Abnormal somatotopic arrangement of sensorimotor interactions in dystonic patients

Stefano Tamburin,1,2 Paolo Manganotti,1 Carlo Alberto Marzi,3 Antonio Fiaschi1 and Giampietro Zanette2

Sections of 1Neurological Rehabilitation, 2Clinical Neurology and 3Human Physiology, Department of Neurological Sciences and Vision, University of Verona, Italy

Correspondence to: S. Tamburin, Dipartimento di Scienze Neurologiche e della Visione, Sezione di Neurologia, Ospedale Policlinico G.B. Rossi, piazzale Scuro, 37134 Verona, Italy E-mail: s_tamburin@yahoo.com

Summary
The aim of the study was to detect abnormalities of sensorimotor interactions and their topographic distribution in the hand muscles of dystonic patients. We investigated the effect of electrical stimulation of the second (D2) and fifth (D5) fingers on the amplitude of motor evoked potentials (MEPs) in response to transcranial magnetic stimulation (TMS) and transcranial electrical stimulation (TES) in the relaxed first dorsal interosseous (FDI) and abductor digiti minimi (ADM) muscles on both sides of eight patients with unilateral hand dystonia (HD) and in four patients with cervical dystonia (CD). Six Parkinson’s disease patients were used as the disease control group and 10 healthy subjects served as normal controls. For each muscle, the digital stimulation was applied to a contiguous finger (CF) and to a non-contiguous finger (NCF). The digital stimulation was set at three times the sensory threshold and preceded TMS or TES at intervals ranging from 10 to 100 ms. In normal subjects, a somatotopic inhibitory effect was detected, since the CF stimulation was significantly more powerful in determining the reduction of MEPs in response to TMS at intervals ranging from 20 to 50 ms. In dystonic patients, on the contrary, the somatopic effect was not present, because both CF and NCF stimulation evoked a consistent MEP inhibition and no significant difference was detected between the conditioning effect of CF and NCF stimulation. These abnormalities were present in the muscles of both the affected and unaffected hands of HD patients, as well as in CD patients. TES conditioning provoked MEP inhibition only at interstimulus intervals (ISIs) <40 ms. Significant MEP potentiation was found at ISIs of 20–40 ms to CF stimulation in Parkinson’s disease patients, while there was no effect after NCF stimulation. These data suggest that MEP suppression in response to digital stimulation is preserved in dystonia, but the somatotopically distributed input–output organization of the sensorimotor interactions is lost in dystonic patients’ hands. The comparison between TMS and TES experiments indicates that abnormalities may be present at both the spinal and the cortical level, at least in some patients. These findings suggest that a mechanism that normally operates in order to focus the effect of somatosensory afferences on the motor system may be impaired in dystonia. This abnormality seems specific to dystonia.

Keywords: dystonia; sensorimotor integration; motor evoked potential; digital nerve stimulation; transcranial magnetic stimulation

Abbreviations: ADM = abductor digiti minimi muscle; CD = cervical dystonia; CF = contiguous finger; D2 = second finger; D5 = fifth finger; FDI = first dorsal interosseous muscle; HD = hand dystonia; ISI = interstimulus interval; MEP = motor evoked potential; NCF = non-contiguous finger; RMT = resting motor threshold; S1 = primary somatosensory cortex; TES = transcranial electrical stimulation; TMS = transcranial magnetic stimulation

Introduction
Dystonia is a neurological disorder whose neurophysiological characteristics consist in an abnormal EMG pattern of cocontraction and an overflow of muscular activity into extraneous muscles during the performance of motor tasks (Sheehy and Marsden, 1982; Berardelli et al., 1998; Hallett, 1998a, b). Though many aspects of the pathophysiology of dystonia remain unclear, several abnormalities have been found in the motor system of dystonic patients (Berardelli
motor cortex (Deuschl et al., 1998; Hallett, 1998).

Since the preparation and execution of movements depends on the processing of sensory afferences (Rothwell, 1994), the study of sensorimotor integration may provide new information concerning the pathogenesis of dystonia. The sensorimotor interactions can be examined by means of transcranial magnetic stimulation (TMS) conditioned by various types of afferent stimuli. Facilitatory and inhibitory effects of peripheral nerve stimulation on motor evoked potentials (MEPs) to TMS have been reported in normal subjects depending upon proprioceptive (Mariorenzi et al., 1991; Deletis et al., 1992; Komori et al., 1992) and cutaneous (Maertens de Noordhout et al., 1992; Clouston et al., 1995; Manganotti et al., 1997) afferences, respectively.

Though sensorimotor interactions have been examined in movement disorders, such as corticobasal degeneration (Strafella et al., 1997), Parkinson’s disease (Delwaide and Olivier, 1990; Fuhr et al., 1992; Yokota et al., 1991; Clouston et al., 1996) and dystonia (Abbruzzese, 2001), as well as in epilepsy of motor areas (Manganotti and Zanette, 2000), these studies did not investigate the topographic distribution of the sensorimotor interactions. Using cutaneous reflexes (Caccia et al., 1973; Deuschl et al., 1995b) and TMS conditioned by electrical digital stimulation (Classen et al., 2000; Tamburin et al., 2001) or by puffs of air applied to different fingers (Terao et al., 1995) in normal subjects, it has been demonstrated that afferences are more effective in conditioning the excitability of motor neurones projecting to a muscle closer to the stimulated receptive field than to more distant muscles. This sensorimotor functional somatotopy is in keeping with anatomical (Jones, 1986) and electrophysiological (Wiesendanger, 1986) evidence demonstrating that the neural activity arising from afferent fibres projects to both the sensory and motor cortices and that in monkeys the cortical receptive and motor fields roughly coincide (Rosen and Asanuma, 1972; Lemon and Porter, 1976).

The mapping of thalamic (Lenz et al., 1999) and primary somatosensory cortex (S1) homunculus representation (Bara-Jimenez et al., 1998; Elbert et al., 1998) in dystonic patients, as well as data from animal models of dystonia (Byl et al., 1996), has documented the presence of a degraded spatial distribution of sensory representations. The study of the topography of sensorimotor interactions could help us understand the link between sensory map abnormalities and the overflow of activity in muscles not physiologically involved in the movement. Moreover, it is important to determine if any abnormality of sensorimotor integration is specific to dystonia or could be found in other movement disorders, such as Parkinson’s disease.

To this end, we report on 12 patients affected by dystonia, in whom the interactions between cutaneous afferences and motor output in the hand were studied. In these patients, we examined changes in MEP amplitude in hand muscles in response to stimulation of a contiguous (CF) and non-contiguous finger (NCF). The results from patients were compared with data from normal subjects. The same experimental protocol was applied to a disease control group composed of six Parkinson’s disease patients, in order to determine the specificity of our findings among different movement disorders.

### Material and methods

#### Subjects

Twelve dystonic patients (seven females, five males, mean age 36.7 ± 8.7 years) and six Parkinson’s disease patients (three males, three females, mean age 58 ± 9.2 years) were enrolled in the study. Ten healthy age-matched subjects (five males, five females, mean age 34.8 ± 8.7 years) volunteered as controls. All the subjects were right-handed according to the Edinburgh inventory (Oldfield, 1971). The study was approved by the ethics committee of the University Hospital, Verona and all subjects gave their written informed consent to participate. Parkinson’s disease patients discontinued drugs 1 day before testing. Eight out of the 12 dystonic patients were affected by hand dystonia (HD) and the remaining patients had cervical dystonia (CD) (Table 1).

#### TMS recording

In all the subjects we evaluated the effect of electrical stimulation of the second (D2) and fifth (D5) fingers on the size of the MEPs evoked in the relaxed ipsilateral first dorsal interosseous (FDI) and abductor digiti minimi (ADM) muscles by TMS. Each muscle was studied in a separate recording session, which lasted <30 min. For compliance reasons, we tested at least one muscle from each side in normal controls and HD patients, one muscle from one side in CD patients, and one muscle from the affected side in Parkinson’s disease patients. Some controls and patients were tested on both muscles from one or both sides. Assuming that some subjects would drop out after the first recording, we decided to alternate between muscles (ADM and FDI) to test first. This experimental setting allowed, for each muscle, a contiguous site of stimulation (D2 for FDI and D5 for ADM) and a non-contiguous site (D5 for FDI and D2 for ADM). The recording procedure consisted in delivering the electrical stimulation on D2 or D5 (conditioning stimulus) followed by the cortical magnetic stimulus (test stimulus). In this conditioning–test paradigm, the interstimulus intervals (ISIs) were measured from the beginning of the digital conditioning stimulus and set at 10, 20, 30, 40, 50, 60, 70, 80 and 100 ms. The electrical conditioning stimulus, consisting of a brief pulse (0.1 ms duration), was delivered at three times the sensory threshold determined for each subject. Pairs of ring electrodes were placed on the distal part of the finger with the cathode 3 cm proximal to the anode. The...
peak-to-peak amplitude of the conditioned MEPs (test response) was measured and expressed as a percentage of the unconditioned response (control response). For each interstimulus interval, eight conditioned and eight unconditioned MEPs were collected. Both visual feedback from an oscilloscope and audio feedback were used to ensure that the recorded muscle was relaxed. To avoid collecting startle and reflex responses, we excluded the first conditioned MEP for each trial from the analysis. All the subjects were trained before the experiment to be fully relaxed during peripheral and magnetic stimulation. Interstimulus intervals between the conditioning stimulus and the TMS were applied randomly.

All the subjects wore earplugs during the experiments and were seated in an armchair with the elbow semiflexed and the forearm pronated, fully relaxed and supported by the arm of the chair. Magnetic stimulation was adjusted to a stimulator output 20% above the resting motor threshold (RMT) of the target muscle (120% of the RMT). Magnetic shocks were delivered with a Novametrix Magstim 200 magnetic stimulator (Magstim Company, Whitland, UK). A mean figure-of-eight focal coil (diameter of each winding 70 mm, peak magnetic field 2.2 T), adjusted over the optimal scalp position, was used to evoke the maximal MEP amplitude in the ADM or FDI muscles. EMG signals were amplified using an OTE Biomedica Phasis electromyograph (Esaote, Florence, Italy) with a bandpass filter setting between 50 Hz and 2 kHz.

**TES**

In order to assess the contribution of the cortex to the sensorimotor integration, transcranial electrical stimulation (TES) was performed in two normal subjects and one HD patient using a Digitimer D180 stimulator (Digitimer, Welwyn Garden City, UK). The electrical stimuli had a time constant of 50 μs and were delivered through Ag–AgCl electrodes attached to the scalp, with the anode 6 cm lateral to the cathode, which was placed on the vertex. In each subject, the TES intensity was adjusted to produce unconditioned MEPs of amplitude similar to the MEPs in response to TMS. In order to minimize the subjects’ discomfort, only the ISIs of interest were studied.

**Statistical analysis**

ANOVA (analysis of variance) and paired t-tests with Bonferroni correction were used to assess the differences in digital stimulation sensory threshold, TMS threshold, MEP latency and unconditioned MEP amplitude between the patients’ affected and unaffected sides and controls. Wilcoxon’s signed rank test was used for the average data from each group to assess the significance of differences between unconditioned and conditioned MEP amplitudes and between MEP amplitudes conditioned by CF and NCF stimulation for each ISI. The possible effect of the side was tested in normal controls with two-way repeated measures ANOVA.

<table>
<thead>
<tr>
<th>Patient</th>
<th>Age (years)</th>
<th>Sex</th>
<th>Diagnosis</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>27</td>
<td>M</td>
<td>Right-sided professional hand dystonia (technician)</td>
</tr>
<tr>
<td>2</td>
<td>32</td>
<td>F</td>
<td>Right-sided dystonic writer’s cramp</td>
</tr>
<tr>
<td>3</td>
<td>34</td>
<td>F</td>
<td>Right-sided hand dystonia</td>
</tr>
<tr>
<td>4</td>
<td>35</td>
<td>M</td>
<td>Left-sided hand dystonia</td>
</tr>
<tr>
<td>5</td>
<td>38</td>
<td>F</td>
<td>Right-sided hand dystonia</td>
</tr>
<tr>
<td>6</td>
<td>40</td>
<td>F</td>
<td>Right-sided dystonic writer’s cramp</td>
</tr>
<tr>
<td>7</td>
<td>46</td>
<td>F</td>
<td>Left-sided hand dystonia</td>
</tr>
<tr>
<td>8</td>
<td>54</td>
<td>M</td>
<td>Right-sided dystonic writer’s cramp</td>
</tr>
<tr>
<td>9</td>
<td>23</td>
<td>M</td>
<td>Cervical dystonia</td>
</tr>
<tr>
<td>10</td>
<td>29</td>
<td>F</td>
<td>Cervical dystonia</td>
</tr>
<tr>
<td>11</td>
<td>37</td>
<td>F</td>
<td>Cervical dystonia</td>
</tr>
<tr>
<td>12</td>
<td>45</td>
<td>M</td>
<td>Cervical dystonia</td>
</tr>
</tbody>
</table>
Results
The motor threshold, the amplitude and the latency of the unconditioned MEPs did not differ significantly between patients and controls for either muscle (Table 2). The amplitude of unconditioned MEPs was slightly larger on FDI muscles than on ADM muscles in both patients and controls, but the difference did not reach statistical significance. No significant difference was detected in the sensory threshold for digital stimulation between patients and controls.

MEPs conditioned by digital electrical stimulation in controls
A total of 26 muscles were studied (seven right FDI, seven right ADM, six left FDI, six left ADM). In all the single muscles tested, MEP inhibition was found in response to the conditioning effect. This inhibition showed a somatotopic distribution.

In the average data, the MEP inhibition to CF conditioning was significant at ISIs ranging from 20 to 50 ms (conditioned MEP amplitude was between 34 and 57% of unconditioned MEP amplitude in right ADM; 32–60% of unconditioned MEP in left ADM; 37–55% of unconditioned MEP in right FDI; 33–58% of unconditioned MEP in left FDI; \( P < 0.05 \)) (Fig. 1). Stimulation of the NCF evoked no effect in the majority of muscles (Fig. 2C), while mild inhibition at ISIs of 40 or 50 ms was found in the remaining muscles (Fig. 2D). No difference was found between right and left sides within either muscle or group.

Table 2 RMT, MEP latency and unconditioned MEP amplitude in controls (right side only) and patients (mean ± SD)

<table>
<thead>
<tr>
<th>Muscles</th>
<th>RMT (% of maximal stimulator output)</th>
<th>MEP latency (ms)</th>
<th>MEP amplitude (µV)</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>ADM muscle</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Normal subjects (7)</td>
<td>44.5 ± 9.2</td>
<td>22.3 ± 1.0</td>
<td>557 ± 187</td>
</tr>
<tr>
<td>Hand dystonia patients</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Affected sides (7)</td>
<td>45.2 ± 8.6</td>
<td>22.5 ± 1.4</td>
<td>602 ± 225</td>
</tr>
<tr>
<td>Unaffected sides (6)</td>
<td></td>
<td>22.3 ± 1.3</td>
<td>599 ± 276</td>
</tr>
<tr>
<td>Cervical dystonia patients (4)</td>
<td></td>
<td>22.5 ± 1.4</td>
<td>605 ± 206</td>
</tr>
<tr>
<td>Parkinson’s disease patients (5)</td>
<td></td>
<td>22.3 ± 1.1</td>
<td>639 ± 292</td>
</tr>
<tr>
<td><strong>FDI muscle</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Normal subjects (7)</td>
<td>45.3 ± 9.8</td>
<td>22.1 ± 1.4</td>
<td>620 ± 135</td>
</tr>
<tr>
<td>Hand dystonia patients</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Affected sides (7)</td>
<td>44.9 ± 10.5</td>
<td>22.3 ± 1.0</td>
<td>596 ± 198</td>
</tr>
<tr>
<td>Unaffected sides (8)</td>
<td></td>
<td>22.1 ± 1.2</td>
<td>623 ± 243</td>
</tr>
<tr>
<td>Cervical dystonia patients (4)</td>
<td></td>
<td>21.9 ± 1.5</td>
<td>633 ± 278</td>
</tr>
<tr>
<td>Parkinson’s disease patients (5)</td>
<td></td>
<td>22.5 ± 0.9</td>
<td>651 ± 315</td>
</tr>
</tbody>
</table>
and left muscles. Figure 2A and B shows an example of the traces from a normal subject, illustrating the unconditioned MEPs and the MEPs conditioned by digital stimulation of the CF and NCF at various ISIs.

**MEPs conditioned by digital electrical stimulation in patients**

Fourteen muscles from the dystonic sides (seven ADM and seven FDI muscles) and 14 muscles from the unaffected sides (six ADM and eight FDI muscles) of the HD patients were studied.

In the average data for the HD patients’ affected sides, the conditioning stimulation applied to the CF produced a significant inhibitory effect at ISIs of 30–50 ms (conditioned MEP amplitude was 48–70% of unconditioned MEP amplitude in ADM and 51–66% of unconditioned MEP amplitude in FDI), and the inhibition in response to NCF stimulation was significant at ISIs of 30–70 ms (conditioned MEP amplitude was 45–67% of unconditioned MEP amplitude in ADM and 51–69% of unconditioned MEP amplitude in FDI) (Fig. 3A). In the average data for the muscles on the HD patients’ unaffected sides, stimulation of the CF produced an inhibitory effect at ISIs of 30–50 ms (conditioned MEP amplitude was 52–60% of unconditioned MEP amplitude in ADM and 40–62% of unconditioned MEP amplitude in FDI), similar to stimulation of the NCF (ISIs 20–50; 38–68% of unconditioned MEP amplitude in ADM and 42–70% of unconditioned MEP amplitude in FDI) (Fig. 3B). No significant

---

**Fig. 2** MEPs elicited in the right ADM by digital conditioning stimulation of the CF (D5, A) and NCF (D2, B) in a normal control at various ISIs. Note the presence of a decrease in MEP amplitude only in response to CF stimulation. Time base = 20 ms per division. (C and D) Time course of the effects of electrical stimulation of the CF and NCF in two controls. In both controls, CF stimulation was more effective than NCF stimulation in reducing MEP amplitude. Vertical error bars show 1 SE.
MEP amplitude was compared with the unconditioned MEP stimulation. *Significant ISIs (P < 0.05) when the conditioned MEP amplitude was compared with the unconditioned response. Vertical error bars show mean amplitude of the conditioned response expressed as a percentage of the unconditioned response. Filled columns, CF stimulation; open columns, NCF stimulation. *Significant ISIs (P < 0.05) when the conditioned MEP amplitude was compared with the unconditioned MEP amplitude.

ANOVAs showed significant effect of ISIs [ADM, F(8,384) = 13.23, P < 0.001; FDI, F(8,416) = 17.49, P < 0.001] and group [ADM, F(4,48) = 15.4; P < 0.001; FDI, F(4,52) = 8.81; P < 0.001]; the effect of finger was significant for ADM [F(1,48) = 4.48, P = 0.039], but not for FDI [F(1,52) = 2.32, P = 0.066]. There was significant interaction between finger and group [ADM, F(4,48) = 7.13, P < 0.001; FDI, F(4,52) = 8.44, P = 0.005]. Post hoc tests showed significant difference between Parkinson’s disease patients and the affected sides of HD patients (ADM, P < 0.001; FDI, P < 0.001), Parkinson’s disease patients and the unaffected sides of HD patients (ADM, P < 0.001; FDI, P < 0.001) and Parkinson’s disease and CD patients (ADM, P < 0.001; FDI, P = 0.015). The remaining post hoc comparisons were not significant, in particular the difference between CD patients and controls, and the comparisons of affected and unaffected sides of HD patients versus controls were not significant. To understand which factors accounted for the significant interaction between finger and group, we performed post hoc comparisons between CF and NCF. Significant differences were found between Parkinson’s disease and all the other groups for CF in both muscles (ADM, P ranged between 0.001 and 0.007; FDI, P ranged between 0.002 and 0.01). For NCF stimulation, significant differences were detected when we compared controls and the affected sides of HD patients (ADM, P = 0.006; FDI, P = 0.01), the unaffected sides of HD patients (ADM, P = 0.01; FDI, P = 0.02) and CD patients (ADM, P = 0.02; FDI, P = 0.01). The remaining post hoc comparisons were not significant; in particular, no significant difference was found between the affected sides of HD patients, the unaffected sides of HD patients and CD patients for either finger.

Figure 3 Time course of the effects of electrical stimulation of the CF and NCF on MEPs elicited in relaxed ADM muscle by focal coil TMS in HD patients. Time courses in the muscles of the affected (A, n = 7) and unaffected (B, n = 6) sides are represented separately. The x axis shows the interval between digital stimulation and cortical stimulation (ms); the y axis shows the mean amplitude of the conditioned response expressed as a percentage of the unconditioned response. Vertical error bars show 1 SE. Filled columns, CF stimulation; open columns, NCF stimulation. *Significant ISIs (P < 0.05) when the conditioned MEP amplitude was compared with the unconditioned MEP amplitude.

Figure 4A and B shows an example of the traces from an HD patient. In all the muscles the digital stimulation evoked MEP inhibition, while no MEP potentiation was found. The stimulation of CF caused inhibition similar to that caused by NCF stimulation in the majority of muscles (11 muscles on the dystonic side and 11 muscles on the unaffected side) (Fig. 4C). In the remaining muscles, stimulation of the NCF resulted in a more pronounced effect than stimulation of the CF (Fig. 4D).

Eight muscles (four ADM and four FDI muscles) were tested in CD patients. In the average data from CD patients, the conditioning stimulation applied to the CF produced a significant inhibitory effect at ISIs of 30–50 ms (conditioned MEP was 50–62% of unconditioned MEP amplitude in ADM and 45–70% of unconditioned MEP amplitude in FDI), and the inhibition in response to NCF stimulation was significant at ISIs of 30–60 ms (conditioned MEP was 52–70% of unconditioned MEP amplitude in ADM and 43–64% of unconditioned MEP amplitude in FDI). No significant difference was found between the amplitude of MEPs conditioned by CF and NCF stimulation at any ISI.

Ten muscles (five ADM and five FDI muscles) from the affected sides of the Parkinson’s disease patients were studied. For all the muscles, stimulation of the CF evoked MEP potentiation, while no significant effect was found for NCF stimulation. In the average data, the conditioning stimulation applied to the CF produced a significant facilitatory effect (conditioned MEP was 133–187% of unconditioned MEP amplitude in ADM at ISIs of 20–40 ms and 142–171% of unconditioned MEP amplitude in FDI at ISIs of 20–50 ms; P < 0.05), while no significant effect was found in response to NCF stimulation at any ISI (conditioned MEP was 94–107% of unconditioned MEP amplitude in ADM and 90–113% in FDI; Fig. 5). The average difference between the amplitude of MEPs conditioned by CF and NCF stimulation was significant at ISIs of 20–40 ms (difference ranged from 46 to 81%; P < 0.05).

Significant differences were found between Parkinson’s disease patients and the affected sides of HD patients (ADM, P < 0.001; FDI, P < 0.001) and group [ADM, F(4,48) = 15.4; P < 0.001; FDI, F(4,52) = 8.81; P < 0.001]; the effect of finger was significant for ADM [F(1,48) = 4.48, P = 0.039], but not for FDI [F(1,52) = 2.32, P = 0.066]. There was significant interaction between finger and group [ADM, F(4,48) = 7.13, P < 0.001; FDI, F(4,52) = 8.44, P = 0.005]. Post hoc tests showed significant difference between Parkinson’s disease patients and the affected sides of HD patients (ADM, P < 0.001; FDI, P < 0.001), Parkinson’s disease patients and the unaffected sides of HD patients (ADM, P < 0.001; FDI, P < 0.001) and Parkinson’s disease and CD patients (ADM, P < 0.001; FDI, P = 0.015). The remaining post hoc comparisons were not significant, in particular the difference between CD patients and controls, and the comparisons of affected and unaffected sides of HD patients versus controls were not significant. To understand which factors accounted for the significant interaction between finger and group, we performed post hoc comparisons between CF and NCF. Significant differences were found between Parkinson’s disease and all the other groups for CF in both muscles (ADM, P ranged between 0.001 and 0.007; FDI, P ranged between 0.002 and 0.01). For NCF stimulation, significant differences were detected when we compared controls and the affected sides of HD patients (ADM, P = 0.006; FDI, P = 0.01), the unaffected sides of HD patients (ADM, P = 0.01; FDI, P = 0.02) and CD patients (ADM, P = 0.02; FDI, P = 0.01). The remaining post hoc comparisons were not significant; in particular, no significant difference was found between the affected sides of HD patients, the unaffected sides of HD patients and CD patients for either finger.
In two normal controls and in the patient, the MEP latency in response to TES was significantly shorter (21.1 ms) than the MEP latency in response to TMS (22.4 ms; paired t test), whereas the amplitude of unconditioned MEPs in response to TMS and TES did not differ significantly.

The effect of conditioning stimulation varied significantly among types of brain stimulation and ISIs. In the first normal subject, digital stimulation of the CF resulted in MEP reduction only at the ISI of 30 ms (conditioned MEP amplitude = 77% of unconditioned MEP amplitude) (Fig. 6). In this subject, a significant difference between the effect of CF stimulation on TMS and TES was detected at the ISI of 40 ms. In the second control, CF stimulation evoked a significant inhibition at 20–30 ms (conditioned MEP amplitude was 53–62% of unconditioned MEP amplitude). When this effect was compared with the inhibition of MEPs in response to TMS, significant differences were found at ISIs of 30 and 40 ms. No significant changes in relation to the baseline were found in either of the controls when the NCF was stimulated (conditioned MEP amplitude was 103–136% of unconditioned MEP amplitude in the first control and 95–118% of unconditioned MEP amplitude in the second control).

In the dystonic patient, MEP suppression was found only at ISIs of 30 ms in response to CF stimulation (56% of unconditioned MEP amplitude) and to NCF stimulation (64% of unconditioned MEP amplitude) (Fig. 6). A significant difference was detected at ISIs of 40 and 50 ms between TES and TMS in response to stimulation of the CF and the NCF.

**TES**

In two normal controls and in the patient, the MEP latency in response to TES was significantly shorter (21.1 ms) than the MEP latency in response to TMS (22.4 ms; paired t test), whereas the amplitude of unconditioned MEPs in response to TMS and TES did not differ significantly.

The effect of conditioning stimulation varied significantly among types of brain stimulation and ISIs. In the first normal subject, digital stimulation of the CF resulted in MEP reduction only at the ISI of 30 ms (conditioned MEP amplitude = 77% of unconditioned MEP amplitude) (Fig. 6). In this subject, a significant difference between the effect of CF stimulation on TMS and TES was detected at the ISI of 40 ms. In the second control, CF stimulation evoked a significant inhibition at 20–30 ms (conditioned MEP amplitude was 53–62% of unconditioned MEP amplitude). When this effect was compared with the inhibition of MEPs in response to TMS, significant differences were found at ISIs of 30 and 40 ms. No significant changes in relation to the baseline were found in either of the controls when the NCF was stimulated (conditioned MEP amplitude was 103–136% of unconditioned MEP amplitude in the first control and 95–118% of unconditioned MEP amplitude in the second control).

In the dystonic patient, MEP suppression was found only at ISIs of 30 ms in response to CF stimulation (56% of unconditioned MEP amplitude) and to NCF stimulation (64% of unconditioned MEP amplitude) (Fig. 6). A significant difference was detected at ISIs of 40 and 50 ms between TES and TMS in response to stimulation of the CF and the NCF.
Discussion

Our data demonstrate that the physiological somatotopic arrangement of cutaneousmotor inhibitory interactions occurring within 100 ms of digital electrical stimulation is lost in the relaxed hand muscles of dystonic patients. This abnormality is not limited to the affected hand but can also be found, to a similar extent, on the unaffected side. The altered topography of sensorimotor integration seems specific to dystonic patients, because the digital electrical stimulation had a completely different effect in Parkinson’s disease.

Sensorimotor integration in dystonic patients

The present experiment confirms that cutaneous afferences have mainly early inhibitory effects on TMS (Maertens de Noordhout et al., 1992; Clouston et al., 1995; Manganotti et al., 1997). More interestingly, in normal subjects stimulation of the CF (D2 for FDI and D5 for ADM) has a more powerful and consistent effect in decreasing MEP amplitude than stimulation of the NCF (D5 for FDI and D2 for ADM).
This topographic MEP inhibition was found in both the FDI and ADM muscles and no differences were detected between the right and left sides. Our results are in keeping with previous data documenting the somatotopy of MEP inhibition to cutaneous afferences (Classen et al., 2000; Tamburin et al., 2001).

We found an abnormal topography of these cutaneomotor inhibitory interactions in dystonic patients, because similar amounts of MEP inhibition were present in response to CF and NCF stimulation. It is noteworthy, in some cases and for some ISIs, that there was greater inhibition to stimulation of the NCF than of the CF. These anomalies were detected to a similar extent in the ADM and FDI muscles. Abbuzzese and colleagues studied the conditioning effect of peripheral stimulation on TMS in dystonic patients but did not examine the topography of the effect (Abbuzzese et al., 2001). Though they reported abnormal MEP facilitation at very long ISIs (200–1000 ms) in patients, MEPSs were equally inhibited in hand muscles in both controls and patients at an ISI of 50 ms, in agreement with our data. Both short- and long-latency sensorimotor connections seem to be impaired in dystonic patients, but in a different manner. While long-latency connections are excitatory rather than inhibitory, short-latency connections are still inhibitory but lose their topographic distribution in dystonia.

We studied a group of unilateral Parkinson’s disease patients to determine if the abnormal sensorimotor somatotopy was present in other movement disorders. Digital afferences caused MEP potentiation only to CF stimulation on Parkinson’s disease patients. Our data are in accordance with previous work testing the effect of afferences on the motor excitability of parkinsonian patients (Delwaide and Olivier, 1990; Fuhr et al., 1992; Clouston et al., 1996). The effect of digital stimulation seems completely different in the two movement disorders. In dystonia there was loss of somatotopy, with preservation of the inhibitory effect. In Parkinson’s disease we found an excitatory effect, with preservation of somatotopy. The abnormal topography of sensorimotor integration seems to be specific to dystonia.

The pathophysiology of idiopathic dystonia is still not completely understood, but recently the attention of researchers has focused on the role of sensory alterations in the pathogenesis of this disease (Hallett, 1995). An animal model of dystonia has been produced in monkeys, assigning them an overload of repetitive movements. In these overtrained monkeys, Byl and colleagues found many distortions of the spatial distribution of the representational zones in area 3b of S1 (Byl et al., 1996). Similarly degraded organization of S1 has been found in dystonic patients by means of magnetic source imaging (Elbert et al., 1998) and cortical somatosensory evoked potential mapping (Bara-Jimenez et al., 1998). Though these studies revealed a new feature of this disease, they did not specify whether the abnormal sensory representation is a major determinant in the pathogenesis of dystonic symptoms. In fact, sensory abnormalities might be simply an epiphenomenon of a common physiopathological mechanism, underlying both abnormal processing of afferences and abnormal control of motor commands, which are alterations that may develop independently. In this connection, the study of sensorimotor integration can contribute new and stronger evidence to our understanding of the role of sensory abnormalities in the pathophysiology of this disease.

The abnormalities of sensorimotor integration that we have found in dystonic patients strongly resemble the topographic alterations of digital representation described in S1 in this disease. Elbert and colleagues reported a reduced distance between the representational zones of the hand digits in dystonic musicians (Elbert et al., 1998). Bara-Jimenez and colleagues not only confirmed this tendency towards fusion of finger representations but also documented the inversion of the mediolateral topography of the fingers in S1 (Bara-Jimenez et al., 1998). It can be hypothesized that the somatotopic degradation of S1 in dystonia may be reflected in sensorimotor interactions, which, as we have demonstrated, are arranged in a similar abnormal fashion. It may be postulated that the degraded S1 representation, by determining abnormal sensorimotor connections, might result in the activation of unwanted muscles, causing the electromyographic finding of cocontraction. From this point of view, our study represents the first experimental report suggesting a functional link between abnormal S1 representation and pathological motor output in dystonic patients.

The digital stimulation that was used in our experiment is thought to affect exclusively cutaneous afferents (Maertens de Noordhout et al., 1992; Clouston et al., 1995; Manganotti et al., 1997). This type of conditioning was preferred to the stimulation of mixed nerves at the wrist, which is less selective since it activates different types of fibres from a larger number of receptive fields. Moreover, the digital stimulation was the same as that used by Bara-Jimenez and colleagues, who reported abnormalities of finger topography in the S1 of dystonic patients (Bara-Jimenez et al., 1998). Grünwald and colleagues reported abnormal processing of muscle spindle afferences in dystonic patients and suggested that the proprioceptive afferences are important in the pathogenesis of dystonia (Grünwald et al., 1997). From our data it is possible to generalize their conclusion, since the inappropriate sensorimotor elaboration would also seem to involve the cutaneous afferences.

It is important to stress that spatially impaired input–output organization is present in the relaxed muscles. This is in agreement with a report of abnormal premovement gating of somatosensory evoked potentials in dystonia (Murase et al., 2000), which is explained by the authors in terms of failure of a central motor programme linking sensory input with movement.

Interestingly, the abnormalities of sensorimotor topography were found on both the affected and the unaffected sides of HD patients, as well as in CD patients, documenting the presence of widespread hand muscle abnormalities, which may constitute a pathophysiological predisposition to the
development of dystonic symptoms. Our report is not isolated, as many researchers have found bilateral anomalies in sensorimotor cortex activation (Tempe and Perlmuter, 1990, 1993), premovement potentials (Deuschl et al., 1995a; Hamano et al., 1999; Toro et al., 2000), intracortical motor excitability (Ridding et al., 1995), motor cortical maps (Byrnes et al., 1998) and S1 hand maps (Elbert et al., 1998) in dystonic patients. Moreover, it is a common experience that focal dystonia can become segmental or generalized and patients with writer’s cramp can develop the same symptoms in the opposite limb when switching the hand used for writing (Sheehy and Marsden, 1982). These data are consistent with the hypothesis that the anomalous sensorimotor connections could represent a predisposition to dystonia, which may become clinically evident when additional factors are involved (i.e. repetitive movements). In other words, dystonic patients may have a lower threshold for the development of dystonic symptoms, suggesting the presence of gene–environment interactions in the pathogenesis of dystonia (Fletcher et al., 1991; Jankovic, 1994).

Anatomical sites of abnormal sensorimotor integration

The amplitude of the conditioned MEPs depends on cortical and spinal mechanisms (Manganotti et al., 1997). For this reason, the conditioning effects on TMS and TES were compared in order to define the anatomical levels of the sensorimotor integration. It is believed that TES activates the axonal hillock of the pyramidal cells, by eliciting D waves, while TMS activates the motor cortex output transsynaptically, by means of I waves. For these reasons, it is thought that TMS depends on both the cortical and the spinal circuitry, while TES reflects mainly modulation at the spinal level (Rothwell et al., 1991; Maertens de Noordhout et al., 1992; Rossini et al., 1994; Clouston et al., 1995; Manganotti et al., 1997; Di Lazzaro et al., 1998). In our subjects, the latency of MEPs in response to TES was shorter (1.2–1.5 ms) than the latency of MEPs in response to TMS, thus confirming that TES, at the stimulus intensities used, elicited predominantly D waves (Rothwell et al., 1991).

In both the normal subjects and the patients, the effect on TMS was present at ISIs up to 40–50 ms, while the effect on TES was detected only up to 30 ms. The different time course of MEP conditioning may be consistent with the presence of two levels at which the effects are generated, namely a spinal level for ISIs of 20–30 ms and a cortical level for ISIs >30 ms. This hypothesis is in agreement with previous studies evaluating the effect of digital conditioning on MEPs in normal subjects (Maertens de Noordhout et al., 1992; Clouston et al., 1995; Manganotti et al., 1997). Moreover, it has been calculated that the minimum afferent conduction time from the digits to the cortex is ~23 ms (Clouston et al., 1995) and the intracortical relay time has been estimated as 3.5–8 ms (Deuschl et al., 1989). This means that cortical inhibition should not begin before 26.5–31 ms. In any event, this point is controversial, since a recent report suggests a cortical contribution to the inhibitory effect at short ISIs (i.e. 22 ms) in slightly contracted hand muscles (Tokimura et al., 2000). The observation that a significant difference between TMS and TES inhibition was detected in one of the normal subjects at 30 ms can be explained by a cortical contribution to the effect occurring at ISIs between 20 and 30 ms. However, only three subjects were studied with TES and a larger number of patients may be necessary to confirm our hypothesis.

Though the precise site of the lesion in primary dystonia is not known, the observation of patients with secondary forms of dystonia suggests the basal ganglia as a possible candidate (Berardelli et al., 1998). The globus pallidus projects bilaterally to the ipsilateral and contralateral thalamus (Hazzati and Parent, 1991) and the basal ganglia project to nuclei in the brainstem and the spinal cord via the pedunculopontine nucleus (Hallett, 1998b). This central position of the basal ganglia in the motor system circuitry may explain the similar impairment of the somatotopy of sensorimotor connections on both sides, as well as the presence of abnormalities at both the cortical and spinal level, documented by our study and previous reports (Nakashima et al., 1989; Panizza et al., 1989; Ridding et al., 1995; Ikoma et al., 1996; Chen et al., 1997).

It has been suggested that the direct and indirect pathways of the basal ganglia may be involved in focusing the motor command by gating sensory inputs for the guidance of movements (Lidsky et al., 1985; Hallett, 1998a, b; Passingham et al., 1998). If the physiological ability to associate the input with the correct motor response is lost, there might be indiscriminate activation of many muscles, causing cocontraction. This tendency towards an input–output mismatch could be increased in the presence of repetitive motor tasks, which may trigger the onset of symptoms (Jankovic, 1994).

In conclusion, the present study has shown that the topographic input–output organization of cutaneousmotor interactions is lost in dystonic patients. This abnormality is present in the resting muscles and to a similar extent on the affected and unaffected sides, suggesting that it may constitute a presymptomatic element in the complex pathophysiology of this disease. These findings may be interpreted to indicate that a mechanism that normally limits the influence of a heterotopic somatosensory afferent signal on motor excitability could be defective in dystonia. Among movement disorders, the alteration seems specific to dystonia, because it was not found in Parkinson’s disease patients.

Acknowledgement

The authors wish to thank Professor John Rothwell for his helpful comments.
References


Received October 31, 2001. Revised February 18, 2002.
Second revision June 18, 2002. Accepted July 2, 2002