary dystonia, where dystonia is the only motor feature (with or without tremor) and there is no neurodegeneration, can be due to *DYT1* (Stojanovic *et al.*, 1995; Leube *et al.*, 1997) or *DYT6* mutations (Valente and Albanese, 2010), but most commonly no gene can be identified.

Despite the 'motor' definition of primary dystonia in common usage, recent studies have revealed that apart from the movement disorder, there are other, non-motor, features in many patients with primary dystonia (Fabbrini *et al.*, 2011; Kuyper *et al.*, 2011). This is perhaps not surprising given the widespread abnormalities detected in non-motor brain regions in functional imaging studies of patients with dystonia. Moreover, even the core abnormality in cortico-striatal-thalamo-cortical circuits (Hallett, 2006) in primary dystonia might be expected to have non-motor consequences given that these circuits have been linked not only to motor but also to sensory, cognitive and reward processing (Graybiel *et al.*, 1994; Yin and Knowlton, 2006). The aims of the present article are to review the evidence for non-motor features of primary dystonia and to discuss their clinical and pathophysiological implications.

Non-motor features in primary dystonia

Sensory abnormalities

Symptoms and signs

Overt sensory signs in a patient with dystonia would indicate diagnoses other than primary dystonia; for example, some

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heredodegenerative forms of dystonia that cause sensory neuropathy (Khan *et al.*, 2003; Schneider and Bhatia, 2010), an incidental second disorder causing the sensory disturbance or secondary mechanical complications from abnormal postures, e.g. nerve root entrapment and carpal tunnel syndrome (Sheehy *et al.*, 1988; Drory *et al.*, 1991).

However, mild sensory symptoms such as discomfort in the neck months before cervical dystonia develops, irritation or dry eyes prior to the development of blepharospasm, and irritation of the throat prior to the development of spasmodic dysphonia has been reported (Ghika *et al.*, 1993). Sometimes, patients interpret their dystonic movements as an attempt to decrease this discomfort (Martino *et al.*, 2005; Defazio *et al.*, 2007). Disease-related pain occurs in up to 70% of patients with cervical dystonia and up to 30% in focal hand dystonia and writer's cramp (Pekmezovic *et al.*, 2009; Tepavcevic *et al.*, 2009). Pain–pressure thresholds have been found to be two times lower in dystonia compared with healthy controls (Lobbezoo *et al.*, 1996). 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.

The 'sensory trick' (geste antagoniste) indicates an involvement of sensory afferent input in dystonia and can be observed in up to 70% of patients with cervical dystonia and in lower percentages in other forms of focal dystonia (Yoshida *et al.*, 1998; Wissel *et al.*, 1999; Masuhr *et al.*, 2000; Naumann *et al.*, 2000; Muller *et al.*, 2001; Lo *et al.*, 2007; Schramm *et al.*, 2007). Electrophysiological studies have shown that the sensory trick modifies EMG recruitment, sometimes even before the hand makes contact with the face (Tang *et al.*, 2007). Although its pathophysiology remains unknown, altered sensorimotor integration could be implicated.

Experimental abnormalities

Apart from these symptoms and signs, there are abnormalities involving sensory input and its integration with motor actions that are revealed by specific experimental techniques. The trigger for these tests was in part a primate model of dystonia in which enlarged and overlapped sensory receptive fields were found (Byl *et al.*, 1996), a finding that was confirmed later in EEG, magnetoencephalographic (Bara-Jimenez *et al.*, 1998; Elbert *et al.*, 1998) and functional MRI studies (Butterworth *et al.*, 2003; Nelson *et al.*, 2009).

A higher temporal discrimination threshold and spatial discrimination threshold have been found in adult-onset primary dystonia (Bara-Jimenez *et al.*, 2000; Sanger *et al.*, 2001; Tinazzi *et al.*, 2002; Aglioti *et al.*, 2003; Fiorio *et al.*, 2003, 2007, 2008*a*; Lim *et al.*, 2003; Molloy *et al.*, 2003; O'Dwyer *et al.*, 2005; Walsh and Hutchinson, 2007; Bradley *et al.*, 2009, 2010, 2011; Scontrini *et al.*, 2009) (Tables 1 and 2). Temporal discrimination threshold is also abnormal in *DYT1* manifesting and non-manifesting mutation carriers (Fiorio *et al.*, 2007), while spatial discrimination threshold is normal in *DYT1* manifesting carriers (Molloy *et al.*, 2003), suggesting a partially different pathophysiology in the two forms of dystonia (Table 1). Abnormal temporal discrimination threshold and spatial discrimination threshold have been found in the affected and unaffected body regions with no correlation with disease severity (Bara-Jimenez *et al.*, 2000; Sanger *et al.*, 2001; Walsh *et al.*, 2009; Scontrini *et al.*, 2011), and in patients' unaffected first and second degree relatives (O'Dwyer *et al.*, 2005; Bradley *et al.*, 2009, 2010, 2011; Walsh *et al.*, 2009), suggesting a primary endophenotypic deficit rather than a deficit secondary to the presence of dystonic contractions (Tables 1 and 2).

Kinaesthesia and vibration-induced illusion of movement have been found to be impaired in patients with adult-onset primary dystonia in the affected and unaffected body regions (Grunewald *et al.*, 1997; Rome and Grunewald, 1999; Frima *et al.*, 2003, 2008; Putzki *et al.*, 2006) and in asymptomatic first degree relatives (Frima *et al.*, 2008), indicating again the probable primary origin of this feature. In fact, vibration not only produces an abnormal perception of the stimulus, but also may induce or worsen focal hand dystonia, which implies that dystonic muscles have an abnormal sensitivity to vibration at rest (Kaji *et al.*, 1995*a*). In addition, blocking the action of muscle afferents with lidocaine abolishes or markedly improves the symptoms in patients with writer's cramp (Kaji *et al.*, 1995*a*; Yoshida *et al.*, 1998). These findings implicate muscle spindle afferent dysfunction or dysfunction in processing of muscle spindle afferent feedback (Table 1).

Mental rotation of corporeal objects (Thayer *et al.*, 2001), reflecting mental simulation of movements, is driven by the central 'body schema', which depends on the integrity of a distributed network involved in the integration of sensory information with motor actions (Vingerhoets *et al.*, 2002; Wolbers *et al.*, 2003; de Lange *et al.*, 2005). Mental rotation is found abnormal in both focal hand dystonia and cervical dystonia (Fiorio *et al.*, 2006). Similarly, both manifesting and non-manifesting *DYT1* carriers are slower than healthy controls in giving laterality judgements on different body parts (Fiorio *et al.*, 2008*b*).

In summary, this evidence suggests the existence of a primary deficit in sensory input and processing in primary dystonia.

Neuropsychiatric abnormalities

Clinical observation of the frequent co-existence of depression and anxiety in patients with dystonia, as well as a growing recognition that cortical–limbic–striatal dysfunction is involved in depression and other neuropsychiatric disorders (Stefurak *et al.*, 2003) forms the background to numerous studies assessing neuropsychiatric abnormalities in primary dystonia (Jahanshahi, 1991; Lauterbach *et al.*, 1992, 2004; Wenzel *et al.*, 1998; Gundel *et al.*, 2001, 2003; Cavallaro *et al.*, 2002; Moraru *et al.*, 2002; Muller *et al.*, 2002; Heiman *et al.*, 2004; Miller *et al.*, 2007; Slawek *et al.*, 2007; Lewis *et al.*, 2008; Lencer *et al.*, 2009; Pekmezovic *et al.*, 2009; Voon *et al.*, 2010). However, most published studies are limited in their methodology; therefore, here we summarize studies which included a large number of patients, where diagnosis was based on the structured clinical interview for DSM-IV or other standardized clinical scales were used and results were compared with healthy controls or another group (Table 1).

From 89 consecutive patients with various forms of focal dystonia, 57.3% had psychiatric disorders (versus 24.1% healthy subjects versus 34.6% patients with hemifacial spasm), which started

Table 1 Overview of the main non-motor features of primary dystonia

Primary dystonia	Sensory abnormalities				Neuropsychiatric abnormalities	
Adult-onset primary dystonia	**Temporal discrimination (higher TDT)**	**Spatial discrimination (impaired SDT)**	**Vibration (impaired VIIM)**	**Impaired mental rotation task**	**Risk for Anxiety (higher)**	**Risk for Depression (higher)**
Blepharospasm	**Yes** (Fiorio 2008; Scontrini 2009; Bradley 2011)	**Yes** (Molloy 2003; Walsh 2007; Walsh 2009)	**Yes** (Grunewald 1997; Yoneda 2000)	not tested	**No** (Fabbrin 2010)	**Yes** {39,3% vs. 4% HC (Fabbrini 2010)}
Focal hand dystonia	**Yes** (Bara-Jimenez 2000; Tamura 2008; Bradley 2009)	**Yes** (Bara-Jimenez 2000; Bradley 2010; Molloy 2003)	**Yes** (Frima 2003; Rome 1999; Putzki 2006)	**Yes** (Fiorio 2006)	**No** (Fabbrini 2010)	**No** (Fabbrini 2010)
Writer's cramp	**Yes** (Sanger 2001; Fiorio 2003; Scontrini 2009)	**Yes** (Sanger 2001; Bradley 2010; Bara-Jimenez 2000)	**Yes** (Yoneda 2000)	**Yes** (affected and unaffected hand but not the feet; Fiorio 2006)	**No** (Fabbrini 2010) **Yes** (Gundel 2001; Lencer 2009)	insufficiently tested
Cervical dystonia	**Yes** (Tinazzi 2004; Scontrini 2009; Bradley 2009; 2010; 2011)	**Yes** (Bradley 2010; Molloy 2003)	**Yes** (Yoneda 2000)	**Yes** (head, hand and feet; Fiorio 2007)	**No** (Fabbrini 2010)	**Yes** {26.4% vs. 6% HC (Fabbrini 2010) 17.95%, no control group (Voon 2010)}
Laryngeal dystonia	**Yes** (Scontrini 2009; Bradley 2009; 2011)	insufficiently tested (Walsh 2009)	not tested	not tested	**No** (Fabbrini 2010)	**Yes** {14.6% vs. 3.7% (Gundel 2007)} **No** (Fabbrini 2010)
Generalized	**Yes** (Tinazzi 2002; Aglioti 2003)	insufficiently tested (Walsh 2009)	not tested	not tested	not tested	not tested
Unaffected relatives	**Yes** in first and second degree (CD, WC, FHD) (Bradley 2009; 2010; 2011)	**Yes** 24% first and second degree (FHD) (O'Dwyer 2005) **Yes**, 50% first degree (CD, WC) (Bradley 2010)	**Yes** 60% first degree (CD) (Frima 2008)	not tested	not tested	Family history of depression in 41,02% of FHD, no control group (Voon 2010)
DYT1 dystonia						
manifesting carriers	**Yes,** tactile, visuotactile (vs. non-carriers) (Fiorio 2007)	**No** (Molloy 2003)	not tested	**Yes** (Fiorio 2008)	**No** (Heiman 2007)	**Yes** (Heiman 2004)
non-manifesting carriers	**Yes,** tactile, visuotactile (vs. non-carriers) (Fiorio 2007)	not tested	not tested	**Yes** (Fiorio 2008)	**No** (Heiman 2007)	**Yes** (Heiman 2004)

The main studies performed are given in the brackets.
CD= cervical ystonia; FHD= focal hand dystonia; SDT= spatial discrimination threshold; TDT= temporal discrimination threshold; VIIM= vibration induced illusion of movement; WC= writer'scramp.

Table 2 Overview of the most important studies assessing temporal discrimination in primary dystonia

References	Cohort	Stimulus	Temporal discrimination threshold	Correlation with motor impairment	Treatment
Bara-Jimenez, 2000	4 WC; 10 FHD; 13 healthy controls	Tactile	Patients: 96.7 ms versus healthy controls: 64.4 ms	No	The last three months no treatment; before that NA
Sanger, 2001	9 WC; 10 healthy controls	Tactile	Patients: 107 ms versus healthy controls: 46 ms	No	The last three months no treatment; before that NA
Tinazzi, 2002	8 Generalized; 1 WC; 1 segmental; 12 healthy controls	Tactile	Patients: 107.3 ms versus healthy controls: 35.7 ms	No	3 BT (6 months before); 2 anti-cholinergics; 5 none
Aglioti, 2003	8 Generalized; 10 healthy controls	Tactile; visual; visuotactile	Significantly higher in patients	Yes, with visuotactile stimuli	4 BT (4–5 months before); 2 anti-cholinergics; 2 none
Fiorio, 2003	14 WC; 13 healthy controls	Tactile; visual; visuotactile	Significantly higher in WC versus healthy controls in tactile and visuotactile No impairment in visual stimuli	Yes	8 None; 6 BT (6 months before)
Tinazzi, 2004	10 CD; 5 cervical pain; 10 healthy controls	Tactile; visual; visuotactile	Significantly higher in CD versus pain and healthy controls in tactile and visuo-tactile No impairment in visual stimuli	NA	8 BT (6 months before); 2 none
Fiorio, 2007	DYT1: 9 MC; 11 NMC; 9 NC; 11 healthy controls	Tactile; visual; visuotactile	Significantly higher in DYT1 MC and NMC carriers versus NC and healthy controls in tactile and visuotactile stimuli	No	3 Untreated; two BT (6 months before); 4 deep brain stimulation GPi
Fiorio, 2008a	19 BS; 19 HMS; 19 healthy controls	Tactile	Significantly higher in BS versus HMS versus healthy controls	No	All BT (5 months before)
Tamura, 2008	11 FHD; 11 healthy controls	Tactile	Significantly higher in FHD versus healthy controls	No	None BT (3 months before)
Scontrini, 2009	35 BS; 30 CD; 8 FHD; 9 LD; 35 healthy controls; 26 HMS	Tactile	Significantly higher in all three body regions–two affected and one unaffected in patients versus healthy controls	No	All BT (5 months before)
Bradley, 2009	20 CD; 13 FHD; 1 LD; 1 musician's dystonia; 42 first-degree relatives; 32 second-degree relatives	Tactile; visual	Significantly higher in 95% CD, 77% FHD; 52% first-degree relatives; 50% second-degree relatives	No	18 Patients, no statistical correlation between TDT and time since last injection (mean: 8.2 weeks)
Bradley, 2010	14 CD; 10 WC; 34 first degree unaffected relatives	Tactile; visual; visuotactile	Significantly higher to all stimuli in 83% of the patients and 41% of the first degree relatives	No	NA
Bradley, 2011	37 CD; 14 WC; 9 BS; 11 LD; 8 musician's dystonia	Tactile; visual; visuotactile	Significantly higher to all stimuli in 97.3% CD, 85.7% WC, 88.8% BS, 90.1% LD, 62.5% musicians, lower sensitivity of the visuotactile stimuli	NA	NA
Scontrini, 2011	24 CD versus healthy controls	Tactile	Significantly higher before and after 1 and 2 months botulinum toxin injections	No	TDT remained significantly higher before and after 1 and 2 months borulinum toxin injections

BS = blepharospasm; BT = botulinum toxin; CD = cervical dystonia; FHD = focal hand dystonia; GPi = globus pallidus interna; HMS = hemifacial spasm; LD = laryngeal dystonia; MC = manifesting carriers; NA = not available; NC = non-carriers; NMC = non-manifesting carriers; TDT = temporal discrimination threshold; WC = writer's cramp.

on average 18.4 ± 13.9 years before the onset of dystonia (Fabbrini *et al.*, 2010) (Table 1). No differences were found between patients with and without psychiatric disturbances with respect to age, dystonia duration and severity, and botulinum toxin treatment duration, implying that psychiatric symptoms were primary rather than a consequence of the motor disorder (Fabbrini *et al.*, 2010). The finding that female patients with cervical dystonia have higher psychiatric comorbidity than female patients with alopecia areata also suggests that this may be a primary feature of the disorder rather than simply a consequence of chronic disease and disfigurement (Gundel *et al.*, 2003).

With regard to depressive disorders, these appear to be more frequent in cervical dystonia, blepharospasm, laryngeal dystonia and focal hand dystonia compared with healthy controls, and there is also more commonly a family history of depression in focal hand dystonia than controls (Gundel *et al.*, 2003; Lencer *et al.*, 2009; Voon *et al.*, 2010) (Table 1). The severity of depression in patients with dystonia is, apart from one study (Gundel *et al.*, 2007), not correlated with the severity of dystonia, suggesting a primary rather than a secondary abnormality. However, some proportion of depression in patients with dystonia may be secondary to motor symptoms and pain as improvement in mood does occur with successful treatment of dystonia (Skogseid *et al.*, 2007; Mueller *et al.*, 2008).

In manifesting and non-manifesting *DYT1* mutation carriers, the risk of recurrent major depressive disorder is increased compared with non-carriers (Heiman *et al.*, 2004). Carriers had earlier age at onset of recurrent major depressive disorder than non-carriers and the severity of motor signs was not associated with the likelihood of recurrent depression. Mutation carriers did not have an increased risk for other affective disorders, such as single major depression or bipolar disorder (Heiman *et al.*, 2004). These findings support the hypothesis that recurrent major depression is an independent expression of the *DYT1* dystonia mutation and is not necessarily a result of experiencing the disability caused by motor symptoms.

This fairly consistent picture of an excess incidence of depression in patients and unaffected gene carriers is less clear with regard to anxiety disorders (Cavallaro *et al.*, 2002; Lencer *et al.*, 2009) (Table 1). An increased frequency of anxiety disorders including obsessive–compulsive disorder and social phobia in patients with adult-onset focal dystonia has been reported by many studies with methodological deficiencies (Bihari *et al.*, 1992*a*, *b*; Broocks *et al.*, 1998; Wenzel *et al.*, 1998; Cavallaro *et al.*, 2002; Moraru *et al.*, 2002). In contrast, in a case–control study on 89 patients, a similar rate of anxiety disorders assessed using the structured clinical interview for DSM-IV, the Yale–Brown Obsessive–Compulsive Scale, the Hamilton Rating Scale for Anxiety and the Beck Depression Inventory was found compared with healthy controls and patients with hemifacial spasm (Fabbrini *et al.*, 2010). In a separate controlled study in *DYT1* mutation carriers, no evidence suggesting higher risk of anxiety disorders in *DYT1* carriers was found (Heiman *et al.*, 2007). Thus, in contrast to depression, anxiety disorders do not seem to represent a primary non-motor feature of dystonia, according to the existing data.

Although beyond the scope of this review in which we focus on primary dystonia, it is of interest that in DYT11 myoclonus dystonia, obsessive–compulsive disorder and alcohol dependence are common in symptomatic gene carriers (Saunders-Pullman *et al.*, 2002). In a more recent study, obsessive–compulsive disorder was not associated with the DYT11 phenotype, while depressive and anxiety symptoms were increased in symptomatic, but not in asymptomatic carriers, pointing to a possible secondary deficit. Moreover, myoclonus dystonia improves with alcohol and this could be the reason for the higher alcohol dependence (Foncke *et al.*, 2009).

In summary, depression appears to represent a primary feature of primary dystonia, whereas other psychiatric abnormalities have a less certain relationship and need additional evaluation.

Cognition

Scott *et al.* (2003) found an attention–executive cognitive deficit on the Cambridge Neuropsychological Test Automated Battery in 14 patients with young-onset generalized (both *DYT1* positive and negative) and adult-onset focal and segmental dystonia, although the security of these data are compromised by the heterogeneity of the group and concomitant therapy with dopaminergic and anti-cholinergic medication. A separate study confirmed the presence of an attention deficit in patients with cervical dystonia compared with healthy controls (Allam *et al.*, 2007), but this improved to control values after botulinum toxin treatment, suggesting that this might be a secondary phenomenon related to the distracting effects of dystonic spasms (Allam *et al.*, 2007). Although not assessed in this study, it seems likely that other non-motor features described above, such as pain and depression, could contribute to the attention deficit as well. In non-DYT1 primary generalized dystonia, no cognitive deficit compared with healthy controls has been detected in two studies (Vidailhet *et al.*, 2005; Pillon *et al.*, 2006), and no cognitive abnormalities have been found in either manifesting or non-manifesting *DYT1* gene carriers (Anca *et al.*, 2003).

In summary, there is evidence of little or no alteration of cognitive functions in primary dystonia, and evidence to suggest that the attention deficit and subtle cognitive alterations in some studies may well be related to the distracting effects of abnormal movements and pain.

Sleep

Some early nocturnal polygraphic studies on blepharospasm, cranial and oromandibular dystonia found impaired sleep efficiency, reduced REM sleep and increased awakenings, which were correlated with disease severity (Silvestri *et al.*, 1990; Sforza *et al.*, 1991). Quantitative analysis of involuntary movements showed that abnormal muscular activity significantly decreased from wakefulness to non-REM and REM sleep. While the abnormal movements progressively decreased they did not disappear, and discharges gradually increased prior to awakening (Sforza *et al.*, 1991).

Impairment in the Pittsburgh Sleep Quality Index was found in patients with focal dystonia compared with healthy controls with

no correlation with dystonia severity scores but a correlation with depression scores, suggesting that sleep disorders may in part be secondary to depression (Avanzino *et al.*, 2010) (Table 1). No excessive daytime sleepiness (Epworth Sleepiness Scale) has been found compared with healthy controls (Avanzino *et al.*, 2010; Paus *et al.*, 2011). Increased daytime sleepiness was found in one study (Trotti *et al.*, 2009), which however could be attributed to the use of anti-cholinergic medications.

In a recent study on 221 patients with cervical dystonia and blepharospasm compared with healthy controls, impaired sleep quality was found in 44, 46 and 20%, respectively, as assessed with Pittsburgh Sleep Quality Index (Paus *et al.*, 2011). There was no correlation with dystonia severity as assessed by the Toronto Western Spasmodic Torticollis Rating Scale and the Jankovic Rating Scale and patients did not experience amelioration of poor sleep by botulinum toxin treatment. Nevertheless, sleep impairment was correlated with depression (Beck Depression Inventory) (Paus *et al.*, 2011). Bruxism and female sex were identified as further risk factors. Approximately 28% of the patients in each group were on anti-depressants, hypnotics and analgesics, which could have affected the results (Paus *et al.*, 2011). No studies addressing these issues have been conducted in DYT1 dystonia.

In summary, it seems that sleep impairment may be a feature of primary dystonia that is independent of the severity of the motor features of the disorder. It is, however, correlated with depression and therefore it is not clear at present if there is a primary sleep abnormality in dystonia. Further studies on sleep in focal dystonia including polysomnographic recordings are warranted to address this issue.

Clinical implications

Quality of life

The impact of non-motor symptoms on 'Quality of Life' in primary dystonia has been assessed in several studies mostly using the short form-36 (SF-36) or in the case of cervical dystonia, the Cervical Dystonia Impact Profile-58 (Gudex *et al.*, 1998; Lindeboom *et al.*, 1998; Ben-Shlomo *et al.*, 2002; Muller *et al.*, 2002; Cano *et al.*, 2006). Pain, depression and anxiety (Ben-Shlomo *et al.*, 2002; Slawek *et al.*, 2007) have been shown to be significant determinants of quality of life in focal and DYT1 dystonia (Ben-Shlomo *et al.*, 2002; Page *et al.*, 2007; Pekmezovic *et al.*, 2009; Tepavcevic *et al.*, 2009; Zhang *et al.*, 2010). Patients with cervical dystonia seem to be more severely impaired by pain and depression than patients with blepharospasm and writer's cramp (Cano *et al.*, 2006; Pekmezovic *et al.*, 2009; Soeder *et al.*, 2009). In one study (Soeder *et al.*, 2009), impaired quality of life positively correlated with depression and anxiety but not with motor impairment as assessed with the Unified Dystonia Rating Scale (Comella *et al.*, 2003). However, this could be due to the poor ability of the Unified Dystonia Rating Scale to capture motor disability and contrasts other studies that used more specific scales; for example, the Toronto Western Spasmodic Torticollis Rating Scale (Comella *et al.*, 1997) and Burke–Fahn–Marsden Scale (Burke *et al.*, 1985; Djebbari *et al.*, 2004; Skogseid *et al.*, 2007). The impact of non-motor symptoms on quality of life indicates the importance of taking non-motor symptoms into account for clinical assessment and treatment when developing and evaluating new treatments for primary dystonia.

Treatment

There are no double-blind trials of oral medications that have specifically addressed the question of treating pain or neuropsychiatric abnormalities associated with dystonia. Indeed, there is a difficulty with regard to using newer anti-depressants in dystonia as there are reports of induction or worsening of dystonia with selective serotonin re-uptake inhibitors (Gerber and Lynd, 1998). For those with major psychiatric problems, dopamine receptor blocking drugs are also relatively contraindicated as they can worsen dystonia. Botulinum toxin treatment provides moderate to marked effect on the quality of life fields of mental health and pain. The impairment of quality of life due to pain, and the botulinum toxin induced improvement (as assessed by the bodily pain SF-36 subscore), are higher in patients with cervical dystonia than focal hand dystonia (Gudex *et al.*, 1997, 1998; Haussermann *et al.*, 2004; Cano *et al.*, 2006; Skogseid *et al.*, 2007; Simpson *et al.*, 2008).

With regard bilateral pallidal deep brain stimulation, mood shows a mild but significant improvement after surgery in Beck Depression Inventory probably partially reflecting upgrading of motor function, but typically no beneficial effect on social functioning and emotional ratings of the SF-36. Pain significantly improves and this is most likely responsible for the overall improvement in quality of life following deep brain stimulation in dystonia (Halbig *et al.*, 2005; Vidailhet *et al.*, 2005, 2007; Kupsch *et al.*, 2006; Mueller *et al.*, 2008; Valldeoriola *et al.*, 2010). Suicide after deep brain stimulation has been reported despite the excellent motor outcome, which could relate to untreated depression occurring as part of the dystonia, or a direct neuropsychiatric complication of deep brain stimulation (Burkhard *et al.*, 2004; Foncke *et al.*, 2006).

Recognition of the importance of non-motor symptoms in the clinical picture of primary dystonia may lead the way towards novel targets to improve the movement disorder. In this regard, the recognition of the sensory components of dystonia has led some to investigate if manipulating sensory input could be a way to correct primary or secondary abnormalities in sensory representations and improve motor symptoms (Candia *et al.*, 2002, 2005; Zeuner *et al.*, 2002; Byl *et al.*, 2003; Zeuner and Hallett, 2003; Bhidayasiri and Bronstein, 2005; Zeuner and Molloy, 2008; Flor and Diers, 2009; McKenzie *et al.*, 2009; Altenmuller and Jabusch, 2010; Machado *et al.*, 2010). Most studies are characterized by small numbers or are single case reports, they are not blinded or randomized, and often without control group, and in some an exact description of the intervention and outcome measures is absent, making appropriate comparisons difficult.

In cervical dystonia, there are controversial results with regard to EMG feedback (Brudny *et al.*, 1976; Korein and Brudny, 1976; Korein *et al.*, 1976; Jahanshahi *et al.*, 1991). Case reports of transcutaneous electrical nerve stimulation or vibration reported an improvement in dystonic symptoms in patients with limb or cervical

dystonia (Bending and Cleeves, 1990; Foley-Nolan *et al.*, 1990; Karnath *et al.*, 2000), while a double-blind, randomized, cross-over study using the same technique in 10 patients with writer's cramp showed a significant improvement that persisted for 3 weeks (Tinazzi *et al.*, 2005). However, a recent report of this same technique in patients with dystonic tremor was found to worsen performance (Meunier *et al.*, 2011). Various types of motor training have been utilized that try to individuate finger movements (Candia *et al.*, 2002; Zeuner and Hallett, 2003). Eight-week sensory training of Braille reading at grade 1 for 30–60 min daily improved not only spatial acuity but also motor symptoms in arm dystonia patients, which was persistent at follow up 1 year later in those who continued Braille practice (Zeuner *et al.*, 2002; Zeuner and Hallett, 2003; Zeuner and Molloy, 2008). A physical therapy programme, in addition to botulinum toxin injections in cervical dystonia, was found to be more efficacious in comparison with botulinum toxin alone (Tassorelli *et al.*, 2006). Taken together, this preliminary work demonstrates how an appreciation of the importance of non-motor symptoms can assist with new therapeutic developments. However, more rigorous larger scale studies with adequate control and long-term follow-up are needed to explore the benefits for this approach.

Pathophysiological implications

The majority of previous pathophysiological work in primary dystonia has concentrated on the motor system. Two clear abnormalities have been demonstrated repeatedly across different forms of the disorder. The first is that mechanisms that usually produce inhibition within the motor system are under functioning; this has been demonstrated at a cortical, brainstem and spinal cord level (Hallett, 2011). Such abnormalities can be present in clinically unaffected body parts and in non-manifesting *DYT1* gene carriers indicating that additional factors may be necessary to produce clinical symptoms of dystonia (Edwards *et al.*, 2003*b*).

The second is that there is an excessive response to experimental protocols that produce plastic changes within the motor system (Quartarone *et al.*, 2003, 2008; Quartarone and Pisani, 2011). Again such abnormalities are present in clinically unaffected body parts, but importantly are not present in non-manifesting *DYT1* gene carriers (Edwards *et al.*, 2006), where a subnormal response to plasticity protocols is seen. This suggests that abnormal brain plasticity may be an essential component of clinical manifestation of dystonia.

Since plasticity depends on the amount of inhibition (Di Lazzaro *et al.*, 2006; McDonnell *et al.*, 2007), an abnormality of plasticity could relate to the abnormality of inhibition.

Recent evidence suggests that loss of inhibition in primary dystonia should not be thought of as a motor system problem, but also extends to the sensory system. Several lines of electrophysiological evidence support this contention. Using somatosensory-evoked potentials recovery curves, loss of inhibition only for the P27 component for the 5-ms interval, which correlated with the temporal discrimination threshold was found, indicating dysfunction within the primary somatosensory cortex (Tamura *et al.*, 2008). A loss of lateral inhibition was demonstrated with somatosensory-evoked potentials from the median and ulnar nerves, where the combined somatosensory-evoked potentials was the sum of both and not less (like in healthy controls) in patients with focal hand dystonia and this could underlie the spatial discrimination threshold impairment (Tinazzi *et al.*, 2000; Frasson *et al.*, 2001). High-frequency oscillations of the N20 component of the somatosensory-evoked potentials, reflect inhibitory post-synaptic potentials (Ozaki and Hashimoto, 2005) and are decreased in focal dystonia (Cimatti *et al.*, 2007).

Experimentally, it is possible to explore the interaction between sensory afferent input and motor output via techniques of short- and long-afferent inhibition. These pair a peripheral sensory stimulus with a motor cortical stimulus at different interstimulus intervals. The resulting inhibitory effects are both γ-aminobutyric acid (GABA) and acetylcholine dependent. While somewhat inconsistent, results do indicate that such short and long latency inhibitory interactions may be abnormal in dystonia, although additional studies in different types of primary dystonia are needed (Kessler *et al.*, 2005; Richardson *et al.*, 2008). Contingent negative variation, which is the EEG activity between two sensory stimuli that trigger a movement and a measure of sensorimotor integration, is abnormal in patients with cervical dystonia and focal hand dystonia (Kaji *et al.*, 1995*b*; Ikeda *et al.*, 1996). Another physiological demonstration of abnormal sensorimotor integration is an abnormality of the somatosensory-evoked potentials during the preparation phase of a sensory triggered movement (Murase *et al.*, 2000). The N30 component is gated (reduced in amplitude) for normal subjects, but not for patients with writer's cramp. On the other hand, the P22 component was gated in the patients, but not for normal subjects.

Apart from electrophysiological studies supporting loss of inhibition in multiple levels, neuroimaging studies support the hypothesis of reduced intracortical inhibition not only at the motor cortical level (Hallett, 2006) but also the somatosensory cortex. Functional MRI has demonstrated overactivity of the primary sensory cortex as response to motor tasks, vibration and sensory tasks (Butterworth *et al.*, 2003; Lerner *et al.*, 2004; Dresel *et al.*, 2006; Nelson *et al.*, 2009). Recently, a functional MRI study demonstrated overactivation as a result of loss of inhibition also in the cingulate cortex, primary and secondary somatosensory cortex and other cortical areas following pure kinaesthetic somatosensory stimulation that did not involve the affected dystonic muscles (Obermann *et al.*, 2010).

Abnormalities in plasticity too should not be seen as a purely motor system problem in dystonia. Repetitive practice is a risk factor for the development of task-specific dystonia, focal hand dystonia and cervical dystonia, and it is possible to speculate that practice-related pain and fatigue could contribute to the development of dystonia (Soland *et al.*, 1996; Chen and Hallett, 1998; Topp and Byl, 1999; Kacar *et al.*, 2004; Lim *et al.*, 2004; Byl, 2007; Torres-Russotto and Perlmutter, 2008; Lin and Hallett, 2009; Schneider *et al.*, 2010; Aranguiz *et al.*, 2011). In a case–control study of 103 patients with writer's cramp, the risk of writer's cramp increased with the time spent writing each day and was also associated with an abrupt increase in the writing

time during the year before onset (Roze *et al.*, 2009). Preceding regional traumas have been implicated as risk factors in 5–21% of patients with adult-onset focal (Sheehy and Marsden, 1980; Schott, 1985; Jankovic and Van der Linden, 1988; Fletcher *et al.*, 1991; Jankovic, 1994; Samii *et al.*, 2000; Factor, 2002) and DYT1 dystonia (Edwards *et al.*, 2003*a*), and trauma is known to facilitate long-term potentiation processes within the related limb representation. This is in keeping with an animal model for blepharospasm where combined corneal irritation and a striatal dopaminergic depletion are required for development of blepharospasm, whereas either factor alone is not sufficient to cause clinical symptoms (Schicatano *et al.*, 1997).

One of the techniques most commonly used to produce plastic changes experimentally in dystonia is paired associative stimulation. This technique combines median nerve stimulation with a motor cortical transcranial magnetic stimulation pulse. In dystonia, paired associative stimulation produces an excessive response (Quartarone *et al.*, 2003; Kojovic *et al.*, 2011; Quartarone and Pisani, 2011) not restricted to the affected body parts (Quartarone *et al.*, 2008) and also a loss of topographical specificity of paired associative stimulation-induced effects (Quartarone *et al.*, 2008). Recently, this abnormal response in dystonia has been shown to normalize with botulinum toxin injections, indicating an important role for afferent input in the generation of abnormal paired associative stimulation responses (Kojovic *et al.*, 2011).

While the discussion above has focused on the importance of sensory deficits in the pathophysiology of dystonia, the neuropsychiatric non-motor features may also integrate with the known pathophysiology of dystonia. The basal ganglia are linked to cortical areas by at least five cortico-striatal–cortical loops (Alexander *et al.*, 1990), which are not anatomically separate, and thus disorders affecting the basal ganglia tend to present with a combination of symptoms arising from a common disturbance of these loops. Data from neuroimaging studies using voxel-based morphometry have shown increased volume in the basal ganglia, especially in the putamen, the thalamus, sensorimotor cortex and cerebellum in sporadic dystonia (Bradley *et al.*, 2010; Pantano *et al.*, 2011; Zoons *et al.*, 2011) and DYT1 manifesting- and non-manifesting carriers (Draganski *et al.*, 2009; Carbon *et al.*, 2011; Ulug *et al.*, 2011). Diffusion tensor imaging shows increased fractional anisotropy in the fibre tracts connecting the basal ganglia, cortex and cerebellum (Fabbrini *et al.*, 2008; Delmaire *et al.*, 2009). Abnormalities in the basal ganglia and cortico-striatal-thalamo-cortical circuits are also implicated in the pathophysiology of depression (Alexander *et al.*, 1990; Haber and Calzavara, 2009). In particular, dysfunction in fronto-striatal circuitry may provide a neurobiological explanation for the higher incidence of neuropsychiatric features in primary dystonia.

Loss of inhibition could again be the common pathophysiological basis since neuroimaging studies in depression show that anterior cingulate cortex, prefrontal cortex, the thalamus, the pulvinar, pallidum/putamen and midbrain regions are hyperactive in depression, implying a loss of inhibition to possibly account for these changes (Fitzgerald *et al.*, 2008; Savitz and Drevets, 2009; Hasler and Northoff, 2011). Indeed, many studies in animal models in depression and neuroimaging studies support a loss of inhibition due to alteration of GABA-A receptors (Hasler and Northoff, 2011).

A hypothesis and future directions

Widespread loss of inhibition and pathologically increased plasticity, therefore, appear to play important roles in the pathophysiology of primary dystonia (Hallett, 2011), and we propose that non-motor features of dystonia may be explained by a common pathophysiological deficit that also underlies the motor symptoms (Quartarone *et al.*, 2003; Kojovic *et al.*, 2011; Quartarone and Pisani, 2011) (Fig. 1).

The question as to what causes loss of inhibition and if this is a primary event or secondary due to some other alteration remains unclear. Preliminary evidence for reduced GABA concentration in basal ganglia and motor cortex in dystonia (Levy and Hallett, 2002) has not been confirmed (Levy and Hallett, 2002; Herath *et al.*, 2010). Nevertheless, a recent voxel-based analysis showed a reduction in GABA-A receptor expression/affinity both in *DYT1* carriers and sporadic patients in primary motor and premotor cortex, primary and secondary somatosensory cortex, and in the motor component of the cingulate gyrus (Garibotto *et al.*, 2011). This could represent a neurochemical correlate of the reduced inhibition; however, these data do not allow conclusions about whether the GABA reduction is more likely to be primary or secondary to some other neurochemical imbalance.

Evidence for dopamine and acetylcholine imbalance in dystonia is well established. D2-receptors are deficient in the putamen in focal dystonia and this could cause a decrease in D2-dependent inhibition of GABA transmission and subsequently a loss of inhibition in the basal ganglia. This abnormality in D2-receptor function has also been found in clinically unaffected *DYT1* gene carriers (Augood *et al.*, 2002), suggesting that D2-receptor dysfunction represents a feature of the non-manifesting carrier state. The role of acetylcholine alterations has been consistently reported in dystonia, also explaining the effect of anti-cholinergic medication (Peterson *et al.*, 2010).

Genetic susceptibility is a key to the pathophysiology of dystonia, indicated by the numerous non-motor abnormalities illustrated in this article (sensory discrimination, vibration induced illusion of movement, mental rotation, neuropsychiatric features), which are found in unaffected first-degree relatives of patients with adult-onset focal dystonia and non-manifesting gene mutation carriers. This genetic background may predispose patients to develop dystonia in the presence of other factors that may have important non-motor components, such as repetitive activity, trauma or emotional arousal. Of interest, in this regard, the role of GABA in the stress response is crucial, since reduced GABA increases sensitivity to stress, and acute and chronic stress leads to reductions of GABA concentrations (Acosta *et al.*, 1993; de Groote and Linthorst, 2007). It may be that a further decrease of inhibition in an already imbalanced inhibitory system could lead to a breakdown of compensatory mechanisms and ultimately to the motor manifestation of dystonia (Fig. 1). Moreover, the

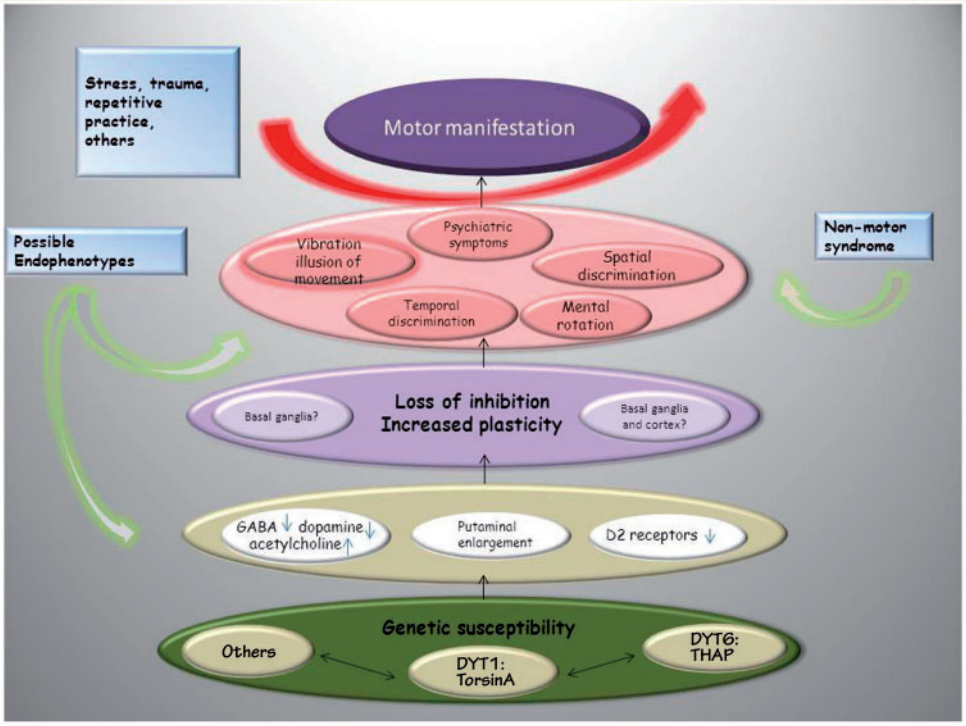

Figure 1 A hypothesis on the pathophysiology of the motor and non-motor features of primary dystonia. Genetic susceptibility could lead to a neurochemical and functional imbalance in the basal ganglia (but possibly even more widespread) that subsequently may lead to a widespread loss of inhibition and increased plasticity, which may underlie the pathophysiology of the non-motor features of primary dystonia. The presence of other factors such as repetitive activity, trauma or emotional arousal and stress, could lead to a breakdown of compensatory mechanisms and ultimately to the motor manifestation of dystonia.

threshold after which, triggered or not by environmental factors, a predisposed carrier manifests motor symptoms is obviously different between carriers, and this could be to some extent due to other genetic factors that influence penetrance, as shown in DYT1 dystonia (Risch *et al.*, 2007).

There are clear routes for future research. One important avenue would be to use non-motor features to identify endophenotypes. In this regard, the sensory tests described above may facilitate the identification of clinically non-manifesting gene carriers within families with dystonia, or may allow us to segregate clinically similar patients (for example, those with cervical dystonia) into different groups for further genetic study. This may help in the identification of new genetic causes of dystonia (Gershon and Goldin, 1986; Leboyer *et al.*, 1998; Gottesman and Gould, 2003; Bradley *et al.*, 2010). None of the current sensory tests available fulfil stringent criteria for a perfect endophenotype as they are abnormal only in a subset of patients and there are floor effects with sensory studies in the normal population due to age, limiting the age range that they are useful (Gescheider *et al.*, 1994; Humes *et al.*, 2009; Roudaia *et al.*, 2010). Nevertheless, among these tests, temporal discrimination threshold seems to be the most promising endophenotype, since it is supported by a bilateral putaminal enlargement shown by voxel-based morphometry in patients and unaffected first-degree relatives (Bradley *et al.*, 2010). In the same study, autosomal dominant transmission of abnormal temporal discrimination threshold was demonstrated in multiplex pedigrees across two generations and no parents with normal temporal discrimination threshold had offspring with abnormal temporal discrimination threshold (Bradley *et al.*, 2010).

A second important research avenue would be to explore the pathophysiology of the non-motor symptoms of dystonia. Here, the origin of the neuropsychiatric symptoms is perhaps of particular importance and interest. Improved understanding of the pathophysiology of non-motor symptoms would aid rational treatment trials of medications to help treat such symptoms. Another important avenue relates to incorporating non-motor features into assessments of the impact of therapies for dystonia. The situation for dystonia in this regard is analogous to that of Parkinson's disease, where in recent years awareness of the importance of non-motor symptoms has led to the development of specific non-motor symptom scales, which have been included as outcome measures in clinical trials. For dystonia, this would allow investigators to capture the effect of treatments on the burden of non-motor symptoms, particularly pain and neuropsychiatric symptoms, in clinical trials.

Conclusions

Non-motor features are part of the primary pathophysiological 'fingerprint' of dystonia and could be partially explained under the same pathophysiological model from which the motor

symptoms are hypothesized to arise. They deserve attention from the clinical point of view, since they strongly influence the quality of life in patients with dystonia and could represent, in combination with pharmacological or surgical treatments, therapeutic targets to relieve dystonia. They are not mere epiphenomena that can be dismissed as peripheral to the main origins of dystonia, but instead demand the same level of research attention as motor features, and to be integrated into future pathophysiological models of this disorder.

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