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Abnormalities of spatial discrimination in focal and generalized dystonia

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Summary

Sensory processing is impaired in focal hand dystonia (FHD), with most previous studies having evaluated only the symptomatic limb. The purpose of this study was to establish whether the sensory system is affected in other types of dystonias and whether the contralateral hand is also involved in FHD. We used a spatial acuity measure (Johnson–Van Boven–Phillips domes) to evaluate sensory spatial discrimination in both hands of patients with different forms of dystonias including primary generalized DYT1 dystonia (associated with a unique deletion in the *DYT1* gene) (*n* = 13), FHD (*n* = 15), benign essential blepharospasm (*n* = 9), cervical dystonia (*n* = 10) and in age-matched controls. Clinical evaluation included the Fahn dystonia scale for the focal dystonia groups and the Marsden–Burke–Fahn scale for the generalized dystonia group. Spatial discrimination was normal in patients with DYT1 dystonia, despite all of these patients having hand dystonia. However, spatial discrimination thresholds were significantly increased in both hands in the focal dystonia groups (thresholds were similar for each group) and did not correlate significantly with either severity or duration of dystonic symptoms. Thresholds were significantly increased in the dominant hand compared with the non-dominant hand only within the FHD group. Our observations demonstrate involvement of both the dominant and non-dominant somatosensory cortices, and suggest that abnormal sensory processing is a fundamental disturbance in patients with focal dystonia. These findings of altered sensory processing in idiopathic focal but not generalized DYT1 dystonia suggest both a primary pathophysiological role for the phenomenon in focal dystonia and divergent pathophysiological processes in the two conditions.

Keywords: focal dystonia; generalized dystonia; spatial discrimination

Abbreviations: BEB = benign essential blepharospasm; CD = cervical dystonia; FHD = focal hand dystonia; SDT = spatial discrimination threshold; SEP = sensory evoked potential

Introduction

Dystonia is characterized by involuntary sustained muscle contractions resulting in twisting and repetitive movements of affected body parts (Fahn *et al*., 1988). Primary torsion dystonia is a heterogeneous disorder with a broad clinical spectrum ranging from early onset generalized disorder to later onset focal dystonias. Early onset of this form is inherited as an autosomal dominant condition with reduced penetrance, and in most cases is due to a unique deletion in the *DYT1* gene (Ozelius *et al*., 1989; Kramer *et al*., 1990; Bressman *et al*., 1994*a*). Unlike early-onset dystonia, the genetic contribution to late-onset focal dystonia is not yet clearly established. Several systematic family studies of patients with late onset focal dystonia have been reported (Waddy *et al*., 1991; Stojanovic *et al*., 1995; Munchau *et al*., 2000). The conclusion from these studies is that the pattern of inheritance is consistent with autosomal dominant transmission with very reduced penetrance. Furthermore, different forms of focal dystonia may present in the same family (Waddy *et al*., 1991; Stojanovic *et al*., 1995), suggesting that focal dystonias may share a common aetiology.

Of all movement disorders putatively associated with basal ganglia dysfunction, dystonia is the least understood in terms of underlying pathophysiology. Although perceived as a motor disorder, several clinical and neurophysiological observations suggest that sensory dysfunction may also be implicated in focal dystonia (Hallett, 1995). For example,

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sensory symptoms may precede the appearance of dystonia (Leis *et al*., 1992), sensory tricks (geste antagoniste) can relieve dystonic postures (Hallett, 1995; Berardelli *et al*., 1998; Naumann *et al*., 2000) and sensory training using Braille reading can improve impaired spatial acuity in patients with focal hand dystonia (FHD) (Zeuner *et al*., 2002). Tonic vibration of the tendon or belly of a given muscle can induce dystonia in patients with hand cramp and peripheral blockade can alleviate dystonic posturing (Kaji *et al*., 1995; Grunewald *et al*., 1997). These sensory phenomena are not surprising because the sensory system provides the major drive to the motor system and the basal ganglia play an important role in the central processing of somatosensory input (Hallett, 1998).

Further evidence for sensory system involvement in focal dystonia comes from neurophysiological and behavioural studies which have demonstrated sensory dysfunction in patients with FHD: abnormal graphaesthesia and stereognosis (Byl *et al*., 1996*a*), impaired spatial and temporal discrimination of somaesthetic stimulation (Tinazzi *et al*., 1999*a*, 2002; Bara-Jimenez *et al*., 2000*a*, *b*) and abnormal kinaesthesia (Grunewald *et al*., 1997). These findings all suggest abnormal sensory processing in focal dystonia. Finally, neuroimaging studies using PET (Tempel and Perlmutter, 1993; Feiwell *et al*., 1999) and MEG (Meunier *et al*., 2001) support these studies suggesting impaired sensorimotor integration in focal dystonia.

Animal and cortical mapping studies have suggested that synchronous inputs can lead to a rearrangement of cortical maps (Wang *et al*., 1995; Byl *et al*., 1996*b*; Xerri *et al*., 1996). The abnormal finger representation in the primary somatosensory cortex (S1) observed in patients with FHD (Bara-Jimenez *et al*., 1998*a*; Elbert *et al*., 1998) has been thought to reflect these enlarged and overlapping receptive fields. This hypersensitivity and expanded cortical representation has raised the question of whether dystonia is actually a sensory disorder produced by an environmental experience. Though a recent MEG study (Meunier *et al*., 2001) suggests that these sensory changes reflect the intrinsic mechanisms of the dystonia itself, it remains unclear what role the sensory changes have in causing the abnormal posturing. Most studies of dystonia have studied the affected limb and contralateral cortex in patients with idiopathic focal dystonia, and there is a paucity of information regarding the involvement of the ipsilateral cortex in unilateral dystonia. With the exception of a recent study using [^{18}F]-fluorodeoxyglucose and PET which demonstrated metabolic overactivity of direct inhibitory projections from the putamen to the globus pallidus interna (Eidelberg *et al*., 1998), the pathophysiology of DYT1 dystonia is unclear.

This study was performed to establish whether sensory processing is altered in DYT1 generalized dystonia and among different subgroups of focal dystonia, and to establish if the contralateral hand is involved in unilateral dystonia.

Subjects and methods

Subjects

Patients were recruited from the Human Motor Control Clinic at the National Institute of Neurological Disorders and Stroke (NINDS), USA. Two case-control studies were performed with two separate control groups: one group for the younger generalized DYT1 dystonia patients and another group for comparison with the focal dystonia group. The DYT1 dystonia group comprised nine males and four females, average age and SD were 35.38 ± 16.1 years; the average age of the normal controls for this group (three males and five females) was 28.90 ± 15.1 years. The focal dystonias studied included: FHD (nine males and six females, average age 54.8 ± 10.6 years); cervical dystonia (CD) (ten females, average age 54.7 ± 13.4 years); and benign essential blepharospasm (BEB) (three males and six females, average age 62.8 ± 10.2 years). The average age and SD of all subjects in the focal dystonia groups was 57.4 ± 4.7 years; the average age of the normal controls (seven females and four males) for the focal dystonia group was 53.3 ± 14.3 years. In the FHD group, 13 of the 15 patients had writer's cramp (simple writer's cramp) whereas, in two patients, dystonia was present at rest or during more than one action (dystonic writer's cramp) (Sheehy and Marsden, 1982); two patients were left-handed and the dominant hand was affected in each case. Patients with BEB and CD were all right-handed. Some of the DYT1 patients were taking medication (Table 2) at the time of the study but, for all groups of patients, botulinum toxin injections were not administered for at least 3 months prior to the study. The effect of medications on spatial discrimination threshold (SDT) has not been investigated, but it is unlikely that the medications outlined in Table 2 decrease the SDT. Patients with a history of peripheral neuropathy, entrapment neuropathies or Raynauds phenomenon were ineligible for the study. The diagnosis of dystonia was made by standard medical history and neurological examination.

The Fahn–Burke–Marsden scale which scores for both disability and severity was used for the DYT1 group (Burke *et al*., 1985). In all groups of focal dystonia, a dystonia disability score was measured (Fahn, 1989). For the BEB and CD group a severity score for the dystonia was also considered (Fahn, 1989). Patients and normal controls gave informed verbal and written consent for this study protocol, which was approved by the NINDS Institutional Review Board.

Sensory testing

SDT was evaluated with the Grating Orientation Task as described in other studies (Johnson and Phillips, 1981; Van Boven and Johnson, 1994; Sanger *et al*., 2001; Zeuner *et al*., 2002). The Grating Orientation Task consists of a commercially available set of eight hemispheric plastic Johnson–Van Boven–Phillips (JVP) domes (Stoelting, Wood Dale, IL,

USA). These domes have ridges and grooves of varying widths (mm): 3.0, 2.0, 1.5, 1.20, 1.0, 0.75, 0.50 and 0.35. The threshold is defined as the dome with which the patient obtains 75% correct response rate. Subjects unable to achieve 75% correct responses for the largest (3 mm) groove widths were assigned a threshold of 3 mm. The dominant and non-dominant hands were tested for each group. Subjects were seated comfortably with eyes closed and the arm was held in a supine position: domes were tested in order of decreasing groove width and a random series of 20 either vertical or horizontal orientations were applied for ~1 s to the palmar surface of the tip of the distal phalanx of the index finger. Subjects were asked to identify the orientation of the grooves, and if unsure were asked to guess, so as to give an answer for all 20 applications given.

Statistical analysis

Descriptive statistics (means, SDs) are presented for the controls and the patient groups. As spatial discrimination ability decreases with age (Stevens and Cruz, 1996; Wohlert, 1996; Sanger *et al*., 2001), the relationship between age and SDT in both patients and controls was examined with linear regression. Kaplan–Meier curves with censoring at 3 mm and stratification by diagnostic groups were computed to compare SDTs by log rank statistics. Cox proportional hazard models provide the SDT comparisons with covariate adjustment for age (Kalbfleisch and Prentice, 1980). SDT differences between dominant and non-dominant hands were evaluated using the Wilcoxon signed rank tests, with Bonferroni corrections for the multiple comparisons made. Finally, within the patient groups, Cox proportional hazards models evaluated the relationships between disease duration, Fahn severity and disability scales on spatial acuity.

Results

The clinical characteristics and severity and disability scores for the dystonia subjects are shown in Table 1. As expected, a significant association between increases in SDTs and age was observed; the SDTs increased with increasing age in both dominant and non-dominant hands for the combined group of controls ($P = 0.046$ and $P = 0.040$, respectively). However, this age-related relationship was not observed in the four patient groups.

The clinical characteristics of the DYT1 dystonia group are outlined in Table 2. Of particular note, all 13 patients in this group had dystonia when writing, and seven of them also had bilateral hand dystonia.

All control subjects had an SDT of <2.2 mm for either hand. However, some patients were unable to detect a gap of 3 mm and were considered censored and assigned a threshold of 3 mm (Table 3). Two patients in the DYT1 group were censored for both hands and, in the focal dystonia subgroups, 10 patients were censored for the dominant hand and nine patients for the non-dominant hand. Four of these patients were unable to detect a gap of 3 mm with either hand. For the DYT1 dystonia group, there was no significant difference in SDTs between patients and age-matched controls for either their dominant or non-dominant hand (Fig. 1A and B). SDTs were significantly greater for the focal dystonia group compared with the control group ($P < 0.001$ for both hands); SDTs did not significantly differ within the focal dystonia sub-groups (FHD, CD and BEB). For both hands, the focal dystonia groups differed significantly from their controls even when controlling for the effects of age (Fig. 2A and B).

SDTs were similar between dominant and non-dominant hands in both the DYT1 group and their controls. Within the focal dystonia sub-groups, a significant difference in SDTs was observed between dominant and non-dominant hands in FHD (corrected Wilcoxon signed rank test $P = 0.02$), but not in the other dystonic groups nor within their normal control group. In each of the dystonia subgroups, neither disease duration nor dystonia scale scores had a significant effect on SDTs.

Discussion

The study's most notable finding is that of normal spatial discrimination in patients with DYT1 dystonia, but decreased discrimination in subjects with a range of focal dystonias compared with normal controls. Although the genetic abnormality has been well described for the autosomal dominant condition of DYT1 dystonia, there is a relative paucity of knowledge regarding its underlying pathophysiology. While focal and generalized dystonia have been assumed to share a common pathophysiology, our findings could suggest otherwise. Most neurophysiological studies to date have focused on focal dystonias. Despite some shared clinical characteristics, primary generalized and focal dystonia differ in many respects. Generalized dystonia is less prevalent than later onset focal dystonia (Nutt *et al*., 1988). DYT1 dystonia usually presents in childhood with single limb involvement, which subsequently progresses to involve other regions (Bressman *et al*., 1994*b*) whereas focal dystonia has a later onset (older than 28 years, with a median onset of 45 years), which usually starts in cervical, cranial or brachial muscles and tends to remain localized in distribution (Fahn *et al*., 1987). If a common pathophysiology is assumed, then patients with DYT1 dystonia might reasonably be expected to have as marked if not greater sensory discrimination impairment than those with focal dystonia. This was not the observation in this study.

Sensory abnormalities have been well described for focal (Hallett, 1995; Byl *et al*., 1996*a*), but not for DYT1 dystonia. A number of interpretations can be proposed to explain our findings of normal SDT in DYT1 dystonia. One possibility is that sensorimotor integration is intact in DYT1 dystonia, whilst another possibility is that sensory function is initially altered but early adaptive or compensatory changes may take place in the sensorimotor system. Of note, two of the

Table 1 *General characteristics in controls and patients with dystonia*

Group (*n*)	Age (years)	Gender (M/F)	Dominant hand (R/L)	Onset age (years)	Duration (years)	Severity score	Disability score (%)
Focal dystonia							
NC (11)	53 (14.3)	4/7	10/1	N/A	N/A	0.0 (0.0)	*100 (0.0)
FHD (15)	55 (10.6)	9/6	13/2	41.7 (15.9)	13.1 (9.9)	N/A	53.2 (19.1)
CD (10)	54 (13.4)	0/10	10/0	44.8 (13.7)	9.9 (6.1)	23.7 (5.6)	32.8 (22.7)
BEB (9)	65 (10.2)	3/6	9/0	54.7 (9.4)	8.2 (4.9)	19.1 (4.6)	36.8 (12.5)
DYT1 dystonia							
NC (8)	29 (15.1)	5/3	6/2	N/A	N/A	0.0 (0.0)	100 (0.0)
DYT1 (13)	35 (16.1)	9/4	12/1	14.5 (10.8)	20.9 (14.1)	32.8 (13.7)	6.3 (2.4)

*100% = unaware of any disability; NC = normal controls; N/A = not available. Values given as means with SDs (in brackets).

Table 2 *Clinical characteristics of patients with DYT1 dystonia*

Patient no.	Age (years)	Symptom duration (years)	Distribution of dystonia	Medication	Severity score	Disability score
1	20	6	Neck, trunk, UEs	nil	36	5
2	13	6	LE, UE	trihexiphenidyl	24	3
3	57	45	UEs, LE, neck	L-dopa, primidone	50	10
4	30	10	Neck, speech, trunk, UEs, LEs	clonazepam	29	3
5	20	10	LEs, UE	nil	24	4
6	24	14	LEs, UEs	BTX	20	3
7	19	8	Neck, torso, LEs, UEs	Baclofen, BTX, clonazepam, trihexiphenidyl	64	6
8	37	25	UEs	nil	18	6
9	39	32	LEs, UEs	nil	21	10
10	54	46	LEs, UEs, speech	carbamazepine	38	10
11	59	15	LEs, UEs	nil	40	6
12	35	30	LEs, UEs	nil	21	6
13	53	25	LEs, UEs	nil	40	7

BTX = botulinum toxin; LE = lower extremity; UE = upper extremity.

Table 3 *SDTs in controls and patients with dystonia*

Group (*n*)	Censored (D/N)	SDT (mm)	
		Dominant hand	Non-dominant hand
Focal dystonia			
NC (11)	0/0	1.46 (0.40)	1.49 (0.36)
FHD (15)	4/3	2.61 (0.38)	2.40 (0.51)
CD (10)	4/1	2.53 (0.55)	2.35 (0.60)
BEB (9)	2/5	2.69 (0.55)	2.70 (0.54)
DYT1 dystonia			
NC (8)	0/0	1.27 (0.26)	1.36 (0.44)
DYT1 (13)	2/2	1.70 (0.71)	1.64 (0.77)

NC = normal controls; D = dominant hand; N = non-dominant hand. Mean SDTs are presented with SDs (in brackets).

13 patients in the DYT1 group were censored. These patients were older than other patients in this group (54 and 59 years, respectively), one had a disease duration of 46 years and another of 15 years (Table 2). This finding cannot be explained on the basis of both patients having hand dystonia, as all 13 patients with DYT1 dystonia had involvement of at least one hand. One possible explanation is that an interaction between disease state and age occurs; more specifically, as the disease process progresses, either the sensory–motor integration becomes abnormal or the early 'adaptation' process of the sensory–motor system breaks down.

SDTs were increased across a range of focal dystonias and these differences remained after adjusting for age. Furthermore, no significant associations were observed between spatial discrimination thresholds and duration, severity and disability of disease. These findings confirm previous reports of abnormal spatial acuity in dominant (Sanger *et al*., 2001; Bara-Jimenez *et al*., 2000*b*) and non-dominant (Sanger *et al*., 2001) hands of patients with idiopathic focal dystonia. In our study, a higher threshold is seen in the dominant hand in FHD. A possible explanation for this finding could be that this represents a secondary phenomenon resulting from plasticity changes in the sensorimotor cortex induced by the dystonic hand movements. Alternatively, repetitive activity of the dominant hand

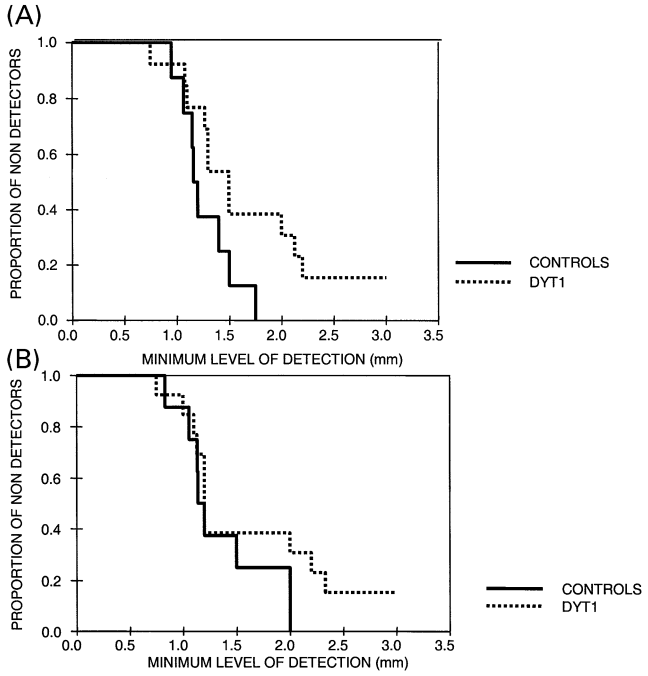

Fig. 1 A Kaplan–Meier curve showing the proportion of DYT1 subjects and normal controls detecting spatial discrimination ⩽3 mm for the dominant (**A**) and non-dominant (**B**) hands, respectively.

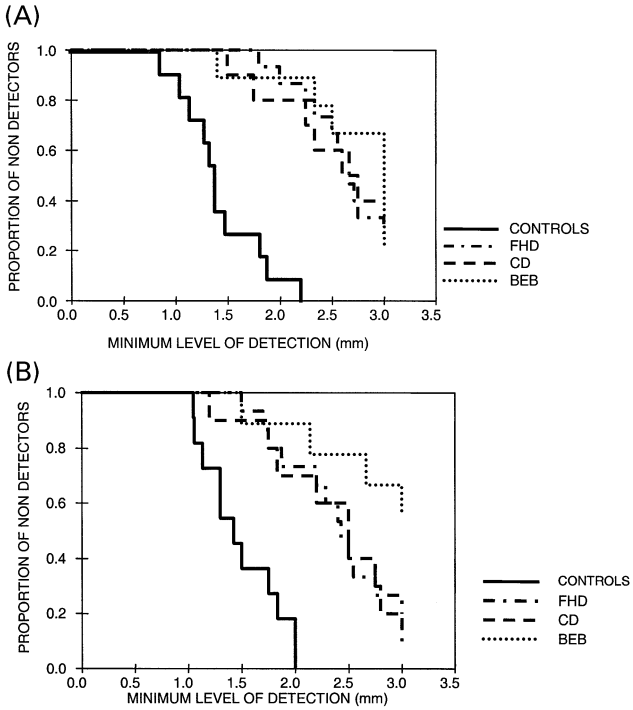

Fig. 2 A Kaplan–Meier curve showing proportion of subjects in each focal dystonia and normal control group, detecting spatial discrimination at a threshold ⩽3 mm for the dominant (**A**) and non-dominant (**B**) hands, respectively.

could lead to worsening of an intrinsic cortical derangement and consequently to the dystonia. The latter hypothesis is supported by a report that some patients with FHD who change hand dominance subsequently develop dystonia in the previously unaffected hand (Sheehy and Marsden, 1982).

Patients with symptoms remote from the site of testing were equally impaired in their performance on spatial discrimination testing. In patients with CD and BEB, thresholds were similarly increased for both hands. These findings and reports of abnormal blink reflexes in patients with spasmodic dysphonia (Cohen *et al*., 1989) and torticollis (Nakashima *et al*., 1990) would support the hypothesis that dystonia may result from a localized abnormality superimposed upon a more widespread dysfunction of sensorimotor processing. This hypothesis is further supported by a study that reported an inability to track vibration-induced illusions of arm movement in patients with torticollis (Grunewald *et al*., 1997) and by Mazzini *et al*. (1994), who reported abnormalities of median nerve sensory evoked potentials (SEPs) in torticollis.

Furthermore, our findings of impaired SDT in both hands of patients with focal dystonia suggest bilateral involvement of the somatosensory cortices in this condition. This observation is consistent with other reports of bilateral cortical sensory changes such as abnormal blood flow in the sensorimotor cortex (Tempel and Perlmutter, 1990) and supplementary motor area (Tempel and Perlmutter, 1993) in response to vibration of the hand and impaired graphaesthesia (Byl *et al*., 1996*a*) and dedifferentiation of sensory finger representations in patients with focal hand dystonia (Meunier *et al*., 2001). Additionally, transcranial magnetic stimulation studies have shown bilateral changes in intracortical inhibition from both motor cortices in patients with FHD (Ridding *et al*., 1995; Rona *et al*., 1998) and EMG studies have revealed co-contraction of agonists and antagonists on both the affected and unaffected sides in patients with focal dystonia (Cohen and Hallett, 1988; Rothwell *et al*., 1988). Furthermore, bilateral abnormal perception of the illusion of vibration-induced movement is described in idiopathic focal dystonia but not in dystonia secondary to Parkinson's disease (Rome and Grunewald, 1999). This finding supports our results suggesting that focal dystonia is a distinct clinical entity.

Abnormalities of SEPs in dystonia have been described (Reilly *et al*., 1992; Mazzini *et al*., 1994; Kanovsky *et al*., 1997; Tinazzi *et al*., 1999*b*; Frasson *et al*., 2001) and results are conflicting. Some authors have reported a decreased amplitude of the N30 in focal dystonia (Mazzini *et al*., 1994; Grissom *et al*., 1995), whereas others have found an increased N30 amplitude in FHD (Reilly *et al*., 1992; Kanovsky *et al*., 1997, 1998). These apparently divergent results may reflect methodological differences (Hallett, 1995). The diagnostic heterogeneity of the groups studied may also contribute to these apparently conflicting results. For example, in one study (Reilly *et al*., 1992) patients with hand dystonia were selected from both generalized and focal dystonia groups. Spatially

separated somatosensory inputs have a reduced inhibition in idiopathic dystonia (Tinazzi *et al*., 2000). Moreover, the recovery function of the SEP after paired median nerve stimulation shows an impaired inhibition at the spinal and cortical level (Frasson *et al*., 2001). These findings of inefficient inhibitory integration of afferent inputs are probably due to altered surround inhibition and could result in an abnormal motor output and co-contraction in idiopathic dystonia. Thus, our findings support the hypothesis that impaired sensory perception in patients with idiopathic focal dystonia may result in impaired sensorimotor integration and dedifferentiation in somatosensory cortical fields leading to the development of focal dystonia (Byl *et al*, 1996*b*; Bara-Jimenez *et al*., 1998; Hallett, 1998).

The relevance of sensory abnormalities to the pathogenesis of dystonia remains unclear. One hypothesis is that such abnormalities may be related to a pre-existing primary disorder that is likely setting up a predisposition to develop focal dystonia. Indeed, DYT1 dystonia patients generally present with less stereotypy of abnormal muscle activation and report less benefit from sensory tricks than do patients with focal dystonia, which could suggest that sensory events are secondary in the former but are primary in the latter. However, it seems unlikely that somatosensory abnormalities alone are causally involved in the pathophysiology of focal dystonia, as sensory discrimination abnormalities are unrelated to the degree of severity of FHD and are not seen in DYT1 dystonia involving the hands. Another hypothesis is that sensory abnormalities may be related to non-specific secondary plastic changes in the sensory cortex. Overall, our results could be interpreted as suggesting that abnormal sensory input may be a trigger for dystonia and/or the brain response to sensory input could be abnormal in focal dystonia.

The expression of all dystonia phenotypes depends on both genetic and environmental components. Those with DYT1 dystonia have a strong genetic basis and environmental influences are probably minimal. In contrast, the expression of focal dystonia is largely dependent on environment factors (repetitive activation, trauma) and genetic influence may be less marked. Observations from this study support this and indicate that primary focal and generalized dystonia are two clinically and pathophysiologically distinct neurological entities. In addition, abnormal sensory processing in all subgroups of focal dystonia studied suggests a possible pathophysiological mechanism linking all the focal dystonias together into a common condition. Given the plasticity of the somatosensory system and based on the hypothesis that abnormal sensory processing could possibly cause a motor disorder, the use of sensory training has been used for treating focal hand dystonia (Byl and Melnick, 1997; Byl *et al*., 1997; Zeuner *et al*., 2002).Thus, our findings may also have therapeutic implications for other forms of focal dystonia including cervical dystonia and blepharospasm. More studies are required to evaluate sensory system function in DYT1 dystonia and these could include SEPs, MEG and kinaesthetic studies. In addition, serial neurophysiological tests over the course of the disease process may help define the underlying pathophysiology of this disorder. Furthermore, the study of other primary dystonias with known genetic defects (for example DYT6 and DYT7 dystonia) may further facilitate our understanding of this group of disorders.

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