Abnormal plasticity of sensorimotor circuits extends beyond the affected body part in focal dystonia

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ABSTRACT

Objective: To test whether abnormal sensorimotor plasticity in focal hand dystonia is a primary abnormality or is merely a consequence of the dystonic posture.

Methods: This study used the paired associative stimulation (PAS) paradigm, an experimental intervention, capable of producing long term potentiation (LTP) like changes in the sensorimotor system in humans. PAS involves transcranial magnetic stimulation combined with median nerve stimulation. 10 patients with cranial and cervical dystonia, who showed no dystonic symptoms in the hand, and nine patients with hemifacial spasm (HFS), a non-dystonic condition, were compared with 10 healthy age matched controls. Motor evoked potential amplitudes and cortical silent period (CSP) duration were measured at baseline before PAS and for up to 60 min (T0, T30 and T60) after PAS in the abductor pollicis brevis and the first dorsal interosseus muscles.

Results: Patients with dystonia showed a stronger increase in corticospinal excitability than healthy controls and patients with HFS. In addition, patients with dystonia showed a loss of topographical specificity of PAS induced effects, with a facilitation in both the median and ulnar innervated muscles. While PAS conditioning led to a prolonged CSP in healthy controls and patients with HFS, it had no effect on the duration of the CSP in patients with cranial and cervical dystonia.

Conclusion: The data suggests that excessive motor cortex plasticity is not restricted to the circuits clinically affected by dystonia but generalises across the entire sensorimotor system, possibly representing an endophenotypic trait of the disease.

Abnormalities in sensory function may play a pivotal role in the pathophysiology of dystonia.[1–3] Recordings of somatosensory evoked potentials have shown that the sensory input at various central nervous system levels is inadequately processed, despite normal afferent conduction through the lemniscal system.[4] Abnormal sensory processing may cause subtle clinical deficits in sensory perception, as revealed by detailed psychophysiological testing.[5 6] Sensory abnormalities can also be detected in body parts unaffected by dystonia.[7 8] Moreover, electroencephalographic[9] and magnetoencephalographic studies[10] have shown distortion of somatosensory maps in the affected and unaffected cortex in writer's cramp. Based on these findings, it has been proposed that abnormal sensory integration constitutes an endophenotypic trait of focal dystonia.[10]

A technique that has already provided useful information on sensorimotor integration in dystonia is paired associative stimulation (PAS).[11] PAS combines a timed interaction between events induced by afferent median nerve stimulation and transcranial magnetic stimulation (TMS) of the primary motor hand area. If appropriately timed, PAS can induce a long lasting increase or decrease in excitability in corticomotor projections to hand muscles innervated by the median nerve.[12 13] We have previously reported that patients with writer's cramp show a larger and less focused increase in corticospinal excitability after the facilitatory PAS protocol compared with healthy subjects.[11] Abnormal associative plasticity is a feature of other focal dystonias as patients with blepharospasm exhibit enhanced paired associative plasticity in the brainstem circuits mediating the blink reflex.[14] The abnormal magnitude of sensorimotor plasticity at the cortical and brainstem level could in part reflect failure of homeostatic mechanisms stabilising excitability levels within a useful dynamic range.[15] How these abnormal plasticity patterns relate to the pathophysiology of focal dystonia remains unclear. The enhanced and less selective neuronal response to paired associative conditioning may facilitate the formation of inappropriate associations between sensory inputs and corticomotor outputs. This, in turn, may favour the development of dystonia during prolonged and excessive motor training.

To date, abnormal patterns of sensorimotor plasticity have only been demonstrated in the sensorimotor circuits that were clinically affected by dystonia. Therefore, it remains unclear whether in dystonia, abnormal sensorimotor plasticity is a primary abnormality or a mere consequence of involuntary dystonic contractions. To address this question, we applied the facilitatory PAS protocol in patients with cranial and cervical dystonia who showed no dystonic symptoms in the hand and in patients with hemifacial spasm (HFS), a disorder causing involuntary contractions of non-dystonic origin in the facial muscles. We expected that, analogous to the pattern found in writer's cramp,[11 16] patients with focal dystonia, sparing the upper limb, would show an excessive and less focal enhancement of corticospinal excitability in response to PAS conditioning. If so, this would imply that excessive sensorimotor plasticity represents an endophenotypic trait of focal dystonias that generalises across the entire sensorimotor system.

MATERIALS AND METHODS

Participants

We studied 10 patients with cranial and cervical dystonia (six females; mean age 52.8 (12.4) years),

Table 1 Clinical features of patients with dystonia and hemifacial spasm (HFS)

Patient No	Age (y)/ sex	Disease duration (y)	Type of dystonia	BTX (months before)	M&S*	Tsui†
Dystonia						
1	50 F	5	CD	3	–	9
2	58 F	0.5	BSP	–	2	–
3	38 F	3	BSP	3	2	–
4	68 F	9	BSP	5	3	–
5	52 M	3	BSP	4	3	–
6	69 F	13	BSP-OMD	6	2	–
7	47 M	5	BSP-OMD-CD	3	4	9
8	32 M	6	CD	3	–	10
9	49 F	2	BSP	3	2	–
10	65 M	3	BSP	3	3	–
HFS			**Side of HFS**		**HFS scale‡**	
1	57 M	2	Right	–	I3 F2	
2	50 F	15	Left	3	I2 F2	
3	38 M	2	Left	5	I2 F4	
4	65 F	4	Left	4	I3 F3	
5	60 M	5	Left	3	I2 F2	
6	68 M	2	Left	3	I2 F2	
7	58 F	8	Right	5	I2 F3	
8	57 F	25	Right	7	I3 F3	
9	53 F	6	Right	3	I3 F3	

*M&S, Marsden and Schacter scale (range 0–4) for blepharospasm.
†Tsui scale (range (0–25) for cervical dystonia.
‡I, intensity (0–4); F, frequency (0–4).
BSP, blepharospasm; BTX, botulinum toxin; CD, cervical dystonia; OMD, oromandibolar dystonia.

nine patients with HFS (five females; mean age 56.2 (8.9) years) and 10 healthy age matched controls (four females; mean age 51.8 (5.6) years). Participants had never been treated with neuroleptic drugs and had no history of other neuropsychiatric diseases. None of the subjects took drugs acting on the central nervous system. All patients had been treated previously with local injections of botulinum toxin type A in the affected muscles. The last botulinum toxin injections had been given at least 3 months before the study. All subjects were right handed according to the Edinburgh inventory.[17] Informed consent was obtained from all subjects and the study was approved by the local ethics committee in accordance with the Declaration of Helsinki on the use of human subjects in experiments.

Patients with dystonia had normal structural MRI scans and tested negative for a mutation in the DYT1 gene. Clinical details of the patients are summarised in table 1.

We assessed the severity of dystonia using the Marsden and Schachter scale (range 0–4) for blepharospasm.[18] The Tsui scale,[19] which scores the degree of head turning, shoulder elevation, and tremor and jerks of the head (range 0–25), was used to assess the symptoms of cervical dystonia. The severity of HFS was graded clinically for intensity and frequency (range 0–4).[20] Both groups of patients had involuntary movements during the experimental testing.

Experimental design

All subjects were seated in a comfortable reclining chair with a head rest which kept their head in a stable position. Resting motor threshold (RMT), motor evoked potentials (MEPs) and the cortical silent period (CSP) were recorded in the abductor pollicis brevis (APB) before PAS (baseline) and immediately (T0), 30 min (T30) and 60 min (T60) after the end of PAS in the arm ipsilateral to the side of HFS, and in the dominant side for patients with dystonia and for controls. MEPs were obtained from the APB and first dorsal interosseus (FDI) muscles to test whether the conditioning effects of PAS were topographically specific.

Transcranial magnetic stimulation

Focal TMS was applied through a standard figure-of-eight coil with mean loop diameters of 9 cm connected to a High Power Magstim 200 stimulator (Magstim, Whitland, Dyfed, UK). The coil was held tangentially to the skull with the handle pointing backwards and laterally at an angle of 45° to the sagittal plane thus generating a posterior–anterior current in the brain. We established the optimal position for activating the contralateral APB muscle by moving the coil in 0.5 cm steps around the presumed primary motor hand area. The site at which stimuli at slightly suprathreshold intensity consistently produced the steepest slope was marked with a pen as the "motor hot spot" and used for TMS of the motor cortex. The same procedure was repeated to determine the "motor hot spot" of the FDI muscle.

Paired associative stimulation

The PAS protocol paired electrical stimulation of the median nerve with single pulse TMS of the contralateral primary motor hand area. The peripheral stimulus preceded the transcranial stimulus by 25 ms. A total of 90 paired stimuli were given at 0.05 Hz for 30 min. PAS was given while the APB and FDI muscles were completely relaxed. The median nerve was stimulated at the wrist using standard bar electrodes with the cathode positioned proximally. A Digitimer D 180 stimulator (Digitimer, Welwyn Garden City, Herts, UK) generated square wave stimuli with a duration of 200 μs. Stimulus intensity was individually adjusted to 300% of the perceptual threshold. The intensity of the transcranial stimulus was adjusted to evoke a peak-to-peak MEP amplitude of approximately 1 mV in the

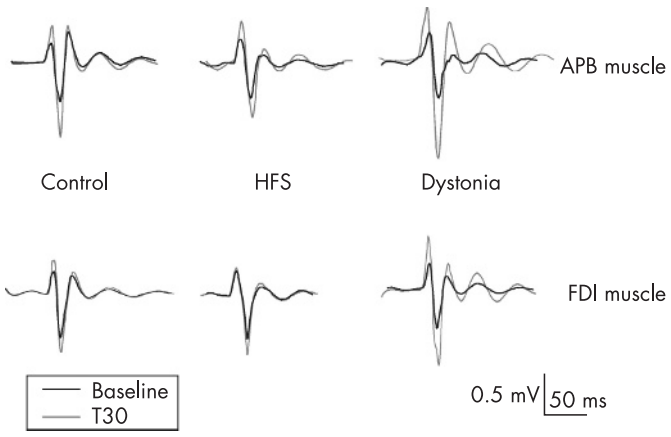

Figure 1 Representative motor evoked potentials from a control subject, a patient with hemifacial spasm (HFS) and a patient with dystonia, recorded from the abductor pollicis brevis (APB) and the first dorsal interosseus (FDI) muscles at baseline and at 30 min (T30) after paired associative stimulation (PAS).

relaxed APB muscle, as determined at the beginning of the experiment.

Assessment of cortical excitability

Single pulse TMS was used to probe corticospinal excitability before and after PAS. The coil position and orientation, and the intensity of the stimulator, were kept constant throughout all experimental sessions. Cortical excitability was assed in blocks of measurements. In each block, we consecutively assessed the RMT, mean MEP amplitude and duration of the CSP. The RMT was defined, according to the guidelines of the International Federation of Clinical Neurophysiology (IFCN) Committee, as the minimum stimulator intensity eliciting MEPs of 50 μV in five out of 10 consecutive trials in the relaxed target muscles.[21] MEPs were recorded from APB and FDI muscles in separate measurements with the centre of the coil placed over the hotspot of the APB or FDI muscle, respectively. For each target muscle, 20 consecutive MEPs were recorded from the completely relaxed target muscle using an interstimulus interval of 5 s. Stimulus intensity was set at a stimulator output that induced MEPs of approximately 1 mV in the right APB muscle.

After MEP measurements at rest, 10 consecutive trials were recorded during isometric contraction to assess the duration of the CSP in the APB muscle. CSP recordings were obtained in a subset of subjects (seven controls, seven patients with HFS, eight with dystonia). Participants performed a tonic contraction of the APB muscle at approximately 15% of their maximum force level with visual feedback through an oscilloscope. CSP from the APB muscle was recorded separately with the TMS coil placed over the hotspot of the corresponding target muscle. Stimulus intensity was set at 130% of RMT of the APB muscle.

Data acquisition and analysis

Surface electromyographic (EMG) activity from the right APB and FDI muscles was recorded with Ag–AgCl surface electrodes using a bipolar belly tendon montage. To ensure complete relaxation, subjects received auditory (speakers) and visual (oscilloscope) feedback of EMG activity. EMG signals were amplified and filtered using a time constant of 3 ms and a high pass filter set at 2.5 kHz (Neurolog System, Digitimer Ltd, Welwyn Garden City, Herts, UK). EMG signals were digitised at a rate of 5 kHz using an analogue–digital interface and stored on a personal computer for offline analysis (CED 1401 interface and Signal Software, Cambridge Electronic Design, Cambridge, UK).

For each block of measurements, the peak-to-peak amplitudes of each MEP (mV) were measured offline, and mean MEP amplitudes were calculated for each stimulation condition (NuCursor software, Sobell Research Department of Motor Neuroscience and Movement Disorders, Institute of Neurology, University College of London, UK). CSP duration of each trial was analysed by means of an automated method, as previously described.[22] The conditioning effects of PAS on RMT, mean MEP amplitude and duration of the CSP were evaluated by separate repeated measures analyses of variance (ANOVA). For each dependent variable, we computed a three way repeated measures ANOVA with *time* (two levels: before intervention vs after intervention) and *muscle* (two levels: APB vs FDI muscle) as within subject factor and *group* (three levels: dystonia, HFS, healthy controls) as between subjects factor. The Greenhouse–Geisser method was used to correct for non-sphericity. For the ANOVA, a non-corrected p value of <0.05 was considered significant. Conditional on a significant F value, post hoc paired sample t tests were used to explore the strength of the main effects and the interactions between the experimental factors. For post hoc comparison, Bonferroni's method was applied to correct for multiple non-independent comparisons. All data are given as mean (SEM).

RESULTS

All participants tolerated the experimental procedures well without reporting any adverse side effects. No differences were found in age, disease duration or duration of botulinum toxin therapy between patients with focal dystonia and those with HFS.

Corticospinal excitability

At baseline, there were no between group differences in RMT or MEP amplitude for the APB and FDI muscles ($p>0.3$). For RMT, repeated measures ANOVA revealed no main effect of time, muscle or group in either muscle. Whereas RMT was unchanged, PAS provoked a lasting increase in mean MEP amplitude in patients and controls. This was confirmed by a strong main effect of the factor time ($F = 36.5$; $p<0.0001$). The magnitude of MEP facilitation differed among groups, as indicated by an interaction between time and group ($F = 6.3$; $p<0.0001$). This was caused by a stronger increase in MEP size in patients with cranio and cervical dystonia than in patients with HFS and healthy controls (fig 1). ANOVA also showed an interaction between time and muscle ($F = 5.6$; $p = 0.001$) because the facilitatory effect of PAS was more pronounced in the APB than in the FDI muscle (fig 1).

To further explore the conditioning effects of PAS on MEP amplitude, we computed separate ANOVAs for each group treating time and muscle as within subject factors. In healthy controls, PAS induced a consistent increase in mean MEP amplitude compared with baseline values, as disclosed by a main effect of time ($F = 12.8$; $p<0.0001$). The facilitatory effect was stronger for MEPs in the APB muscle, as reflected by an interaction between time and muscle ($F = 4.7$; $p = 0.005$) (fig 2A). Likewise, PAS produced a somatotopically specific facilitation of MEP in patients with HFS with a main effect of time ($F = 9.6$; $p<0.0001$) and an interaction between time and muscle ($F = 4.7$; $p = 0.005$) (fig 2B). In patients with dystonia, PAS evoked a different pattern of MEP changes. The

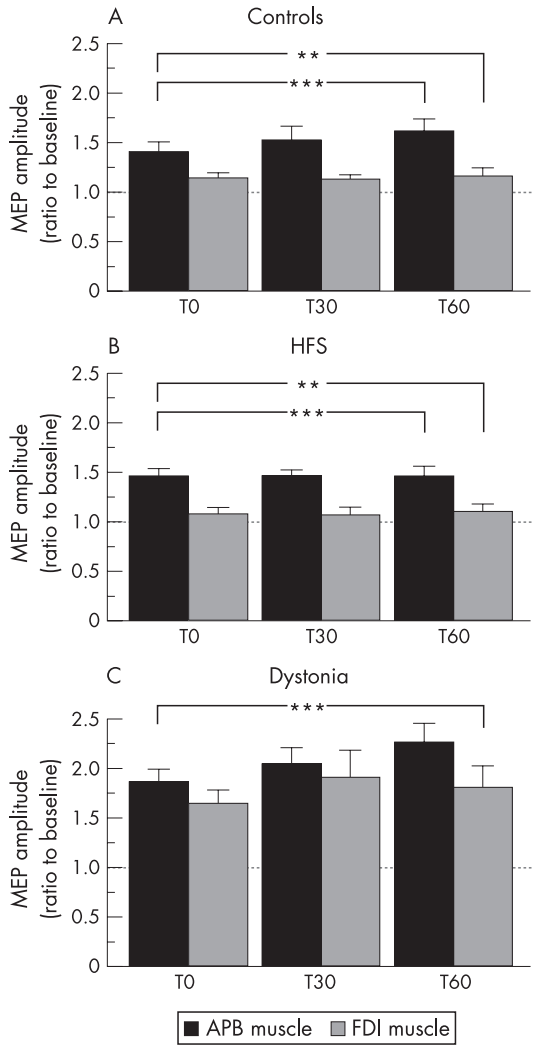

Figure 2 Effect of paired associative stimulation (PAS) on motor evoked potential (MEP) amplitude. The data are plotted as a ratio of baseline. In control subjects (A) and patients with hemifacial spasm (HFS) (B), MEP size increased persistently up to 1 h after the end of PAS and selectively in the abductor pollicis brevis (APB) muscle. (C) Large increase in MEP amplitude in the APB muscle in cranial and cervical dystonia and loss of topographical specificity with facilitation of MEP size in the ulnar innervated first dorsal interosseus (FDI) muscle. ***p<0.0001: main effect of time; **p = 0.005: time × muscle interaction at repeated measures ANOVA.

post-interventional increase in MEP amplitude was higher and less somatotopically specific. This was reflected in the ANOVA which showed a strong main effect of time (F = 19.4; p<0.0001) but no interaction between time and muscle (F = 1.3, p = 0.3) (fig 2C).

Post hoc t tests revealed that PAS stimulation induced a significant and persistent increase in MEP amplitude (table 2) at T0, T30 and T60 (p<0.01) in the APB muscle in all three groups of subjects. A significant facilitation of the MEPs in the FDI muscle (p<0.01) was only observed in patients with dystonia.

Cortical silent period

At baseline, the duration of CSP was significantly shorter in dystonic patients than in patients with HFS and healthy controls (main effect of group: F = 4.6; p = 0.02) (fig 3). There was also a main effect of time (F = 13.2, p<0.001) and an interaction between time and group (F = 2.6; p = 0.03). This was due to prolongation of the CSP after PAS in healthy controls and patients with HFS but not in dystonic patients.

Table 2 Paired associative stimulation induced time dependent changes in motor evoked potential amplitude (mV)

	Baseline	T0	T30	T60
Controls				
APB	0.9 (0.07)	1.2 (0.07)**	1.3 (0.1)**	1.4 (0.1)**
FDI	0.9 (0.1)	1.02 (0.1)	1.03 (0.1)**	1.04 (0.1)
HFS				
APB	0.7 (0.04)	1.03 (0.07)**	1.03 (0.07)**	1.04 (0.1)**
FDI	0.8 (0.08)	0.8 (0.08)	0.8 (0.1)	0.9 (0.1)
Dystonia				
APB	0.8 (0.05)	1.5 (0.1)***	1.6 (0.2)***	1.8 (0.2)***
FDI	0.8 (0.09)	1.3 (1)***	1.4 (0.2)***	1.3 (0.1)***

Data are mean (SEM).
**p<0.01, ***p<0.001, paired t test.
APB, abductor pollicis brevis; FDI, first dorsal interosseus; HFS, hemifacial spasm muscle.

DISCUSSION

This study found that cranial and cervical dystonia is associated with an altered response to PAS conditioning of sensorimotor circuits supplying the unaffected upper limb. Patients with dystonia showed a stronger increase in corticospinal excitability than healthy controls and patients with HFS. In addition, patients with dystonia showed loss of topographical specificity of PAS induced effects, with facilitation in both the median and ulnar innervated muscles. Whereas associative stimulation led to a prolonged CSP in healthy controls and patients with HFS, PAS had no effect on the duration of CSP in dystonic patients. We discuss the implications of these results in light of the current pathophysiological concepts of focal dystonia.

Confirming previous work,[11 12 23] the facilitatory PAS protocol produced a long lasting increase in corticospinal excitability which lasted for up to an hour in healthy individuals. The conditioning effect was topographically specific because the increase in excitability only occurred in corticospinal projections

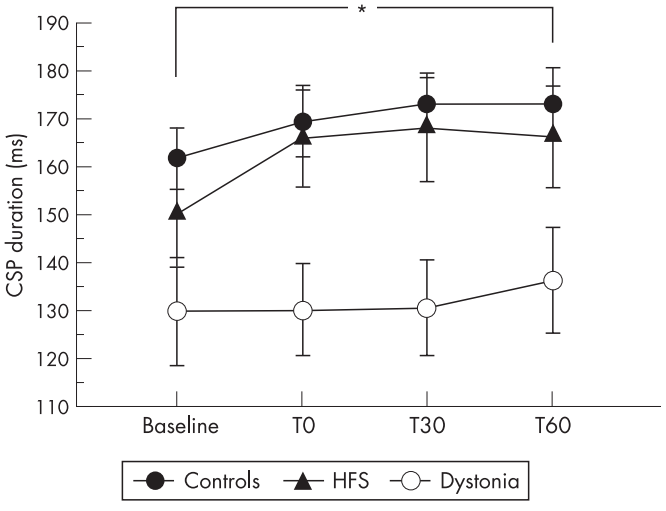

Figure 3 Increase in cortical silent period (CSP) duration after paired associative stimulation (PAS) in control subjects and patients with hemifacial spasm (HFS). Lack of CSP prolongation is seen in cranial and cervical dystonia after PAS. *p = 0.03: time × group interaction, repeated measures ANOVA.

to the APB muscle innervated by the median nerve but not in the FDI muscle innervated by the ulnar nerve.

In patients with HFS, a non-dystonic movement disorder of peripheral origin causing unilateral involuntary facial movements, PAS induced an identical pattern of excitability changes as in healthy controls. This observation has two implications. Firstly, the presence of involuntary facial spasms per se does not interfere with induction of paired associative plasticity in the sensorimotor system. Secondly, the normal pattern of PAS induced cortical reorganisation in HFS suggests that the abnormal plasticity found in patients with cranial and cervical dystonia is not causally linked to the presence of involuntary muscle contractions in the face or neck. We propose that the excessive sensorimotor plasticity found in focal dystonia reflects an intrinsic abnormality of the basic mechanisms underlying sensorimotor neuroplasticity rather than arising from dystonic movements themselves. This is not to say that the presence of dystonic symptoms cannot trigger sensorimotor reorganisation. In fact, patients with psychogenic dystonia exhibit alterations in cortical and spinal excitability that can be found in patients with organic dystonia, suggesting that dystonic movements and posturing might alter cortical excitability and interfere with spinal inhibition.[24]

It has been shown previously that botulinum toxin injected in the neck muscles modifies the long latency reflexes evoked in the unaffected thenar muscles.[25] In the present study, botulinum toxin might have partially influenced PAS induced effects by changing the peripheral sensory input, via Ia fibres, and producing changes in CNS excitability.[26 27] However, we believe that this possibility is unlikely because HFS patients (also treated with botulinum toxin) had a normal PAS response and most of our patients had blepharospasm affecting the orbicularis oculi muscles where only a few or no muscle spindles are found.[28]

Patients with cranial and cervical dystonia showed an abnormal response to PAS, similar to what we have previously reported in patients with writer's cramp.[11] This implies that different forms of focal dystonias share an anomalous response pattern to sensorimotor stimulation. Of note, patients with cranial and cervical dystonia had no dystonic symptoms in the upper limb, yet they showed an abnormal sensorimotor reorganisation in response to PAS. This finding provides evidence that in focal dystonia, abnormal sensorimotor plasticity is also expressed in neuronal circuits that are clinically unaffected by dystonia. Our results are similar to those of Edwards and colleagues[29] who demonstrated that patients with cervical dystonia, similar to manifesting carriers of the DYT1 mutation, have alteration of synaptic plasticity in a district not affected by dystonia, tested with an inhibitory rTMS protocol (theta burst stimulation), which is know to induce LTD-like changes in the motor cortex. However, this intervention does not involve somatosensory stimulation, only motor circuits. We propose that abnormal sensorimotor plasticity constitutes an additional endophenotypical trait of focal dystonia that is independent of its clinical manifestation.

In patients affected by cranial and cervical dystonia and writer's cramp,[11 16] the facilitatory PAS protocol produced a larger and less focal increase in the excitability of corticospinal output neurons after PAS than in healthy controls. As the excitability changes induced by facilitatory PAS may share features of long term potentiation (LTP) of synaptic efficacy,[12] these results provide converging evidence for abnormal enhancement of LTP-like plasticity in focal dystonia. Patients with writer's cramp also show an enhanced and less focal suppression of MEP amplitude in response to an inhibitory PAS protocol.[16] As MEP suppression in response to inhibitory PAS is thought to be caused by long term depression (LTD) of synaptic efficacy,[13] it has been proposed that LTD-like sensorimotor plasticity is also abnormally enhanced in focal dystonia.[16] Hence it can be concluded that LTP-like as well as LTD-like plasticity is abnormal with respect to both gain and spatial organisation in focal hand dystonia and presumably in other focal dystonias. Especially in task specific dystonias, over expression of LTP-like plasticity is likely to be more relevant to the pathophysiology of dystonia because enhanced LTP-like plasticity will sensitise the motor system to peripheral input and produce over activity within the sensorimotor system.

Although our findings indicate an increase in expression of LTP-like plasticity in the sensorimotor system that generalises beyond the affected limb, we can only speculate about the mechanisms that mediate the abnormal reactivity of the sensorimotor circuits in focal dystonia. A candidate mechanism is a generalised abnormality in sensory processing which may involve increased amplification and less focal central processing of the afferent input within the sensorimotor system. A generalised abnormality in sensory processing is suggested by several psychophysiological studies. For instance, a raised somatosensory temporal discrimination threshold was detected in patients with focal hand dystonia in either the affected or unaffected side.[30] Moreover, an increased spatial discrimination threshold was found on both hands of patients with unilateral focal hand dystonia,[30] on the hands of patients with cervical dystonia and blepharospasm[8] and also in unaffected first degree relatives of patients with cervical dystonia.[31] Finally, MEP suppression following peripheral stimulation is defective in patients with focal hand dystonia, in keeping with an abnormal central processing of sensory input.[32]

A second contributing factor may be reduced excitability of inhibitory circuits at the cortical level. Deficient activity of inhibitory circuits has been demonstrated at various levels of the central nervous system in focal dystonia.[33 34] It is conceivable that highly synchronised sensory inputs evoked by median nerve stimulation in the PAS protocol were abnormally processed in the primary motor cortex because of deficient inhibition. Of note, the duration of the CSP was shortened in patients with cranial and cervical dystonia relative to healthy controls and patients with HFS, indicating decreased excitability of intracortical GABAergic circuits.[35 36] In addition, patients with writer's cramp lacked the normal PAS induced CSP change. Hence we assumed that in the patients with cranial and cervical dystonia, as in focal hand dystonia, the mechanisms that facilitate the excitability of the corticospinal output to the affected limb were abnormally reactive.

There are several lines of evidence reporting the fact that a subtle neurophysiological deficit can be detected in focal hand dystonia in the non-affected side, in keeping with a more intrinsic deficit in patients with dystonia.[8 30] Moreover, the CSP was shortened in both non-manifesting and manifesting carriers of the DYT1 gene mutation,[37] in the sternocleidomastoid muscles of both sides in cervical dystonia and in the affected and unaffected hand in focal hand dystonia.[38] Positron emission tomography based endophenotyping has also shown an increased covariance of regional activity among several subcortical structures, including the lentiform nucleus, pons and midbrain in DYT1 carriers with and without dystonia, suggesting the presence of a (genetically determined) subclinical deficit.[39]

Overall, these data suggest that in cranial–cervical dystonias as well as in focal hand dystonia, there is an increased maladaptive tendency to strengthen sensory–motor associations. This defect might contribute to the abnormalities of movement control seen in dystonia. Task specific focal hand dystonias are probably a product of a genetic background and an environmental insult.[3] That is, dystonia develops with excessive writing or playing an instrument only in those persons who are genetically predisposed. Convincing evidence already underlines the strong genetic influence in focal dystonias.[40 41] The abnormal sensorimotor plasticity may be the intrinsic deficit (genetic predisposition) that along with environmental factors such as repetitive movements in musician's cramp or peripheral nerve system injury or trauma induces dystonia. The model of altered associative plasticity in focal dystonias may be an important link in demonstrating how environmental influences can trigger dystonia.[42]

In conclusion, the present findings provide direct evidence that the mechanism underlying neuronal plasticity is abnormal in focal dystonia even in cortical areas that are clinically uninvolved. We propose that this abnormal sensorimotor plasticity in focal dystonia is one endophenotypic trait of the disease.

Competing interests: None.

Ethics approval: The study was approved by the local ethics committee in accordance with the Declaration of Helsinki on the use of human subjects in experiments.

REFERENCES

1. **Hallett M.** Disorder of movement preparation in dystonia. *Brain* 2000;**123**:1765–6.
2. **Abbruzzese G,** Berardelli A. Sensorimotor integration in movement disorders. *Mov Disord* 2003;**18**:231–40.
3. **Defazio G,** Berardelli A, Hallett M. Do primary adult-onset focal dystonias share aetiological factors? *Brain* 2007;**130**:1183–93.
4. **Tinazzi M,** Rosso T, Fiaschi A. Role of the somatosensory system in primary dystonia. *Mov Disord* 2003;**18**:605–22.
5. **Bara-Jimenez W,** Shelton P, Sanger TD, *et al*. Sensory discrimination capabilities in patients with focal hand dystonia. *Ann Neurol* 2000;**47**:377–80.
6. **Peller M,** Zeuner KE, Munchau A, *et al*. The basal ganglia are hyperactive during the discrimination of tactile stimuli in writer's cramp. *Brain* 2006;**129**:2697–708.
7. **Fiorio M,** Gambarin M, Valente EM, *et al*. Defective temporal processing of sensory stimuli in DYT1 mutation carriers: a new endophenotype of dystonia? *Brain* 2007;**130**:134–42.
8. **Molloy FM,** Carr TD, Zeuner KE, *et al*. Abnormalities of spatial discrimination in focal and generalized dystonia. *Brain* 2003;**126**:2175–82.
9. **Hamano T,** Kaji R, Katayama M, *et al*. Abnormal contingent negative variation in writer's cramp. *Clin Neurophysiol* 1999;**110**:508–15.
10. **Meunier S,** Garnero L, Ducorps A, *et al*. Human brain mapping in dystonia reveals both endophenotypic traits and adaptive reorganization. *Ann Neurol* 2001;**50**:521–7.
11. **Quartarone A,** Bagnato S, Rizzo V, *et al*. Abnormal associative plasticity of the human motor cortex in writer's cramp. *Brain* 2003;**126**:2586–96.
12. **Stefan K,** Kunesch E, Cohen LG, *et al*. Induction of plasticity in the human motor cortex by paired associative stimulation. *Brain* 2000;**123**:572–84.
13. **Wolters A,** Sandbrink F, Schlottmann A, *et al*. A temporally asymmetric Hebbian rule governing plasticity in the human motor cortex. *J Neurophysiol* 2003;**89**:2339–45.
14. **Quartarone A,** Sant'angelo A, Battaglia F, *et al*. Enhanced long-term potentiation-like plasticity of the trigeminal blink reflex circuit in blepharospasm. *J Neurosci* 2006;**26**:716–21.
15. **Quartarone A,** Rizzo V, Bagnato S, *et al*. Homeostatic-like plasticity of the primary motor hand area is impaired in focal hand dystonia. *Brain* 2005;**128**:1943–50.
16. **Weise D,** Schramm A, Stefan K, *et al*. The two sides of associative plasticity in writer's cramp. *Brain* 2006;**129**:2709–21.
17. **Oldfield RC.** The assessment and analysis of handedness: the Edinburgh inventory. *Neuropsychologia* 1971;**9**:97–113.
18. **Marsden CD,** Schachter M. Assessment of extrapyramidal disorders. *Br J Clin Pharmacol* 1981;**11**:129–51.
19. **Tsui JK,** Eisen A, Stoessl AJ, *et al*. Double-blind study of botulinum toxin in spasmodic torticollis. *Lancet* 1986;**2**:245–7.
20. **Tolosa E,** Marti MJ, Kulisevsky J. Botulinum toxin injection therapy for hemifacial spasm. *Adv Neurol* 1988;**49**:479–91.
21. **Rossini PM,** Barker AT, Berardelli A, *et al*. Non-invasive electrical and magnetic stimulation of the brain, spinal cord and roots: basic principles and procedures for routine clinical application. Report of an IFCN committee. *Electroencephalogr Clin Neurophysiol* 1994;**91**:79–92.
22. **Daskalakis ZJ,** Molnar GF, Christensen BK, *et al*. An automated method to determine the transcranial magnetic stimulation-induced contralateral silent period. *Clin Neurophysiol* 2003;**114**:938–44.
23. **Morgante F,** Espay AJ, Gunraj C, *et al*. Motor cortex plasticity in Parkinson's disease and levodopa-induced dyskinesias. *Brain* 2006;**129**:1059–69.
24. **Espay AJ,** Morgante F, Purzner J, *et al*. Cortical and spinal abnormalities in psychogenic dystonia. *Ann Neurol* 2006;**59**:825–34.
25. **Naumann M,** Reiners K. Long-latency reflexes of hand muscles in idiopathic focal dystonia and their modification by botulinum toxin. *Brain* 1997;**120**:409–16.
26. **Abbruzzese G,** Berardelli A. Neurophysiological effects of botulinum toxin type A. *Neurotox Res* 2006;**9**:109–14.
27. **Trompetto C,** Curra A, Buccolieri A, *et al*. Botulinum toxin changes intrafusal feedback in dystonia: a study with the tonic vibration reflex. *Mov Disord* 2006;**21**:777–82.
28. **Goodmurphy CW,** Ovalle WK. Morphological study of two human facial muscles: orbicularis oculi and corrugator supercilii. *Clin Anat* 1999;**12**:1–11.
29. **Edwards MJ,** Huang YZ, Mir P, *et al*. Abnormalities in motor cortical plasticity differentiate manifesting and nonmanifesting DYT1 carriers. *Mov Disord* 2006;21:2181–6.
30. **Fiorio M,** Tinazzi M, Bertolasi L, *et al*. Temporal processing of visuotactile and tactile stimuli in writer's cramp. *Ann Neurol* 2003;**53**:630–5.
31. **O'Dwyer JP,** O'Riordan S, Saunders-Pullman R, *et al*. Sensory abnormalities in unaffected relatives in familial adult-onset dystonia. *Neurology* 2005;**65**:938–40.
32. **Abbruzzese G,** Marchese R, Buccolieri A, *et al*. Abnormalities of sensorimotor integration in focal dystonia: a transcranial magnetic stimulation study. *Brain* 2001;**124**:537–45.
33. **Berardelli A,** Rothwell JC, Hallett M, *et al*. The pathophysiology of primary dystonia. *Brain* 1998;**121**:1195–212.
34. **Sohn YH,** Hallett M. Disturbed surround inhibition in focal hand dystonia. *Ann Neurol* 2004;**56**:595–9.
35. **Siebner HR,** Dressnandt J, Auer C, *et al*. Continuous intrathecal baclofen infusions induced a marked increase of the transcranially evoked silent period in a patient with generalized dystonia. *Muscle Nerve* 1998;**21**:1209–12.
36. **Werhahn KJ,** Kunesch E, Noachtar S, *et al*. Differential effects on motorcortical inhibition induced by blockade of GABA uptake in humans. *J Physiol* 1999;**517**:591–7.
37. **Edwards MJ,** Huang YZ, Wood NW, *et al*. Different patterns of electrophysiological deficits in manifesting and non-manifesting carriers of the DYT1 gene mutation. *Brain* 2003;**126**:2074–80.
38. **Rona S,** Berardelli A, Vacca L, *et al*. Alterations of motor cortical inhibition in patients with dystonia. *Mov Disord* 1998;**13**:118–24.
39. **Asanuma K,** Ma Y, Okulski J, *et al*. Decreased striatal D2 receptor binding in non-manifesting carriers of the DYT1 dystonia mutation. *Neurology* 2005;**64**:347–9.
40. **Brancati F,** Valente EM, Castori M, *et al*. Role of the dopamine D5 receptor (DRD5) as a susceptibility gene for cervical dystonia. *J Neurol Neurosurg Psychiatry* 2003;**74**:665–6.
41. **Defazio G,** Aniello MS, Masi G, *et al*. Frequency of familial aggregation in primary adult-onset cranial cervical dystonia. *Neurol Sci* 2003;**24**:168–9.
42. **Quartarone A,** Siebner HR, Rothwell JC. Task-specific hand dystonia: can too much plasticity be bad for you? *Trends Neurosci* 2006;**29**:192–9.

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