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Abnormal sensorimotor plasticity in organic but not in psychogenic dystonia

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Dystonia is characterized by two main pathophysiological abnormalities: 'reduced' excitability of inhibitory systems at many levels of the sensorimotor system, and 'increased' plasticity of neural connections in sensorimotor circuits at a brainstem and spinal level. A surprising finding in two recent papers has been the fact that abnormalities of inhibition similar to those in organic dystonia are also seen in patients who have psychogenic dystonia. To try to determine the critical feature that might separate organic and psychogenic conditions, we investigated cortical plasticity in a group of 10 patients with psychogenic dystonia and compared the results with those obtained in a matched group of 10 patients with organic dystonia and 10 healthy individuals. We confirmed the presence of abnormal motor cortical inhibition (short-interval intracortical inhibition) in both organic and psychogenic groups. However, we found that plasticity (paired associative stimulation) was abnormally high only in the organic group, while there was no difference between the plasticity measured in psychogenic patients and healthy controls. We conclude that abnormal plasticity is a hallmark of organic dystonia; furthermore it is not a consequence of reduced inhibition since the latter is seen in psychogenic patients who have normal plasticity.

Keywords: associative plasticity; organic dystonia; psychogenic dystonia; paired associative stimulation; transcranial magnetic stimulation

Abbreviations: AMT = active motor threshold; ANOVA = analysis of variance; APB = abductor pollicis brevis; FDI = first dorsal interosseus; LAI = long afferent inhibition; LICI = long interval intracortical inhibition; MEP = motor evoked potential; PAS = paired associative stimulation; RMT = resting motor threshold; SAI = short afferent inhibition; SICI = short interval intracortical inhibition; TMS = transcranial magnetic stimulation

Introduction

The large literature on the pathophysiology of primary dystonia identifies two main areas of abnormality: reduced excitability of inhibitory circuits in spinal, brainstem and cortical motor circuits (Berardelli, 2006; Defazio *et al*., 2007; Quartarone *et al*., 2008*b*), together with increased responsiveness to repetitive transcranial magnetic stimulation (TMS) protocols that are thought to induce synaptic plasticity in the motor cortex (Quartarone *et al*., 2006). Indeed, the two effects may even be linked since work in both animal and human brain has shown that synaptic plasticity is enhanced when inhibition is reduced, for example by treatment

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with the gamma-aminobutyric acid (GABA) blocking drug bicuculline (Hess and Donoghue, 1996), or by peripheral deafferentation (Ziemann *et al*., 1998).

Reduced inhibition and increased plasticity are seen in unaffected muscles of patients with focal dystonia (Ridding *et al*., 1995; Quartarone *et al*., 2008*a*). Thus they are thought to be primary abnormalities rather than secondary to dystonic muscle contraction. Indeed it is tempting to speculate that they are the cause of dystonia, with reduced inhibition leading to overflow of muscle contraction to unwanted muscles, and increased plasticity being involved, for example, in the prevalence of focal dystonias in skilled musicians or the appearance of dystonia after minor peripheral injury (Quartarone *et al*., 2006).

Two recent studies have examined inhibitory circuits in patients with psychogenic dystonia. Espay *et al*. (2006) found that these patients had the same abnormalities of short and long interval intracortical inhibition (SICI and LICI), cortical silent period and spinal reciprocal inhibition as patients with primary dystonia. However, since they studied affected parts of the body it was unclear whether the effects were secondary to the assumption of dystonic postures, or were a primary, possibly predisposing factor. Avanzino *et al*. (2008) tried to address this question by measuring inhibition in the unaffected arm of patients with fixed dystonia of the other arm or in the legs that were thought to be psychogenic in origin. They found the same abnormalities and suggested that the reduced inhibition in these individuals might be a factor that predisposes them to develop dystonic features rather than other movement disorders.

Neither of these studies investigated plasticity. Indeed, if it was increased as in primary dystonia, then it would cast doubt on the role of pathophysiological abnormalities in producing symptoms of organic dystonia since psychogenic dystonia can, by definition, disappear, often in a very short space of time, with successful treatment. The present study addressed this question by investigating motor cortical plasticity in a group of patients with definite or probable psychogenic dystonia. For comparison with previous reports, we used the paired associative stimulation (PAS) protocol in which an electrical stimulus to the median nerve at the wrist is paired with a TMS pulse to the contralateral motor cortex hand area 25 ms later (Stefan *et al*., 2000). We also measured SICI to confirm previous observations (Espay *et al*., 2006; Avanzino *et al*., 2008) of reduced inhibition in psychogenic dystonia and explored short and long afferent inhibition (SAI/LAI) since these had been reported to be normal in this group of patients (Avanzino *et al*., 2008).

Materials and Methods

Participants

We studied 10 patients with definite or probable psychogenic dystonia (nine females; mean age 46.5 ± 14.2 years), 10 patients with organic dystonia (six females; mean age 52.8 ± 12.4 years) and 10 healthy age-matched controls (six females; mean age 51.8 ± 5.6 years). Patients with psychogenic dystonia were recruited from National Hospital for Neurology and Neurosurgery, London and diagnosed according to Fahn and Williams' criteria (1988). Table 1 shows the clinical features of the psychogenic dystonia group. Patients with organic dystonia were recruited from the Department of Neuroscience, University of Messina. Table 2 shows the clinical features of the organic dystonia group. All drugs affecting the central nervous system were withdrawn at least 1 week prior to the study; patients receiving botulinum toxin injections were examined at least 3 months after the last injection. Informed consent was obtained from all participants 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.

Experimental design

All participants were seated in a comfortable reclining chair during the experiment and asked to relax while looking straight ahead.

Transcranial magnetic stimulation (TMS) was applied using a Magstim 200 stimulator (The Magstim Company Ltd, Whitland, South West Wales, UK) connected to a figure of eight coil (9 cm diameter) oriented to induce posterior-anterior current flow approximately perpendicular to the central sulcus over the hand area of motor cortex (M1). Motor evoked potentials (MEPs) were recorded from surface electrodes over the contralateral abductor pollicis brevis (APB) and first dorsal interosseus (FDI) muscles on the dominant side of the patients and controls. Signals were recorded, amplified and filtered with a Digitimer D360 (Digitimer Ltd, UK) (bandwidth 5 Hz to 1 kHz), acquired at a sampling rate of 5 kHz through a 1401 plus AD laboratory interface (Cambridge Electronic Design, Cambridge, UK) and stored on a personal computer for off-line analysis (Signal software; Cambridge Electronic Devices, Cambridge, UK). Experiments were performed with subjects fully relaxed and with their eyes opened. The level of baseline EMG activity was carefully monitored and trials with background EMG activity were rejected. The amplitude of MEPs was measured peak to peak (mV) and then averaged.

We first determined the location of the 'hot spot' for evoking MEPs in the FDI and APB muscles and marked this on the scalp. Then, with the coil at this location we measured the resting and active motor threshold (RMT and AMT) according to the criteria of Rossini *et al*. (1994).

We first measured SICI at rest in the APB muscle as originally described by Kujirai *et al*. (1993). In brief, the test stimulus intensity was set to produce a MEP of approximately 1 mV peak to peak in the APB muscle, while the conditioning intensity was adjusted to 80% AMT. SICI was assessed at an inter stimulus interval (ISI) of 2 ms. Twenty trials were recorded for the ISI of 2 ms and randomly intermingled with twenty trials in which MEPs were elicited by the test stimulus alone. The amount of inhibition was quantified as the size of the conditioned response divided by the size of the test response and expressed as a percentage.

SAI and LAI were assessed in the APB muscle using the techniques described respectively by Tokimura and Chen (Chen *et al*., 1999; Tokimura *et al*., 2000). In brief, the intensity of the test TMS pulse was adjusted to produce a MEP of approximately 1 mV peak to peak. The conditioning pulse was an electrical stimulus to the median nerve at the wrist (cathode proximal) using a square wave pulse with a pulse width of 200 μs. The intensity was set just above the threshold for evoking a visible twitch of the thenar muscles (approximately three times perceptual threshold). The interstimulus interval was 25 ms for SAI and 200 ms for LAI. Twenty control and conditioned responses were randomly intermixed and the mean amplitude of the conditioned response expressed as a percentage of the test response alone.

Table 1 Demographic and clinical features of patients with psychogenic dystonia

	Age/ gender	Disease duration (years)	Type and site of onset/ precipitating factor	Course	Clinical diagnosis
1	68 F	15	Leg foot/peripheral injury (dancing)	Generalization	Probable psychogenic dystonia
2	50 M	5	Right hand/no clear precipitant	Generalization	Clinically established psychogenic dystonia
3	44 F	11	Sub acute in right foot/right knee arthroscopy	Spread to right hand and neck	Clinically definite psychogenic dystonia[IV]
4	56 F	16	Gradual in right hand/no clear precipitant	Spread to left hand	Probable psychogenic dystonia[I]
5	29 F	6	Right foot/previous episode of acute jaw deviation, which resolved/no clear precipitant	Stable	Probable psychogenic dystonia[I,II,VI]
6	29 F	12	Left leg/back pain	Spread to right leg and generalization	Documented psychogenic dystonia
7	63 F	13	Gradual in right leg/no clear precipitant	Stable	Probable psychogenic dystonia[VII]
8	41 F	8	Left hand/trauma right forearm	Spread to right hand	Probable psychogenic dystonia
9	30 F	4	Left arm following peripheral injury (fracture left scaphoid bone and subsequent immobilization)	Stable	Probable psychogenic dystonia
10	55 F	4	Neck dystonia/no clear precipitant	Spread to face, jaw, left arm	Clinically definite psychogenic dystonia

Roman numbers are used to specify clinical features of psychogenic dystonia in individual patients: I = multiple somatizations; II = previous unexplained complaints despite appropriate investigations; III = self-inflicted injuries; IV = obvious psychiatric disturbances; V = false weakness; VI = no anatomical sensory loss; VII = other incongruent movements.

Table 2 Demographic and clinical features of patients with organic dystonia

	Age/ gender	Disease duration (years)	Type of dystonia	BTX (months before)
1	50 F	5	CD	3
2	58 F	0.5	WC	//
3	38 F	8	BSP	3
4	68 F	9	BSP	5
5	52 M	3	WC	4
6	69 F	13	OMD	6
7	47 M	5	BSP–OMD–CD	3
8	32 M	6	CD	3
9	49 F	2	WC	3
10	65 M	3	WC	3

BSP = Blepharospasm; OMD = oro-mandibular dystonia; WC = writer's cramp; BTX = botulinum toxin.

Short interval intracortical inhibition (SICI), LAI and SAI were measured in 8 of the 10 subjects in each group. PAS was measured on all 10 individuals as described by Stefan and co-workers (2000). In brief, 90 pairs of stimuli were given every 20 s using electrical stimulation of the median nerve at the wrist and TMS of the hand area of motor cortex. The intensity of the median nerve stimulus was set just above the threshold for evoking a visible twitch of the thenar muscles (approximately three times perceptual threshold) and the intensity of the TMS pulse was ~115%–125% of RMT (to elicit MEPs with a peak-to-peak amplitudes of 1.0 mV).

Prior to applying PAS (baseline), we first measured the amplitude of 20 test MEPs in the FDI and APB muscles using a stimulus intensity set to produce approximately a 1 mV MEP. After PAS, we re-measured MEPs using the same intensity of stimulation immediately after (T0) and 30 min (T30) after the end of PAS.

Statistical analysis

The conditioning effects of PAS on RMT and mean MEP amplitude were evaluated by separate repeated-measures analyses of variance (ANOVA). For each dependent variable, we computed a three-way repeated-measures ANOVA with '*time*' (three levels: baseline, T0, T30) and '*muscle*' (two levels: APB versus FDI muscle) as within-subject factor and '*group*' (three levels: psychogenic dystonia, organic dystonia, healthy controls) as between-subjects factor.

To explore differences regarding LAI and SICI we performed a factorial ANOVA with group as between subjects factor and ISI as within subject 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. All data are given as mean ± SEM.

Results

None of the participants reported any adverse side effects from any of the interventions. Table 3 gives the RMTs and AMTs in each group of subjects as well as the TMS intensity used to produce the standard 1 mV MEP in the FDI and APB muscles in the following experiments.

Paired associative stimulation

The effects of PAS have been reported to depend on the level of attention to the stimulated body part (Stefan *et al*., 2004). In order to control for this, we asked all participants to count and recall the number of electrical stimuli which were delivered

Table 3 RMTs and AMTs in each group of subjects as well as the TMS intensity used to produce the standard 1mV MEP in the FDI and APB muscles

	Psychogenic dystonia	Organic dystonia	Healthy controls
AMT (APB)	38 ± 4	39 ± 3	37 ± 4
RMT (APB)	47 ± 6	46 ± 3	44 ± 5
Intensity MEP 1 mV (APB)	62 ± 9	60 ± 7	59 ± 6
RMT (FDI)	45 ± 5	44 ± 3	45 ± 4
Intensity MEP 1 mV (FDI)	54 ± 8	56 ± 7	55 ± 5

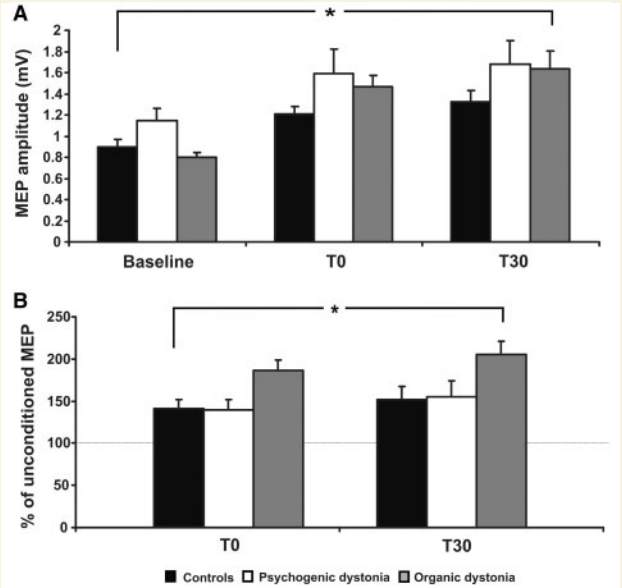

Figure 1 Effect of PAS on MEPs amplitude. The data are plotted as absolute MEP values expressed in mV (**A**) and in percentage of unconditioned MEP (**B**). Patients with organic dystonia (grey column) display a significant increase of MEPs amplitude in APB muscle compared with control subjects (black columns) and psychogenic patients (white column). *Time × Group interaction ($P = 0.003$).

at wrist level during the procedure. All groups performed at >95% accuracy.

The mean group data are shown in Figs 1 and 2, which plot for each muscle (APB, FDI) the absolute amplitudes of the MEP at baseline, immediately after and 30 min after PAS, as well as the percentage changes in size relative to baseline for the two time-points after PAS. Statistics were performed on the MEP amplitude (mV) data. Figure 3 is a scatter plot of the individual data points from each participant showing the percentage MEP facilitation after PAS in APB and FDI muscles in healthy subjects, psychogenic dystonia (affected side), psychogenic dystonia (unaffected side) and organic dystonia.

At baseline, there were no between-group differences in RMT or MEP amplitudes for the APB and FDI muscle (all comparisons: $P > 0.3$). Whereas RMT was unchanged, PAS provoked a lasting increase in mean MEP amplitudes in patients and controls.

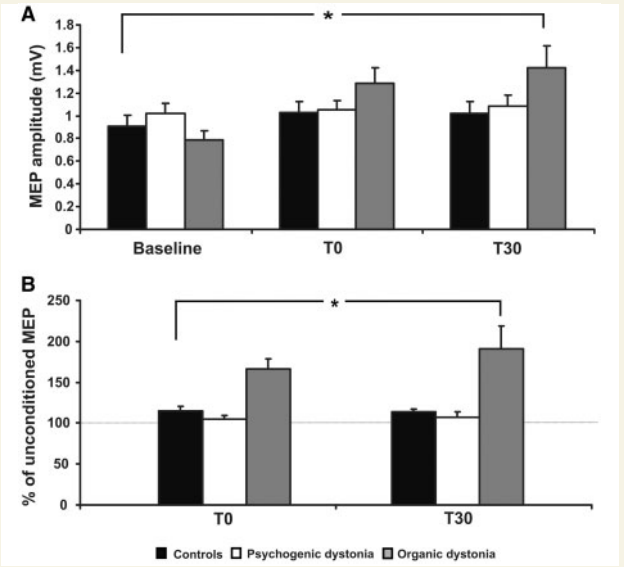

Figure 2 Effect of PAS on MEPs amplitude. The data are plotted as absolute MEP values expressed in mV (**A**) and in percentage of unconditioned MEP (**B**). Patients with organic dystonia (grey column) display a significant increase of MEPs amplitude in FDI. On the contrary, control subjects (black columns) and psychogenic patients (white column) do not show any significant increase in MEP amplitude. *Time × Group interaction ($P = 0.003$).

Data were analysed using a repeated measures ANOVA with time (before intervention versus after intervention), group and muscle (APB muscle versus FDI muscle) as main factors. There was a significant main effect of time [$F(2,18) = 67.5$; $P < 0.0001$]. This was caused by an overall increase in mean peak-to-peak MEP amplitudes after associative stimulation in all three groups. In addition, there was also a time × group interaction [$F(4,36) = 4.7$; $P = 0.003$] because associative stimulation induced a stronger increase in MEP size in patients with organic dystonia compared with healthy controls and psychogenic dystonia. There was also a significant time × muscle interaction [$F(2,18) = 6.7$; $P = 0.006$]. This was due to the fact that the facilitatory effect of associative stimulation was more pronounced in the APB muscle compared with the FDI muscle (Figs 1 and 2). However, the three way interaction of time × muscle × group was not significant [$F(4,36) = 0.4$; $p = 0.8$], indicating that there was no difference between the groups in the topographic specificity of PAS.

To explore within-group effects, we computed separate two-factorial ANOVAs for each group, with time and muscle as within-subject factors. In patients affected by organic dystonia, ANOVA revealed only a prominent main effect for the factor time [$F(2,18) = 28.7$; $P < 0.00001$] but no significant time × muscle interaction [$F(2,18) = 0.4$; $P = 0.6$], whereas, in healthy controls and in patients with psychogenic dystonia, ANOVA demonstrated both a main effect for the factor time [healthy controls: $F(2,18) = 14$; $P = 0.0002$; psychogenic dystonia: $F(2,18) = 6.8$; $P = 0.006$] and a time × muscle interaction [healthy controls: $F(2,18) = 6.4$; $P = 0.008$; psychogenic dystonia: $F(2,18) = 5$; $P = 0.02$].

Post hoc *t*-tests revealed that PAS induced a significant and persistent increase in MEP amplitudes at T0 and T30 ($P < 0.01$)

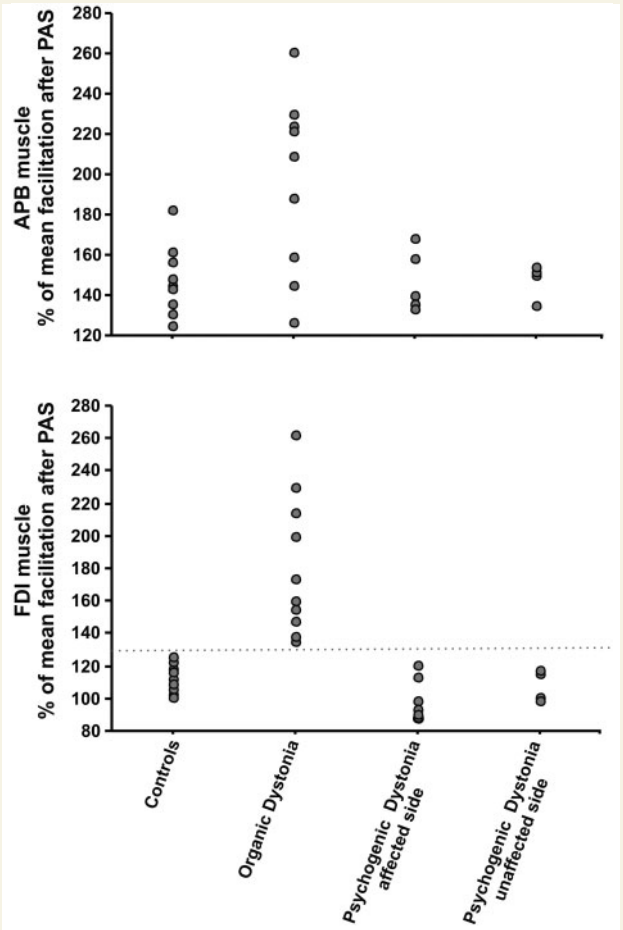

Figure 3 Scatter plot of the percentage MEP facilitation after PAS (average of T0 and T30) in APB and FDI in healthy subjects, psychogenic dystonia affected side, psychogenic dystonia unaffected side and organic dystonia.

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 organic dystonia.

Finally we compared the amount of PAS or SICI in the four patients with clinically definite and in the remaining six patients with probable psychogenic dystonia. There was no significant difference between the values ($P>0.7$; unpaired t-test). This can also be seen in the overlap of individual data points in Fig. 3.

Short intracortical inhibition

ANOVA showed a significant group effect on SICI [$F(2,14)=16.3$; $P=0.002$]. *Post hoc* testing showed that SICI was significantly reduced in organic dystonia [$t(1,7)=3.8$, $P=0.006$] and in psychogenic dystonia [$t(1,7)=13.6$, $P=0.00003$] compared with healthy subjects. There was no significant difference between organic and psychogenic dystonia [$t(1,7)=0.3$, $p=0.7$] (Fig. 4).

Long and short afferent inhibition

ANOVA did not reveal any statistical difference between SAI and LAI in organic patients, psychogenic patients and healthy subjects

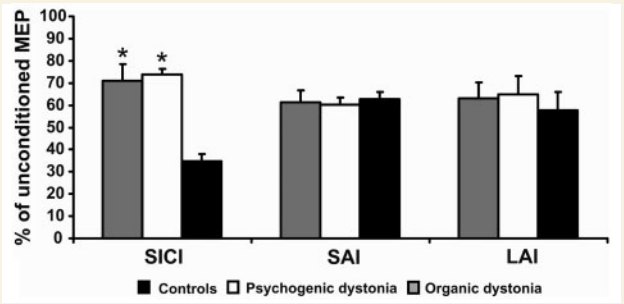

Figure 4 SICI, SAI and LAI in organic dystonia (grey column), psychogenic dystonia (white column) and control subjects (black columns). The data are plotted in percentage of unconditioned MEP. *Significant group effect on SICI ($P=0.002$).

(organic dystonia: SAI 61.4 ± 5.4%, LAI 62.9 ± 7.2%; psychogenic dystonia: SAI 60.2 ± 3.3%, LAI 64.8 ± 8.2%; healthy subjects: SAI 62.6 ± 3.9%, LAI 57.6 ± 8.3%; $F(2,18)=0.2$; $P=0.8$) (Fig. 4).

Discussion

The present data confirm previous reports that the excitability of SICI is reduced compared with healthy subjects in patients with either organic or psychogenic dystonia (Espay *et al*., 2006; Avanzino *et al*., 2008). We also confirmed that short and long latency afferent inhibition are normal in both patient groups (Avanzino *et al*., 2008). The novel results concern the paired associative measure of motor cortical plasticity (Stefan *et al*., 2000). As reported previously we found that patients with primary dystonia have an increased response to the median nerve PAS protocol, with enhanced facilitation of MEPs in both the median innervated APB muscle as well as the ulnar innervated FDI (Quartarone *et al*., 2003; Weise *et al*., 2006). In contrast, healthy subjects as well as patients with psychogenic dystonia had normal facilitation in APB and, as expected from the usual topographic organization of PAS, absent facilitation in FDI. It is unlikely that we underestimated the size of the PAS effect in the psychogenic dystonia group. Indeed, they could maintain muscle relaxation in hand muscles, and they attended to the stimuli as well as the patients with primary dystonia. We conclude that patients affected by psychogenic dystonia lack the increased plasticity typical of organic dystonia, even though they share abnormalities of SICI.

There are a number of factors that may have influenced the data from our psychogenic patients. First, only four of the patients were clinically definite cases, whereas the other six were classified as probable. Although it is impossible to make firm statistical conclusions on the basis of such small numbers, we found no evidence for any differences in the amount of PAS in these two subgroups, suggesting that it is unlikely that our data was contaminated by patients who were wrongly classified. In addition, if the clinically probable patients were to turn out to be healthy normal subjects then we would have expected them to have normal levels of SICI, rather than reduced SICI equal to that in our clinically definite patients [and like that in the clinically

definite patients reported by Espay *et al*. (2006)]. A second factor could have been that 4 out of the 10 psychogenic patients were studied on their unaffected side. However, this seems an unlikely explanation of our results since Avanzino and associates (2008) have previously found abnormal SICI in unaffected body parts of a similar group of patients. A final factor concerns the mechanism of increased PAS in organic dystonia. It has been suggested (Rosenkranz *et al*., 2007) that differences in the slope of the input–output (I/O) relationship of TMS intensity to MEP size could contribute to the measured increase in plasticity in patients with organic dystonia. Although we did not evaluate this explicitly in the present experiments, the intensity of stimulation required to produce a 1 mV MEP was the same percentage above threshold in all subject groups, which suggests that at least around the intensities used here, the I/O relationships were similar. As noted in the introduction, two main categories of electrophysiological abnormalities have been described in patients with organic dystonia. These are reduced excitability of a number of inhibitory systems in cortex, brainstem and spinal cord (Berardelli 2006; Defazio *et al*., 2007), and increased responsiveness to probes of synaptic plasticity (Quartarone *et al*., 2008*b*). Reduced inhibition seems unlikely to be a causal factor in organic dystonia since patients with psychogenic dystonia have very similar abnormalities. As suggested by Espay *et al*. (2006) and Avanzino *et al*. (2008), it seems more likely that reduced inhibition may predispose susceptible individuals to develop psychogenic dystonia. In contrast, we suspect that reduced SICI may interact with another factor (such as abnormal plasticity) to produce organic dystonia.

Our present data also confirmed that SAI and LAI were the same in organic and psychogenic dystonic patients, and controls (Espay *et al*., 2006; Avanzino *et al*., 2008). Previous studies suggested that there might be LAI abnormalities in patients with writer's cramp, but not in patients with cervical dystonia (CD) (Abbruzzese *et al*., 2001; Kessler *et al*., 2005). The fact that we studied mixed groups of arm, neck and leg dystonia may explain why we failed to see specific deficits in LAI.

The data confirmed that patients with organic dystonia have an increased response to the excitatory PAS protocol, coupled with a loss of topographical specificity such that increased MEPs are observed in both the median nerve innervated APB muscle as well as the ulnar innervated FDI. In contrast we found that the response to the PAS protocol in psychogenic patients was indistinguishable to healthy controls. We therefore suggest that (i) organic dystonia may require the combination of reduced inhibition (as demonstrated in the SICI data here as well as the additional spinal deficits in reciprocal inhibition noted by Espay *et al*., 2006) plus enhanced plasticity to manifest; whereas (ii) reduced inhibition alone might, when combined with other psychological features, predispose individuals to develop psychogenic dystonia.

In animal models, GABAergic inhibitory circuits appear to have an important modulating effect on the induction of long-term potentiation at cortical synapses. Indeed, Hess *et al*. (1996) found that it was only possible to induce long-term potentiation in horizontal connections after reducing GABA transmission with bicuculline. Individuals with psychogenic dystonia have reduced SICI and shorter contralateral silent periods compared to normal (Espay *et al*., 2006; Avanzino *et al*., 2008), both of which are thought to involve GABAergic connections ($GABA_A$ and $GABA_B$, respectively; see Reis *et al*., 2008 for review). Thus we might have expected that they would have a tendency towards increased cortical plasticity. However this was not the case. The implication is that not only is the abnormal plasticity seen in organic dystonia unlikely to be secondary to reduced inhibition, but that it may also be a primary causal factor in producing and/or maintaining symptoms.

In conclusion, the findings of the present study confirm that patients with organic dystonia have an increased response to a standard PAS protocol compared with healthy individuals. This may indicate that they have an increased tendency to strengthen sensory–motor associations, perhaps leading to the formation of unwanted muscle contractions and clinical dystonia. This abnormality is not seen in patients with psychogenic dystonia, even though the two conditions share abnormalities in measures of sensorimotor inhibition. We therefore suggest that an increased response to PAS is a hallmark of organic dystonia and that it may be an important contributor to the motor symptoms of the disease.

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