Abnormalities of motor cortex excitability preceding movement in patients with dystonia

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Summary
In patients with dystonia, abnormal movements are commonly triggered or made worse by voluntary action. By means of transcranial magnetic stimulation (TMS), we investigated changes in motor cortex excitability before the execution of wrist voluntary movements in patients with upper limb dystonia and normal control subjects. Magnetic stimulation was delivered by two Magstim 200 stimulators connected through a Bistim module to a figure-of-eight coil placed over the motor area of the forearm extensor muscles. A subthreshold (80% of the rest motor threshold) conditioning stimulus was delivered 3 ms before the suprathreshold (120% of the rest motor threshold) test stimulus and the degree of inhibition of the conditioned motor evoked potentials (MEPs) was taken as an indicator of intracortical inhibition. MEPs were recorded over the forearm extensor muscles of the right arm. To study MEP amplitudes and intracortical inhibition before the onset of wrist extension in the pre-movement condition, TMS pulses were delivered from 0 ms to 100 ms after the go-signal. Besides the pre-movement condition, intracortical inhibition and the unconditioned MEP size were also investigated at rest and during tonic wrist extension. In healthy subjects studied before the wrist movement, the unconditioned MEP amplitude increased progressively and intracortical inhibition decreased significantly. Before movement in dystonic patients, the unconditioned MEP amplitude remained significantly unchanged from resting values and intracortical inhibition decreased less than it did in healthy subjects. In both groups studied during contraction, the unconditioned MEP amplitude increased and intracortical inhibition decreased from values at rest. In conclusion, these findings from reaction time tasks in patients with primary dystonia provide evidence of abnormal pre-movement motor cortex excitability. This abnormality is due to an altered release or running of motor programmes.

Keywords: cortical excitability; movement preparation; dystonia

Abbreviations: aMTh = active motor threshold; FMESD = Fahn–Marsden Evaluation Scale for Dystonia; ISI = interstimulus time interval; MEP = motor evoked potential; rMTh = rest motor threshold; RT = reaction time; TMS = transcranial magnetic stimulation

Introduction
In primary dystonia, studies with transcranial magnetic stimulation (TMS) techniques have shown abnormalities in motor cortex excitability (Berardelli et al., 1998). Mavroudakis et al. (1995) and Ikoma et al. (1996) investigated the input–output relationship of the motor system. When the levels of background contraction or stimulus intensities are increased, the size of responses increases more steeply in patients with dystonia than in normal subjects. Using the paired shocks technique with short interstimulus intervals (ISIs) in muscles at rest, Ridding et al. (1995a), and Gilio et al. (2000) found a diminished inhibition of the test response in dystonic patients, suggesting decreased cortical inhibition. The changes in the input–output curve and the reduction in intracortical inhibition have been interpreted on the basis of an abnormal cortical facilitation secondary to altered basal ganglia input to the motor cortex.

Dystonia is generally worsened by voluntary movement (Cohen and Hallett, 1988) and, in some patients, is even triggered by the execution of specific motor tasks (‘action dystonia’) (Fahn et al., 1998). In some patients, dystonic movements commonly appear with special actions and are not present at rest. Common examples are the task-specific dystonias seen with writing or playing musical instruments.
These clinical observations suggest that producing voluntary movement causes abnormal cortical excitability in patients with dystonia; whether these changes precede movement onset remains unclear.

Because the abnormalities of cortical excitability found in patients at rest do not necessarily reflect a motor cortical dysfunction in producing movement, in this study we investigated cortical excitability in patients with dystonia preparing a motor action. We examined the changes in the size of muscle evoked potentials (MEPs) after TMS and in intracortical inhibition before the execution of a voluntary wrist movement, during a simple reaction time (RT) paradigm in patients with arm dystonia. These results were compared with the same TMS variables obtained at rest and during voluntary contraction.

**Material and methods**

**Subjects**

We studied ten patients with arm dystonia (nine males and one female; mean age 44.9 ± 4.4 years) and eight healthy volunteers (three males and five females; mean age 40 ± 1.3 years). All subjects gave their informed consent and the experimental procedures were approved by the Ethics Committee Neurophysiological Research, Department of Neurological Sciences. Eight patients had focal dystonia, one segmental and the other patient generalized dystonia. All patients had dystonia involving the right arm, triggered or worsened by writing.

Patients were assessed clinically with the Dystonia Movement Scale of the Fahn–Marsden Evaluation Scale for Dystonia (FMESD) (Weiner and Lang, 1989). The functional impairment of the dystonic arm was evaluated with the Arm Severity section. The degree of disability of the dystonic arm was evaluated with the Handwriting section of the FMESD (Table 1). All the patients received their last botulinum toxin type A injection in the affected forearm extensor muscles at least 4 months before the study.

**Table 1  Clinical details of the dystonic patients**

<table>
<thead>
<tr>
<th>Patient</th>
<th>Age (years)</th>
<th>Duration of illness (years)</th>
<th>Type of dystonia</th>
<th>Affected side</th>
<th>Arm disability</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>33</td>
<td>2</td>
<td>Writer’s cramp</td>
<td>Right</td>
<td>2</td>
</tr>
<tr>
<td>2</td>
<td>50</td>
<td>9</td>
<td>Writer’s cramp</td>
<td>Right</td>
<td>2</td>
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<tr>
<td>3</td>
<td>28</td>
<td>13</td>
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<td>2</td>
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<tr>
<td>4</td>
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<td>12</td>
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<td>2</td>
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<tr>
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<td>37</td>
<td>9</td>
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<tr>
<td>6</td>
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<tr>
<td>7</td>
<td>44</td>
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<td>Dystonic writer’s cramp</td>
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<tr>
<td>8</td>
<td>62</td>
<td>7</td>
<td>Dystonic writer’s cramp</td>
<td>Right</td>
<td>3</td>
</tr>
<tr>
<td>9</td>
<td>56</td>
<td>6</td>
<td>Upper limb primary dystonia</td>
<td>Right</td>
<td>12</td>
</tr>
<tr>
<td>10</td>
<td>30</td>
<td>15</td>
<td>Primary generalized</td>
<td>Both</td>
<td>15</td>
</tr>
</tbody>
</table>

Arm severity and disability scales of the Dystonia Movement Scale of the FMESD.

These clinical observations suggest that producing voluntary movement causes abnormal cortical excitability in patients with dystonia; whether these changes precede movement onset remains unclear.

**Stimulation technique**

Paired-TMS (conditioning test paradigm) was delivered through two Magstim 200 magnetic stimulators connected by a Bistim module to a figure-of-eight coil (outer diameter 8 cm). The coil was placed over the forearm extensor muscles motor area of the left hemisphere (contralateral to the affected side in patients). A conditioning stimulus was delivered 3 ms before a test stimulus. Motor threshold was calculated at rest (rMTh) and during contraction [active motor threshold (aMTh), about 20% of the maximum effort], and was defined as the lowest intensity able to evoke a MEP with an amplitude of 100 μV in at least five of ten consecutive trials. The intensity of the conditioning stimulus was set at 80% and the test stimulus at 120% of rMTh. Unconditioned MEPs were evoked using single TMS pulses at 120% rMTh intensity.

**Recording technique**

The EMG signal was recorded through a pair of surface electrodes (AgCl) placed over the extensor forearm muscles on the right side. The EMG signal was amplified (Digitimer D360, Digither Ltd, Welwyn Garden City, UK), bandpassed (3 Hz–1 KHz) and analysed off-line on a PC using dedicated software (SIGAVG 6.32, Cambridge Electronic Design).

**Experimental paradigms**

Experiments were conducted with the subjects seated comfortably. The MEP amplitude and the intracortical inhibition were studied in the forearm extensor muscles with subjects at rest, before a rapid triggered maximal wrist extension and during tonic wrist extension (20% of the maximal contraction). EMG activity was monitored with audiovisual feedback during all experimental conditions (Tektronix 5103N oscilloscope, Cambridge, UK). Eight trials were collected and averaged for each condition.

In the pre-movement study, the computer generated a go-signal (a loud beep) at random intervals (from 5 to 7 s) and the
subjects had to extend the wrist rapidly after the beep. Single and paired magnetic stimuli at 3 ms ISI were randomly delivered from 0 to 100 ms after the acoustic go-signal. Because of the intra- and inter-individual variation in the duration of the RT to collect eight to ten traces with identical intervals between the magnetic stimuli and the EMG onset, 400–500 trials were recorded for each subject.

**Measurements**

The background EMG activity preceding the stimulus artefact was measured to recognize unwanted dystonic movements. The amplitude of the MEP was measured peak-to-peak and the amplitude of the conditioned MEP (‘intracortical inhibition’) was expressed as a percentage (±SE) of the unconditioned responses. The duration of the RT for the rapid wrist extension was calculated from the trials with and without TMS as the time elapsing between the acoustic go-signal and the onset of the EMG activity.

In recordings obtained by randomly delivering single or paired-TMS after the go-signal, the intervals elapsing between the stimulus artefact and the onset of movement ranged from 139 to 60 ms. For data analysis, we grouped the unconditioned and test responses obtained in four 20-ms bins of the RT calculated from the stimulus to the EMG onset (first bin for stimulus-to-EMG interval 139–120 ms, second bin 119–100 ms, third bin 99–80 ms and fourth bin 79–60 ms before the movement). The amplitude of each conditioned MEP obtained by paired stimuli delivered during the RT was expressed as a percentage of the unconditioned control MEPs obtained by a single stimulus delivered during the RT at the corresponding bins. The time course of the amplitude of the unconditioned and test responses was also calculated plotting the data against the intervals between the go-signal and the TMS pulse.

**Statistical analysis**

All results are given as mean ± SE. Results from healthy subjects and patients at rest and during tonic contraction were compared using separate between-group ANOVA (analysis of variance) for repeated measures with factors ‘group’ and ‘conditioning’. In the pre-movement paradigm, separate between-group ANOVAs for repeated measures with factors ‘group’ and ‘bin’ or ‘interval between go-signal and TMS’ were used to compare conditioned and unconditioned MEP data from the four bins. In trials with TMS, RT data were analysed with between-group ANOVA for repeated measures with factors group and ISI (time elapsing between the go-signal and TMS). Tukey’s honestly significant difference test was used for post hoc analysis. We also analysed data for the subgroup of patients with focal dystonia (n = 8) separately from those of normal subjects. P values <0.05 were considered significant. Spearman rank correlations were assessed between the neurophysiological variables obtained in each experimental condition and the clinical features shown in Table 1.

**Results**

**MEP and intracortical inhibition at rest**

None of the EMG recordings from patients or healthy subjects showed background activity. Healthy subjects and patients had similar rMTh and aMTh (rMTh: healthy subjects 51 ± 3%, patients 54.7 ± 3%; F for factor group = 0.1, P = 0.7; aMTh: healthy subjects 41 ± 2%, patients 40 ± 2%, F for factor group = 0.9, P = 0.5) and unconditioned MEP amplitude (healthy subjects 0.49 ± 0.05 mV, patients 0.4 ± 0.05 mV; F for factor group = 1.5, P = 0.2) (Fig. 1).

In the paired pulse paradigm, the intensity of the conditioning stimuli was significantly lower than the aMTh in healthy subjects and dystonic patients (intensity of the conditioning stimuli: 43.7 versus 41.2 in normal subjects; 41.1% versus 40% in patients).

In both groups, a sub-threshold conditioning stimulus delivered 3 ms before the test stimulus inhibited the test MEP response (normal subjects 36.8 ± 6%, patients 63.02 ± 8.6%, F for factor conditioning = 50, P < 0.001), but the test MEP was less inhibited in patients than normal subjects (significant interaction of group by conditioning F = 6, P = 0.027) (Fig. 2).

**MEP and intracortical inhibition before movement**

None of the EMG recordings from patients or healthy subjects showed background activity preceding the acoustic stimulus or during the RT.

No difference was found in unconditioned MEP amplitudes in patients and controls (F for factor group = 2.13, P = 0.16). MEP amplitude changed in the bins preceding movement onset (F for factor bin = 4.5, P = 0.008), with a significant interaction of group by bins (F = 3.4, P = 0.02). Post hoc analysis showed that, in healthy subjects, the MEP size increased in size in the fourth bin preceding movement onset but, in patients, it remained unchanged (Figs 3 and 4). A separate analysis of the unconditioned MEP amplitude plotted against the intervals between the go-signal and the TMS pulse showed a main effect of factor interval between the go-signal and TMS (F = 2.9, P = 0.006), and a significant group by interval interaction (F = 2.5, P = 0.02) (Fig. 5).

Comparison of the amplitude of the MEPs obtained at rest and that obtained during the first bin preceding movement onset showed no difference between healthy subjects and patients (F for factor group = 0.6, P = 0.4). In both groups, MEP amplitude in the first bin of the RT was larger than that obtained at rest (F for factor rest vs. bin = 4.6, P = 0.05) (Fig. 1).

Before movement, during RT, a sub-threshold conditioning stimulus significantly inhibited the test response in both groups (F for group = 0.59, P = 0.81; Fig. 2). The degree of
test MEP inhibition changed significantly in the bins before movement ($F$ for factor bin = 29.2, $P < 0.0001$), with a significant interaction of group by bin ($F = 12.3$, $P < 0.0001$). Post hoc analysis showed that, in healthy subjects, the inhibition of test MEP decreased significantly from the third bin preceding movement onset, but in patients it remained unchanged (Figs 2, 3 and 4). A separate analysis of the test MEP amplitude plotted against the intervals between the go-

**Fig. 1** MEP amplitude at rest, in the bins preceding rapid wrist extension, and during contraction in healthy subjects (continuous line) and dystonic patients (dashed line). First bin for stimulus-to-EMG interval corresponds to 139–120 ms, second bin 119–100 ms, third bin 99–80 ms and fourth bin 79–60 ms before the movement. Data correspond to mean ± SE mV.

**Fig. 2** Intracortical inhibition at rest, in the bins preceding rapid wrist extension, and during contraction in healthy subjects (continuous line) and dystonic patients (dashed line). First bin for stimulus-to-EMG interval corresponds to 139–120 ms, second bin 119–100 ms, third bin 99–80 ms and fourth bin 79–60 ms before the movement. Data correspond to mean ± SE mV.
signal and the TMS pulse showed a main effect of factor interval between go-signal and TMS \((F = 3.9, P = 0.004)\) and a significant group by interval interaction \((F = 3.1, P = 0.01)\) (Fig. 5).

Comparison of the degree of the conditioned MEP inhibition at rest and during the first bin preceding movement onset showed that healthy subjects had more inhibited responses than patients \((F \text{ for factor group} = 5.4, P = 0.046)\). In both groups, the amplitude of the unconditioned MEP was similar at rest and in the first bin preceding movement onset \((F \text{ for factor rest versus first bin} = 0.5, P = 0.5)\) (Fig. 2).

**MEP and intracortical inhibition during contraction**

In both groups, the aMTh and the amplitude of unconditioned MEP were similar (normal subjects 1.1 ± 0.2 mV; patients 1.38 ± 0.2 mV; \(F = 0.71, P = 0.41\)). In both groups, the unconditioned MEP amplitude was significantly larger during contraction than at rest \((F \text{ for factor contraction} = 21.7, P = 0.003)\) (Fig. 1).

In both groups, a sub-threshold conditioning stimulus delivered 3 ms before the test stimulus significantly inhibited the test response (normal subjects 87.2 ± 4.9%; patients 84 ± 5.7%, \(F \text{ for factor conditioning} = 5.3, P = 0.03\)) without between group differences.

In both groups, the conditioning stimulus inhibited the test MEP less during contraction than at rest \((F \text{ for factor rest versus contraction} = 24.8, P = 0.02)\) (Fig. 2).

**Reaction time**

In trials without TMS, the RT was similar in healthy subjects and patients (healthy subjects 137 ± 3 ms, patients 148 ± 4 ms; \(F \text{ for factor group} = 3.5, P = 0.08\)). In trials with single and paired-TMS pulses, the duration of RT progressively increased with increasing interval between the go-signal and the TMS stimulus in both patients and controls. ANOVA showed a main effect for factor ISI \((F = 150, P = 0.0000)\), but not for factor group \((F = 10.9 P = 0.09)\), with a significant interaction of group by ISI \((F = 2.47, P = 0.04)\). Post hoc analysis showed that, in both groups, TMS lengthened the RT when delivered at least 30 ms after the go-signal. In addition, RT lengthened slightly more in patients than in controls (mean RT during TMS trials at all ISIs 151 ms in patients versus 139 ms in controls; mean difference ~12 ms) (Fig. 6).

**Clinical evaluation**

Spearman’s rank test disclosed no significant correlation between patients’ FMESD scores and the neurophysiological variables investigated \((P > 0.05)\).
**Fig. 4** Intracortical inhibition 70 ms before wrist extension in a representative healthy subject (left panel) and in a dystonic patient (right panel). In both subjects, the first trace represents the MEPs by a single stimulus and the second trace represents the MEPs by paired-TMS stimulation during the reaction time. Each trace is the average of four single EMG trials. Horizontal calibration is 70 ms and vertical calibration is 0.5 mV. Note the decrease in intracortical inhibition in the healthy subject, but not in the dystonic patient.

**Fig. 5** Amplitude of the unconditioned MEP (upper panel) and test MEP (lower panel) plotted against the ISIs between the go-signal and single and paired-TMS in healthy subjects (continuous line) and dystonic patients (dashed line). Data correspond to mean ± SE mV (upper panel) and mean ± SE % (lower panel).
**MEP amplitude, intracortical inhibition and RT in the sub-group of patients with focal dystonia**

A separate analysis between the subgroup of patients with focal dystonia and normal subjects yielded similar results for the TMS variables (rMTh, aMTh, MEP size, intracortical inhibition) tested at rest, during contraction and before movement to those found between all patients and controls: rMTh: 55 ± 3%, \( F \) for factor group = 0.1, \( P = 0.7 \); aMTh: 42 ± 2%, \( F \) for factor group = 0.4, \( P = 0.5 \); unconditioned MEP amplitude at rest 0.42 ± 0.06 mV, \( F \) for factor group = 0.76, \( P = 0.39 \); intracortical inhibition at rest 63.69 ± 10.9%, \( F \) for factor conditioning = 4.8, \( P = 0.04 \); unconditioned MEP amplitude before movement 0.6 ± 0.1 mV, \( F \) for factor group = 0.05, \( P = 0.81 \); intracortical inhibition before movement 72 ± 9%, \( F \) for factor group = 4.6, \( P = 0.05 \); MEP amplitude during contraction 1.4 ± 0.3 mV, \( F \) for factor group = 0.6, \( P = 0.4 \); and intracortical inhibition during contraction 84 ± 7%, \( F \) for factor group = 0.08, \( P = 0.7 \).

Trials without TMS yielded a RT similar to that observed in healthy subjects (145 ± 5 ms; \( F \) for factor group = 1.4, \( P = 0.25 \)).

**Discussion**

The novel finding in this paper is the abnormal motor cortex excitability before the execution of a voluntary wrist movement in patients with dystonia. This abnormality appears relevant to the pathophysiology of action dystonia. Before discussing our findings in patients with dystonia, we consider it important to understand the pre-movement changes we observed in healthy subjects.

**Changes in MEP amplitudes and intracortical inhibition in healthy subjects**

In the healthy subjects we studied, MEPs significantly increased in amplitude compared with the rest condition before the onset of a rapid voluntary wrist extension, and during the execution of voluntary tonic muscle contraction. Although this finding remained significant regardless of whether we plotted the data in bins from the TMS pulse and EMG onset, or against the intervals between the go-signal and the TMS pulse, grouping the data in bins reduced inter-subject variability and better emphasized changes in cortical excitability before a movement.

Previous brain stimulation studies have shown a facilitation of the motor response at ~80 ms before the onset of EMG activity, suggesting that before the onset of a voluntary movement the excitability of primary motor cortex increases (Starr et al., 1988; Pascual-Leone et al., 1994; Hoshiyama et al., 1996; Chen et al., 1998). During muscle contraction, the MEP amplitude also increases by changes in both cortical and spinal excitability (Rothwell et al., 1991).
As previously reported in healthy subjects at rest (Kujirai et al., 1993; Ridding et al., 1995a; Gilio et al., 2000), paired-TMS elicited significant test MEP inhibition. This inhibition is due to the activation of intracortical GABAergic inhibitory interneurons. When we delivered paired stimulation before a rapid wrist extension, intracortical inhibition progressively decreased during the bins closest to movement onset. This finding confirms those of Reynolds and Ashby (1999) and suggests that, before the onset of movement, the excitability of intracortical inhibitory interneurons decreases to allow the selective facilitation of the motor cortex for the forthcoming movement. In addition, the degree of intracortical inhibition was significantly reduced during voluntary contraction (Ridding et al., 1995b; Reynolds and Ashby, 1999). This is probably due to a widespread increase in cortical excitability, with a down-regulation of the activity of the inhibitory interneurons that project onto the populations of corticomotorneuronal cells involved in the ongoing movement (Ridding et al., 1995b).

These findings suggest that movement involves not only an increase in the amount of excitability in the motor cortex, but also a decrease in the amount of inhibition. Interestingly, we found that the MEP facilitation and intracortical inhibition before a voluntary movement had different time courses. Intracortical inhibition decreased in earlier bins before the MEPs increased in size, implying that facilitation and inhibition are separate processes. This finding confirms previous suggestions that in this part of the motor system, movement control works like a car that releases the brakes before pressing the gas pedal (Floeter and Rothwell, 1999).

Changes in MEP amplitudes and intracortical inhibition in patients with dystonia

Our experiments at rest and during contraction confirmed previously reported findings that patients with dystonia have normal MEP amplitude (Ikoma et al., 1996), reduced intracortical inhibition at rest (Ridding et al., 1995a; Gilio et al., 2000) and normal inhibition during contraction (Rona et al., 1998).

The new finding in this study is that TMS testing before movement disclosed that MEP amplitude and intracortical inhibition both had abnormal time courses in patients. These abnormalities were clearly disclosed by analysing the data grouped in bins from the TMS pulse to the EMG onset. Time courses in patients lacked the increase in MEP size and the reduction in intracortical inhibition before the onset of wrist extension seen in healthy subjects. A first explanation is that the go-signal alerted patients to start the movement less effectively than it alerted normal subjects, therefore inducing a less efficient motor reaction. But patients and normal subjects had similar RTs, as previously reported for a number of motor tasks (Inzelberg et al., 1995; Kaji et al., 1995; Currà et al., 2000a).

Previous papers have demonstrated that TMS pulses delivered before the onset of a voluntary movement can modify the duration of the RT (Day et al., 1989; Berardelli et al., 1994; Sawaki et al., 1999). In dystonia, the Cortical Silent periods evoked by suprathreshold stimuli have a shorter duration than in healthy subjects (Rona et al., 1998; Currà et al., 2000b). TMS may therefore have a differential effect on the RT duration in patients and healthy subjects, particularly if TMS is given close to the onset of movement. In our study, we found that in trials with TMS the RT increased slightly more in patients than in controls (mean between-group difference 12 ms). This finding implies that TMS delivered close to the EMG onset might have delayed the onset of movements more in patients than in controls. It might have also evoked responses in an earlier phase of pre-movement excitability in patients than in controls. However, we found that the between-group difference in RT was about half the duration of the 20-ms bin, i.e. the analysis epoch in which we grouped and averaged the unconditioned and test responses. Because the difference in TMS-induced RT lengthening is below the time resolution of the bin, all possible consequences of this delay on the amplitude of the conditioned and test MEPs collapse within the analysis epoch, i.e. the bin. Nevertheless, even though TMS differentially affected the RT in patients and controls, the magnitude of this effect cannot explain the slower progression of pre-movement cortical excitability found in patients with dystonia.

Another possibility is that patients pre-activated muscles before movement, so that the MEP was already facilitated in size, thus reducing intracortical inhibition, as demonstrated in normal subjects by Ridding et al. (1995b). Yet in our study, this is unlikely because we carefully monitored the EMG activity preceding movement onset by audiovisual feedback and we rejected all the recordings without EMG silence. Furthermore, because most patients tested had dystonia mainly triggered by movements, we found no between-group difference in MEP amplitude.

Intracortical inhibition before movements might also have differed in the two groups because MEPs differed in size in patients and healthy subjects. At the same bins, patients had smaller sized test MEPs than healthy subjects. Hence, the difference could explain the diminished change in intracortical inhibition. This hypothesis nevertheless seems unlikely because in healthy subjects the MEP amplitude increase followed the reduction of intracortical inhibition. A further mechanism to be excluded is a dysfunction of spinal cord mechanisms. Because we tested muscles at rest before the onset of voluntary movement, the proprioceptive inflow was absent. Hence, the abnormalities of MEP and intracortical inhibition seen in patients before movement cannot be explained by changes in the feedback from the upper limb muscles. Previous studies in normal subjects engaged in an RT task involving foot plantar flexion have shown that the spinal cord excitability tested with the H-reflex technique was increased before movement. But this phenom-
enon is thought to depend on reduced descending presynaptic inhibition on Ia afferents, and not on increased excitability of the alpha-motoneurons (Eichenberger and Ruegg 1984; Ruegg and Drews, 1991). Another finding that makes increased spinal excitability unlikely is that in both groups, the intensity of the conditioning stimulus used to test intracortical inhibition during the RT was lower than the aMTh. Hence, the lack of changes in MEP amplitude and intracortical inhibition is therefore unlikely to arise from spinal mechanisms.

The interpretation we favour is that MEP size and intracortical inhibition remained unchanged owing to a specific abnormality of motor cortex excitability in the phase that precedes the execution of a voluntary movement. In both groups, the MEP during the first RT bin was larger than that obtained at rest. This difference strongly suggests that in dystonic patients cortical excitability also increases slightly, early before a movement, but does not increase enough to ensure the further increase seen in normal subjects close to the EMG onset. This early increase may simply reflect how the motor cortex re-adapts its excitability from rest to the motor set of an RT paradigm.

In healthy subjects, we found that intracortical inhibition diminished on average 100 to 60 ms before the onset of the voluntary movement and the MEP size increased on average 80 to 60 ms before the EMG onset. At the intervals studied, the patients lacked the increase in MEP size and the reduction in intracortical inhibition before the onset of wrist extension. On the other hand, MEP amplitude and intracortical inhibition showed a similar behaviour in patients and healthy subjects during contraction. A plausible reason why intracortical inhibition failed to increase in patients is that because patients already have reduced intracortical inhibition at rest; they may need a smaller or later decrease to achieve a normal level of intracortical inhibition during a contraction. To give a definite answer to this question, we would have needed to investigate time intervals just before movement onset. The shortest time between TMS and EMG onset we studied was 60 ms. We did this largely to avoid a between-group difference in the EMG onset delay caused by suprathreshold TMS pulses delivered immediately before movement onset.

Although we did not test MEPs and intracortical inhibition immediately before movement onset, one hypothesis to explain the similar MEP size and intracortical inhibition seen in patients and healthy subjects during contraction is that, in dystonic patients, the changes in MEP amplitude and intracortical inhibition operate after the last bins we investigated. Hence, primary motor area excitability needed to produce movement might change later in patients than in healthy subjects. The feed-forward mechanism controlling cortical activation could therefore be abnormally short-lasting and consequently generate an uncontrolled output from the cortex to the muscles, thereby resulting in dystonic movements.

Why dystonic patients are unable to modulate the MEP size and the degree of intracortical inhibition before movement is unclear. A first answer is that their basal ganglia disorder impairs the fine-tuning of cortical excitability needed to trigger and perform a voluntary movement. The motor task we studied involved releasing and running a pre-built motor programme that codes for the activation of agonist muscles and possibly for the inhibition of antagonists. The weak intracortical inhibition may reflect the inability of the basal ganglia to inhibit the competing motor programs once the desired program has been selected for release (Mink, 1998). With this TMS method, the MEP inhibition is thought to be mediated by cortical mechanisms. The abnormalities observed in dystonic patients may reflect an abnormal feedback from the basal ganglia to motor cortical areas, with a flattening of the excitability of the cortical motoneuron pool during voluntary contraction (Rona et al., 1998).

Even though our experiments showed that, in dystonic patients, the primary motor area remained unchanged during the interval studied, patients had no delays in starting the movement. This finding suggests that, in dystonia, the speed for a motor reaction is related neither to changes in the activity of γ-aminobutyric acid-A (GABA-A) inhibitory interneurons nor to the number of corticospinal neurons recruited by single TMS pulses (i.e. changes in MEP size and intracortical inhibition).

Dystonic patients’ inability to activate the cortical motor areas properly before movement is in line with other neurophysiological observations showing that patients with dystonia prepare for movement abnormally, including evidence from studies using contingent negative variation (Kaji et al., 1995; Ikeda et al., 1996; Hamano et al., 1999), premotor potentials (Feve et al., 1994; Deuschl et al., 1995; Van der Kamp et al., 1995) and event-related desynchronization (Toro et al., 2000).

In conclusion, our results suggest that the motor cortical excitability that precedes a voluntary movement is abnormally modulated in dystonia. The lack of an MEP facilitation and the absence of changes in intracortical inhibition normally present before movement suggest that in patients with dystonia (probably owing to the underlying abnormal output from the basal ganglia), the primary motor cortex cannot properly recruit the corticospinal neurons required to perform the desired movement.

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