The corticomotor representation of upper limb muscles in writer’s cramp and changes following botulinum toxin injection

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Summary
Transcranial magnetic stimulation was used to investigate the properties of the corticomotor pathway and to map the primary motor cortex projection to hand and forearm muscles during a sustained isometric contraction in a group of subjects with writer’s cramp of varying duration. Corticomotor threshold, motor evoked potential amplitude and latency, and silent-period duration were normal on both sides in all subjects. The maps of the corticomotor projection were displaced relative to normal in all subjects, and in some cases were distorted in shape, with extensions of the lateral borders and the emergence of almost discrete secondary motor areas. The degree of map distortion and displacement was greatest in subjects with long-standing writer’s cramp (>5 years), and was bilateral in some cases. Injection of botulinum toxin into affected muscles demonstrated that the alterations in map topography were not fixed, and could be temporarily reversed during the period when the clinical effects of the injection were greatest, with the maps returning to their original positions as the effects of the injection wore off. It is concluded from this study that there are slowly evolving reorganizational changes in the primary motor cortex in writer’s cramp, and that these changes may be secondary to altered afferent inputs from both clinically affected and unaffected muscles.

Keywords: writer’s cramp; botulinum toxin; transcranial magnetic stimulation; mapping

Abbreviations: APB = abductor pollicis brevis; FDI = first dorsal interrosseous; MEP = motor evoked potential; TMS = transcranial magnetic stimulation

Introduction
Writer’s cramp manifests as an unwanted contraction of muscles of the upper limb with writing (Sheehy and Marsden, 1982). It forms part of a group of task-specific occupational cramps which also includes musician’s cramp (Newmark and Hochberg, 1987). While writer’s cramp is believed to be a form of dystonia, it is unlike other forms of dystonia in that, in its simple form, inappropriate muscle activation occurs during a particular (highly skilled) co-ordinated motor act, and does not occur during other activities which may require a similar level of precision.

The pathophysiology of idiopathic dystonia is uncertain. However, it is generally believed to arise from alterations in basal ganglia regulatory loops involving premotor cortical areas (Burton et al., 1984; Marsden et al., 1985; Rothwell and Obeso, 1987; Hallett, 1997). In the case of writer’s cramp, the task-specific nature of the disorder suggests that there may also be alterations in the function of executive motor centres, a concept which is supported by the results of a number of physiological studies. The surface negative component of the movement-related cortical potential prior to self-paced finger movement has a slower rise in patients with writer’s cramp than in control subjects (Deuschl et al., 1995). PET studies have demonstrated impaired activation of primary motor cortex in subjects with writer’s cramp during writing (Ceballos-Baumann et al., 1997). Transcranial magnetic stimulation (TMS) studies in writer’s cramp have shown evidence of abnormal cortical excitability (Ikoma et al., 1996) and impaired inhibition in the motor cortex as measured with double-pulse TMS (Ridding et al., 1995), a reduction in the duration of the cortical silent period after single-pulse TMS (Filipovic et al., 1997), changes in the amplitude of the motor evoked potential (MEP) (Mavroudakis
et al., 1995) and alterations in the topography of the corticomotor projection (Thompson et al., 1996).

With the exception of the PET activation studies, the abnormalities demonstrated in these studies were present during motor tasks that did not evoke the clinical symptoms of writer’s cramp, such as simple finger movement or sustained contractions, and even while at rest. Impairments in sensorimotor interaction has also been described in writer’s cramp during non-specific motor tasks, including impaired reciprocal inhibition of wrist flexors at rest (Nakashima et al., 1989), inappropriate modulation of electromyographic activity during sustained contraction (Valls-Solé and Hallett, 1995), impaired sensorimotor activity during a grasping task (Odergren et al., 1996) and abnormal activation of primary sensorimotor cortex during peripheral vibration (Tempel and Perlmutter, 1993). The importance of sensory integration in writer’s cramp is further supported by the observation that sensory tricks can relieve symptoms in some cases (Sheehy and Marsden, 1982; Marsden and Sheehy, 1990), that afferent block by local injection of anaesthetic into affected muscles can reduce writer’s cramp (Kaji et al., 1995a, b), and that injection of botulinum toxin into affected muscles can also relieve symptoms, either by direct weakening of the muscle (inhibiting acetylcholine release from pre-synaptic terminals; see Jankovic and Brin, 1991) or by altering afferent feedback from the muscle (Cohen et al., 1989; Karp et al., 1994).

Taken together, these studies point to an impairment in the function of executive motor centres and in some aspects of sensorimotor interaction in subjects with writer’s cramp. In the present study we have used magnetic stimulation to investigate the properties of the corticomotor pathway and the topography of the primary motor cortex projection to the hand and forearm muscles during a controlled isometric contraction in a group of subjects with writer’s cramp of varying durations. The objectives of the study were to determine, first, whether there are any fundamental changes in the organization of the cortical motor projection to the muscles involved and secondly, whether any changes in cortical organization persist following the therapeutic injection of botulinum toxin into the affected muscles.

**Methods**

**Subjects**

Studies were performed on eight subjects with simple writer’s cramp and seven with dystonic writer’s cramp (aged 26–65 years, six female and nine male) (Table 1). The duration of the disorder ranged from 1 to 35 years. Five of the 15 subjects were studied 1 week before and again 4–6 weeks after their first injection of botulinum toxin. Eighteen normal right-handed subjects (aged 21–56 years) served as control subjects for studies of the first dorsal interosseous (FDI) muscle. Subjects gave written informed consent, and the study had the approval of the human rights committee of the University of Western Australia.

**MEP recording**

MEPs were recorded from electrodes taped over the motor point and the metacarpophalangeal joint of the APB, FDI, flexor carpi ulnaris, extensor carpi radialis longus, flexor pollicis longus, and/or biceps muscles on both sides. EMG signals were amplified (×1000) and band-pass filtered from 20 Hz to 2 kHz, before being digitized at 2 kHz for 500 ms following each stimulus. Cortical stimulation was carried out during a monitored low level contraction of the target muscle. This simple contraction did not result in dystonic posturing in any of the writer’s cramp subjects. During recordings, the r.m.s (root mean square) EMG level was displayed on a computer screen, and cortical stimuli were only delivered when this level was maintained by the subject at 10 ± 3% of maximum.

**Corticomotor thresholds**

TMS was delivered using a MAGSTIM 200 stimulator (Whitland, Dyfed, UK) with a 5-cm diameter figure-of-eight coil which was held tangential to the skull, and aligned in the para-sagittal plane with the handle posterior. The junction of the coil was held over the site to be stimulated. A snugly fitting cap, with pre-marked stimulus sites was placed over the subject’s head. The cap was positioned using the nasion–inion line and the inter-aural line (the line passing through the vertex and joining the left and right pre-auricular creases). Stimulus sites were marked using a latitude–longitude coordinate system in which latitude was defined as the distance over the scalp from the vertex, and longitude as the distance along a line of constant latitude from the inter-aural line. Latitude was marked in 1-cm steps, and longitude in 2-cm steps. The longitude was at half the spatial resolution of the latitude, as the shape of the coil, which induces current flow in the anteroposterior axis, means that a shift of the coil in this direction has a lesser effect on the focus of the induced current flow, and there is therefore little accuracy to be gained from increasing the spatial resolution in this direction.

**Corticomotor thresholds**

To determine cortical motor threshold, sites near the estimated centre of the corticomotor projection to the target muscle were explored at a stimulus intensity sufficient to evoke an MEP of ~1 mV in amplitude, to determine the site at which the largest MEPs could be obtained. At this site, the stimulus intensity was then increased in 5% steps from a level below threshold, until an MEP and associated silent period could be measured with at least two of four stimuli. This level was used as threshold. The threshold was determined separately on each side. During mapping studies, stimulus intensity was set at 20% of stimulator output above threshold.
Table 1  Clinical details of 15 subjects with writer’s cramp

<table>
<thead>
<tr>
<th>Case</th>
<th>Age (years)</th>
<th>Sex</th>
<th>Hand</th>
<th>Duration (years)</th>
<th>Clinical characteristics of writer’s cramp</th>
<th>Target muscle (*mouse units)</th>
<th>Muscle studied</th>
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<tr>
<td>1</td>
<td>41</td>
<td>F</td>
<td>R</td>
<td>1</td>
<td>Simple, difficulty holding pen with thumb and II finger –</td>
<td>–</td>
<td>APB/FDI</td>
</tr>
<tr>
<td>2</td>
<td>47</td>
<td>M</td>
<td>R</td>
<td>1</td>
<td>Dystonic, tremor, contraction of forearm muscles –</td>
<td>–</td>
<td>APB</td>
</tr>
<tr>
<td>3</td>
<td>43</td>
<td>M</td>
<td>R</td>
<td>1</td>
<td>Simple, II finger extension, forearm pronation, tremor –</td>
<td>–</td>
<td>APB</td>
</tr>
<tr>
<td>4</td>
<td>46</td>
<td>F</td>
<td>R</td>
<td>2</td>
<td>Simple, thumb and II finger flexion –</td>
<td>–</td>
<td>APB</td>
</tr>
<tr>
<td>5</td>
<td>39</td>
<td>M</td>
<td>L</td>
<td>5</td>
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<td>–</td>
<td>APB</td>
</tr>
<tr>
<td>6</td>
<td>65</td>
<td>M</td>
<td>R</td>
<td>10</td>
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<td>–</td>
<td>APB/FDI</td>
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<tr>
<td>7</td>
<td>26</td>
<td>M</td>
<td>R</td>
<td>15</td>
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<td>8</td>
<td>57</td>
<td>M</td>
<td>R</td>
<td>15</td>
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<td>APB</td>
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<tr>
<td>9</td>
<td>40</td>
<td>F</td>
<td>R</td>
<td>22</td>
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<td>–</td>
<td>APB</td>
</tr>
<tr>
<td>10</td>
<td>51</td>
<td>M</td>
<td>R</td>
<td>35</td>
<td>Dystonic, tremor at wrist, thumb and II finger –</td>
<td>–</td>
<td>APB/FDI</td>
</tr>
<tr>
<td>11</td>
<td>60</td>
<td>M</td>
<td>R</td>
<td>2</td>
<td>Simple, hyperflexion of IPJ of thumb and II finger –</td>
<td>FPL (50), FDS (50)</td>
<td>FPL</td>
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<td>12</td>
<td>55</td>
<td>F</td>
<td>R</td>
<td>6</td>
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<td>ECRL (100)</td>
<td>ECRL/FCU</td>
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<td>F</td>
<td>L</td>
<td>7</td>
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<td>FCU (100)</td>
<td>FCU/APB</td>
</tr>
<tr>
<td>14</td>
<td>44</td>
<td>M</td>
<td>R</td>
<td>7</td>
<td>Dystonic, extension of elbow, discomfort in elbow –</td>
<td>Triceps (100)</td>
<td>Biceps/FDI</td>
</tr>
<tr>
<td>15</td>
<td>49</td>
<td>F</td>
<td>R</td>
<td>9</td>
<td>Simple, ulnar flexion of wrist, discomfort in forearm –</td>
<td>FCU (100)</td>
<td>FCU/APB</td>
</tr>
</tbody>
</table>

R = right; L = left; APB = abductor pollicis brevis; ECRL = extensor carpi radialis longus; FCU = flexor carpi ulnaris; FDI = first dorsal interosseous; FDS = flexor digitorum sublimis; FPL = flexor pollicis longus; IPJ = interphalangeal joint.

One mouse unit corresponds to the calculated median lethal dose (LD$_{50}$) of the reconstituted botulinum toxin injection in mice.

Cortical mapping

Beginning at the centre site used for threshold determination, four stimuli were delivered at sites of increasing, then decreasing, longitude until an MEP could no longer be evoked (anteroposterior map borders). This pattern was repeated for increasing then decreasing latitude until all map borders had been determined. Stimuli were a minimum of 5 s apart and subjects rested briefly between stimulation at each site.

From these data, the mean peak-to-peak MEP amplitude and the silent-period duration were determined for each stimulus site. The location of each stimulus site was converted from an absolute position in centimetres to an angular position on an idealized sphere of half-circumference given by the subject’s inter-aural distance. A complete map was generated by spherical spline interpolation between stimulus sites. This resulted in a fit function which enabled the estimated MEP amplitude and silent-period duration to be determined at any given latitude/longitude value. The mapping protocol was based on that described in detail in Wilson et al. (1993a).

The centre of each map was determined from the location of the peak map value, and was defined by two distances, the distance from the vertex (latitude) and the distance from the inter-aural line along a line of constant latitude (anterior positive). These distances were expressed in millimetres based on a standardized inter-aural distance of 37 cm. Basic parameters of corticomotor conduction (MEP amplitude, latency and silent-period duration) were calculated from the MEP waveforms obtained with stimulation at the centre site.

Statistics

Figures quoted for the control group are mean ± SD. Parameters for individual writer’s cramp subjects were compared with the control data at a significance level of $P < 0.01$ [$t$(17) = 2.90, two-tailed t test].

Results

Control group

Control subjects exhibited a remarkable degree of symmetry between sides for all waveform and map parameters for both the APB and FDI muscles. Corticomotor threshold, MEP amplitude and latency and silent-period duration were similar with stimulation of both hemispheres, and the position and shape of the MEP maps and silent-period maps were also similar for both hemispheres. Consequently, inter-hemispheric comparisons proved most valuable in detecting subtle abnormalities in the dystonic group.

Corticmotor thresholds

There was no inter-hemisphere difference in corticomotor threshold in 15 out of 18 subjects for the APB muscle, and in six out of nine subjects for the FDI muscle. In the remaining subjects the threshold was 5% (of stimulator output) higher on the non-dominant side. The mean threshold on the dominant side for APB and FDI was 53.5 ± 7% and 52.5 ± 4.6%, respectively, and on the non-dominant side it was 54.4 ± 7% (APB) and 53.1 ± 4.6% (FDI).

MEP parameters

The MEP latency difference between the dominant and non-dominant sides for both the APB and FDI muscles was <1 ms for all control subjects (mean values 20.8 ± 1.9 versus 20.9 ± 1.8 ms for APB, and 21.3 ± 2.2 versus 21.4 ± 2.1 ms for FDI). There was no significant difference in
KEY: Superior view of head, centred on vertex (V). Dotted circles mark one third and two thirds of the distance from the vertex to the pre-auricular crease. Maps scaled to percentage of their maximum amplitude.
MEP amplitude between dominant and non-dominant sides for either APB or FDI (mean values 7.5 ± 4.7 versus 6.2 ± 3.3 mV for APB, and 6.0 ± 4.9 versus 5.8 ± 3.4 mV for FDI). The mean dominant to non-dominant amplitude ratio was 1.2 ± 0.4 for both APB and FDI. Likewise there was no significant difference in silent-period duration between the dominant and non-dominant sides for either muscle, the mean silent-period durations being 171 ± 29 versus 170 ± 24 ms for APB, and 175 ± 35 versus 182 ± 42 ms for FDI. The mean dominant to non-dominant ratio of the silent-period duration was 1.0 ± 0.1 for APB and FDI.

Cortical maps

MEP maps from control subjects were similar in shape for the APB and FDI muscles on both sides, and were oval and elongated in the anteroposterior axis (Fig. 1A and B). The mean position of the centre of the APB map in the mediolateral axis was 54 ± 4 mm from the vertex on the dominant side, and 55 ± 4 mm from the vertex on the non-dominant side, and for the FDI map, 54 ± 3 mm (dominant side) and 57 ± 3 mm (non-dominant side) from the vertex. For five control subjects in whom mapping of the non-dominant APB was repeated after an interval of 1 week, the variation in map position in the mediolateral axis was <1 mm. The inter-hemisphere difference in the distance of the map centres from the vertex was <3 mm in all control subjects for both APB and FDI (Fig. 2A).

The mean position of the MEP map in the anteroposterior axis, expressed as distance from the inter-aural line, was 1 ± 7 mm on the dominant side and 2 ± 6 mm on the non-dominant side for the APB, and 0 ± 10 mm (dominant side) and 2 ± 8 mm (non-dominant side) for the FDI. The inter-hemisphere difference in map centres from the inter-aural line was <9 mm for both muscles in all control subjects (Fig. 2A).

In keeping with a previous study, the silent-period maps were centred at a location very similar to the MEP map and were of a similar shape, but they extended over a wider area encompassing and surrounding the MEP map (Wilson et al., 1993b). The inter-hemispheric difference in silent-period map location was <3 mm in the mediolateral direction, and <11 mm in the anteroposterior direction for both the APB and FDI. The mean difference in the centre of the silent-period maps compared with the corresponding MEP map was <3 mm in the mediolateral direction and <7 mm in the anteroposterior direction for both muscles on both sides (Fig. 3A).

Untreated writer’s cramp

MEP latency, MEP amplitude, corticomotor threshold and silent-period duration were normal on each side for both APB and FDI in all subjects. The inter-hemisphere differences for MEP latency and corticomotor threshold were normal for both APB and FDI, as were the dominant : non-dominant MEP amplitude and silent-period duration ratios (Table 2).

For all subjects in whom mapping of the APB was performed, there was an asymmetry in map position. The map on the dominant side was medially displaced relative to the map on the non-dominant side by 5–7 mm in three subjects (Cases 3, 13 and 15), laterally displaced by 5–17 mm in nine subjects (Cases 1, 2 and 4–10), and displaced 41 mm anteriorly to 22 mm posteriorly in five subjects (Cases 5, 6, 8, 10 and 15). In three subjects (Cases 6, 7 and 9) the...
Fig. 3 Scatter diagrams of the difference in location between the MEP and silent-period maps for the APB and FDI in the mediolateral (M–L) and anteroposterior (A–P) directions for all subjects in the control group (A) and the writer’s cramp group (B) (closed circles = writing side; open circles = non-writing side). The close relationship between the centres of the MEP and silent-period maps was not maintained on the dominant side in eight maps (six subjects), all of whom had a silent-period map which was medially positioned relative to the MEP map.

centre of the map on the dominant side was located outside the lateral normal limit (80, 73 and 70 mm from the vertex, respectively; normally <66 mm), and in one of these cases (Case 6), the map on the non-dominant side was also laterally displaced (73 mm from the vertex; normally <67 mm).

The FDI was also mapped in four of these subjects (Cases 1, 6, 7 and 10), and in two subjects the map on the dominant side was laterally displaced relative to the map on the non-dominant side (7 mm for Case 6 and 16 mm for Case 10). These relative displacements were in the same direction as the APB map (7 mm and 8 mm, respectively). For Case 6, the centres of the maps on both sides were also displaced outside the normal lateral limit (82 mm and 75 mm from the vertex, dominant and non-dominant side, respectively: normally <63 and 66 mm, respectively), while for Case 10, the map was laterally displaced on the dominant side only (68 mm from the vertex). The inter-hemispheric difference in map position was outside the normal range in one subject in whom mapping was carried out for the FDI only (Case 14, 5 mm medial and 10 mm posterior on the dominant side).

The changes in the position of the maps were greater in subjects with a history of writer’s cramp of >5 years (up to 17 mm) compared with subjects affected for <2 years (up to 6 mm, Fig. 2B). Furthermore, some long-term sufferers displayed abnormalities in map shape with lateral extensions of the map border for one or more muscles (Fig. 1D–G). Finally, three long-term sufferers displayed bilateral map displacement and/or bilateral asymmetric map shapes (Fig. 1D, E and G). These map changes in the long-term group contrasted with the more subtle abnormalities seen in the short-term group, as illustrated in Fig. 1C, in whom there was a small but significant displacement of the APB map on the writing side, a normally positioned map on both sides for the FDI muscle, and all maps were approximately symmetrical in shape as in normal subjects (Fig. 1A and B).

In all cases the silent-period maps encompassed and surrounded the associated MEP map for both APB and FDI on both the dominant and non-dominant sides. There were 13 subjects in whom the MEP maps of either or both the APB and the FDI were displaced on the dominant side relative to the non-dominant side, and in all but one of these subjects the silent-period map was also displaced on the dominant side. However, the normally close relationship between the centres of the silent period and MEP maps (<3 mm difference) was not maintained on the dominant side in six subjects, all of whom had a silent-period map which was medially positioned relative to the MEP map (Fig. 3).

**Treated writer’s cramp**

Serial studies were performed on five writer’s cramp subjects 1 week before and 4–6 weeks after their first botulinum toxin injection (Table 1 and Fig. 4). Four of these subjects were again studied ~3 months after the injection (prior to their second injection) when the clinical effects of the first injection had passed. The corticomotor projection to the injected muscle was investigated in four subjects (Cases 11–13 and 15), one of whom also had mapping of a functionally related muscle (Case 12). For the remaining subject (Case 14), a functionally related but non-injected muscle was investigated (Table 1). There were no changes in corticomotor threshold or MEP latency after injection in either the injected or the non-injected muscles in any of the subjects. However, MEP amplitude and silent-period duration were reduced for the injected muscle by 30–80% and 55–85%, respectively.

In all cases, prior to injection, the MEP maps of the muscles selected for injection, as well as some functionally related muscles on the dominant side, were displaced medially (range 5–17 mm) with respect to the non-dominant side. At 4–6 weeks after injection, the MEP maps of all injected muscles and of one functionally related but non-injected muscle on the dominant side had moved laterally (range 6–17 mm) to a more normal position compared with the non-dominant side. When studied again 3 months post-injection, these maps had moved medially (range 4–8 mm), returning towards their original position (Fig. 4). During the same period, there was no more than a 3-mm shift in the position of the maps on the non-dominant side. In four subjects (Cases
Table 2 Comparing the dominant (D) and non-dominant (ND) sides in 13 writer's cramp subjects before any treatment

<table>
<thead>
<tr>
<th>Case</th>
<th>Muscle studied</th>
<th>Latency (ms)</th>
<th>Threshold (%)</th>
<th>Amplitude ratio (D/ND)</th>
<th>SP duration ratio (D/ND)</th>
<th>MEP</th>
<th>Silent period</th>
</tr>
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<tbody>
<tr>
<td></td>
<td>(D–ND)</td>
<td>(D–ND)</td>
<td>(D–ND)</td>
<td>(D–ND)</td>
<td>(D–ND)</td>
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<td>(D–ND)</td>
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<tr>
<td>1</td>
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<td>0.5</td>
<td>–5</td>
<td>0.97</td>
<td>1.02</td>
<td>6*</td>
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<td>0.91</td>
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<td>0.97</td>
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*Parameters are outside the normal range.

In control subjects, the location of the maps on the two sides corresponded very closely and map shapes were oval and symmetric in both the mediolateral and anteroposterior axes. On the other hand, the maps in all the dystonic subjects showed a variety of changes in their spatial location and shape. These differences consisted of a displacement in the map centre for one or more affected or unaffected muscles.

Discussion

The present study has shown alterations in the topography of the corticmotor projection to the hand and forearm muscles in writer’s cramp, and that the changes in map topography can be temporarily reversed by botulinum toxin injection into affected muscles. These changes were not associated with any significant changes in corticomotor threshold, silent-period duration or corticospinal conduction times.

Normal corticmotor thresholds have been reported previously by a number of investigators of writer’s cramp and other focal dystonias (Mavroudakis et al., 1995; Ridding et al., 1995; Ikoma et al., 1996). However, there is evidence from TMS of abnormal corticmotor excitability in patients with focal dystonia, as shown by an increased ratio of MEP amplitude in the resting and activated conditions (Mavroudakis et al., 1995), and an abnormal increase in MEP amplitude with increasing stimulus intensity (Ikoma et al., 1996), although we did not find a greater MEP amplitude with stimuli 20% above threshold during a 10% isometric contraction. In addition, we did not find changes in the duration of the silent period under our experimental conditions (Mavroudakis et al., 1995; Filipovic et al., 1997).

The most significant finding in the present study was of alterations in the topography of the corticomotor projection to the hand. TMS preferentially activates, both directly and trans-synaptically, fast conducting corticospinal fibres which project monosynaptically to alpha motor neurons (Day et al., 1989; Rothwell et al., 1991; Burke et al., 1993). By varying the site of stimulation, and relating MEP amplitude to stimulus site, a scalp map can be generated which is related to the origin and spatial distribution of these fibres. Thus, for a specific muscle, the scalp map is a representation of the surface topography of the primary corticomotor projection to the muscle. These maps are not a true reflection of the spatial extent of the representation of the muscle in the motor cortex, as factors relating to the size of the stimulating coil, current spread and the depth of the site of stimulation in the brain all combine to give a falsely large map (Thickbroom et al., 1997). However, the centre of these maps is an indication of the location below the scalp of those cells which project with the lowest threshold to the target muscle, and differences in the shape of the maps are likely to reflect asymmetries in the spatial arrangement of these cells in the cortex. In the present study, emphasis has therefore been given to the precise location of the centre of the corticomotor maps and their shape, rather than map area.

In control subjects, the location of the maps on the two sides corresponded very closely and map shapes were oval and symmetric in both the mediolateral and anteroposterior axes. On the other hand, the maps in all the dystonic subjects showed a variety of changes in their spatial location and shape. These differences consisted of a displacement in the map centre for one or more affected or unaffected muscles.
on the writing side and in some subjects also the non-writing side, and asymmetries in map shape with the appearance of almost discrete secondary maps lateral to the primary representation in some subjects. The presence of abnormalities on the non-writing side is of interest as it is known that in some cases of writer’s cramp, symptoms may also develop in the non-dominant hand (Marsden and Sheehy, 1990), as was the case in one of our subjects. When the maps of more than one muscle in the same limb were displaced, the displacement was of a similar magnitude and in the same direction for each muscle, and further, when the map of only one muscle was displaced, the maps of other limb muscles on the same side were often extended in the same direction, particularly in long-standing cases. These patterns suggest a degree of reorganization within the motor strip which may initially develop in a single or a few muscles, but which may eventually lead to a more general rearrangement of the motor output to multiple muscles in a manner which preserves the overall motor sequence of the classic homunculus (Penfield and Rasmussen, 1950).

The shift in the spatial location of the primary corticomotor projection to affected and unaffected muscles in the dystonic group may indicate a primary alteration in the corticomotor control system which leads to dystonia or it may reflect an adaptive change in the corticomotor system in response to altered inputs from other areas. The involvement of executive motor centres has some support from the task-specific nature of the disorder. However, the current mapping study was carried out during a simple isometric motor task which did not evoke dystonic symptoms and abnormalities were seen in the maps of clinically unaffected as well as affected muscles, including muscles on the non-writing side. Rather, this widespread change in corticomotor output maps, and the finding of greater changes in longer standing cases, point to a slowly evolving reorganization of the primary corticomotor output in writer’s cramp, and suggest that this may be an adaptation of the motor cortex to dysfunction in other centres.

The primary motor cortex receives inputs from a wide range of cortical and subcortical centres (Rothwell, 1994). However, in relation to dystonia it is of interest to consider two main inputs to the motor cortex which may underlie the reorganization of motor output: the basal ganglia and the sensorimotor system. Implication of the basal ganglia in dystonia follows from the occurrence of dystonia in patients with identifiable lesions of the putamen or pallidum (Burton et al., 1984; Marsden et al., 1985; Pettigrew and Jankovic, 1985; Rothwell and Obeso, 1987; Lee and Marsden, 1994). The basal ganglia project to multiple motor and premotor areas, and may regulate corticomotor output either directly or indirectly (Hoover and Strick, 1993). It is possible that changes in the regulatory influence of the basal ganglia result in a reduction in the excitability of intracortical inhibitory circuits in writer’s cramp (Ridding et al., 1995). Localized pharmacological blockade of inhibitory circuits in the cortex can expand the forelimb muscle representation in the rat (Jacobs and Donoghue, 1991), possibly as a result of unmasking of lateral excitatory projections from neighbouring pyramidal neurons. It is of interest that the silent-period maps of muscles on the non-writing side were positioned very closely to the corresponding MEP maps, whereas on the writing side, the silent-period maps were not always coincident with the MEP maps. The duration of the silent period is thought to be related to intracortical inhibitory processes (Wilson et al., 1993; Priori et al., 1994), and thus the relative shift in the silent-period maps may reflect underlying changes in the normal spatial pattern of excitation and inhibition within the motor cortex, and may be part of the mechanism for map displacement.

A number of human and non-human studies have demonstrated that altered sensory inputs can also result in reorganization of corticomotor output. In the monkey, following nerve section, stimulation of the region of cortex which previously projected to the deafferented body part can evoke movement in neighbouring muscles (Donoghue and Sanes, 1988; Donoghue et al., 1990; Sanes et al., 1990). In the human, changes in the MEP have been reported following stimulation of muscle afferents or nerves (Claus et al., 1988; Day et al., 1991; Deuschl et al., 1991; Kasai et al., 1992). Changes in MEP or map parameters have also been demonstrated in response to a wide range of sensorimotor effects, including voluntary contraction, acquisition of motor skills, in Braille readers, and following limb amputation (Cohen et al., 1991, 1993; Pascual-Leone and Torres, 1993; Pascual-Leone et al., 1995; Pascual-Leone, 1996; Wilson et al., 1995). The involvement of the sensory system in dystonia is supported by a number of observations. In the early stages of the condition, sensory tricks can be employed by subjects to relieve symptoms (Sheehy and Marsden, 1982; Marsden and Sheehy, 1990), there is an impaired capacity for subjects to integrate sensory information during a

Fig. 4 Serial studies in four writer’s cramp subjects before and after their first botulinum toxin injection. Maps of injected and non-injected muscles at 1 week before injection (A), and 1 month (B) and 3 months (C) after injection. The crosses mark the centre of each map (red for the maps of the injected (writing) side). The blue line indicates the alignment in the mediolateral axis of the maps at 1 and 3 months with respect to the initial pre-injection maps. Before injection, the maps for the writing side were located medially compared with the non-writing side in all cases. The maps for the un.injected side showed good reproducibility in position and shape at 1 and 3 months after injection. For the injected side the maps show: in Cases 13 and 15, a lateral shift in the flexor carpi ulnaris (FCU) map 1 month after injection of the FCU muscle, with a return of the map towards its pre-injection position at 3 months; in Case 12, a lateral shift in the extensor carpi radialis longus (ECRL) map without any shift in the FCU map 1 month after injection of the ECRL muscle; and in Case 14, a lateral shift in the bicep map 1 month after injection of the tricep muscle, with a return of the map to its pre-injection position at 3 months.
precision grip task (Odergren et al., 1996), reciprocal inhibition is abnormal in writer’s cramp (Nakashima et al., 1989; Chen et al., 1995), and changes in voluntary EMG in response to peripheral inputs are not normal in writer’s cramp (Valls-Solé and Hallett, 1995).

The findings in relation to botulinum toxin injection provide the strongest support for the hypothesis that the changes in the topography of the corticomotor projection result from altered afferent feedback from the dystonic muscles. The alterations in map topography were not fixed, and could be temporarily reversed during the period when the clinical effects of botulinum toxin injection were greatest. As the effects of the injection wore off, the maps tended to return to their original positions. Botulinum toxin inhibits acetylcholine release from pre-synaptic terminals, thus blocking neuromuscular transmission in extrafusal muscle fibres (Jankovic and Brin, 1991). However, it is likely that the neuromuscular junctions of gamma motor neurons are also blocked, resulting in decreased spindle afferent activity (Filippi et al., 1993; Kaji et al., 1995a; Priori et al., 1995; Rosales et al., 1996). The importance of spindle discharge in writer’s cramp is further supported by the observation that vibration can reproduce symptoms in subjects with writer’s cramp, and that temporary relief can be obtained following local anaesthesia (Kaji et al., 1995b). PET activation studies have also demonstrated alterations in cerebral blood flow in primary sensorimotor cortex of subjects with writer’s cramp during muscle vibration (Tempel and Perlmutter, 1993). Thus, it is possible that, by blocking gamma motor neuron transmission, botulinum toxin injection results in reduced muscle spindle activity, and that the resulting changes in muscle afferent input lead to a temporary reorganization of the corticomotor representation towards normal. Central reorganization following botulinum toxin injection has also been suggested from the firing patterns of motor units in injected muscles in subjects with cervical dystonia (Gelb et al., 1991). While no changes in PET activation patterns were found following botulinum toxin injection in subjects with writer’s cramp (Ceballos-Baumann et al., 1997), the changes in map topography found in the present study indicate that a reorganizational process is occurring within the motor cortex, but this may not necessarily lead to significant changes in regional cerebral blood flow during movement.

It is concluded from this study that there are slowly evolving reorganizational changes in the primary motor cortex in writer’s cramp, and that these changes are a response to alterations in sensorimotor input. The finding of map displacement for clinically unaffected as well as affected muscles suggests that while writer’s cramp manifests as a focal form of dystonia, there may be more widespread abnormalities of motor control mechanisms in affected individuals. These abnormalities are present even in subjects with the simple form of writer’s cramp during an isometric muscle contraction. Thus the clinical features of writer’s cramp may be a manifestation of a more generalized and basic disorder of sensorimotor interaction. The normalization of corticomotor maps after botulinum toxin injection suggests that changes in corticomotor control may play an important part in the improvement which occurs in writer’s cramp after treatment.

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