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Abnormal acute changes in upper limb muscle cortical representation areas in the patients with writer's cramp during co-activation of distal and proximal muscles

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Abstract

Aim: We analysed cortical muscle representation areas during single muscle activation and during the co-activation of several upper arm muscles in the patients with writer's cramp to determine the possible occurrence of abnormal dynamic somatotopic changes in M1, in addition to the static map abnormalities already described in this form of dystonia.

Methods: Using transcranial magnetic stimulation, we assessed cortical representations of medial deltoid, extensor carpi radialis and the first dorsal interosseus muscles in eight patients with writer's cramp and in eight healthy control subjects. Cortical maps were obtained during distal muscles' activation either in isolation or in conjunction with voluntary medial deltoid co-activation.

Results: This study showed a difference in the organization of cortical representations of these muscles between the patients with dystonia and control subjects. The first dorsal interosseus and the extensor carpi radialis cortical representation areas were larger in the dystonic group. The cortical representations became larger when the medial deltoid was simultaneously co-activated, and this effect was not observed in the control group. In the dystonic group, the three cortical muscle representations largely overlapped and their centres of gravity were closer.

Conclusion: Patients with dystonia showed not only a different spatial organization of muscle cortical representation areas, but also abnormal acute somatotopic changes during proximal muscle co-activation. Task-specific motor impairment in writer's cramp may result not only from lack of cortical inhibition and the well-known anomalous cortical organization observed in these patients, but also from abnormal patterns of proximo-distal functional muscle coupling.

Keywords cortical reorganization, focal hand dystonia, motor control, muscle coordination, transcranial magnetic stimulation.

Different techniques such as functional imagery, direct cortical stimulation and transcranial magnetic stimulation (TMS) are used to study the representations of body parts on the cortical surface. Single-pulse TMS allows the recording of motor-evoked potentials (MEP) in a target muscle and the mapping of muscle representation areas on the motor cortex (Wassermann *et al.* 1992, Wilson *et al.* 1993). It has been established

that cortical muscle representations can be modified by training (Pascual-Leone *et al.* 1994, 1995, Classen *et al.* 1998, Pearce *et al.* 2000, Tyč *et al.* 2005, see for review Tyč & Boyadjian 2006), pathological situations and after injury to the peripheral or central nervous system (Cohen *et al.* 1993, Cicinelli *et al.* 1997, Byrnes *et al.* 1999, Liepert & Weiller 1999, Di Lazzaro *et al.* 2004).

Focal hand dystonia (FHD) is a task-specific form of primary dystonia. Repetitive movement seems to be at the onset of this pathology as it has been commonly observed in writer's cramp (WC) and musician's dystonia. However, repetitive movement is not the only trigger (Rosenkranz *et al.* 2005) because many patients with WC often have a history of average hand use. It may reflect a maladaptative response of the brain to the repetitive performance of stereotyped movements. Focal hand dystonia is associated with the impaired modulation of intracortical inhibition (ICI) during the performance of precise manual tasks, which may contribute to a lack of specificity in the primary motor cortex output (Stinear & Byblow 2004).

Given that the patients with dystonia develop inappropriately high levels of muscle activity during movement, and because increased muscle activity levels during motor training are capable of modifying cortical muscle representation areas, we asked whether or not cortical representations are dynamically modifiable in the patients with dystonia in a task-specific fashion. As it is known that the use of several muscles in a movement induces greater overlapping of their cortical representations (Tyč *et al.* 2005), and likewise that the patients with FHD contract several muscles inappropriately during simple movements and show enlarged maps of hand muscles (Schabrun *et al.* 2009), we studied whether or not the cortical representation maps of three upper limb muscles were modified in the patients with dystonia. More specifically, we studied the cortical representation of distal muscles during their co-activation with a proximal muscle, as we have shown that the excitability of distal muscles is modified during co-activation with a proximal muscle in the patients with dystonia, in contrast with a lack of such an effect in control subjects (Boyadjian *et al.* 2011). We mapped the cortical representations of the medial deltoid (MD), the extensor carpi radialis (ECR) and the first dorsal interosseus (FDI) muscles during their activation alone and during their co-activation in normal and dystonic subjects.

Materials and methods

Subjects

Eight patients with dystonia and eight control subjects, all right-handed, participated in this study (56 ± 5 and 52 ± 3 years old, respectively, no statistical difference between the two groups, $P < 0.5$). All participants signed a free, informed consent form for this study, which was approved by the local Ethics Committee. The control subjects were healthy and free of any neurological signs or symptoms. The patients with WC showed a slight variability in clinical characteristics, such as dystonic posture of the wrist. The clinical features of the patients with WC are shown in Table 1.

Table 1 Baseline clinical characteristics of the patients with writer's cramp

Patient	Sex	Age (years)	Duration (years)	Sign during writing	Other symptoms	Score*
B	F	44	10	Slow writing, increased pressure on pen, cocontraction of flexors and extensors of fingers, flexion of wrist	None	2
C	M	60	18	Slow writing, increased pressure on pen, flexion of wrist, overflow in arm muscles	Difficulties with fine manual tasks	2
D	F	43	?	Slow writing, increased pressure on pen, extension of second finger, flexion of wrist	Writing and keyboard	4
E	M	75	6	Slow writing, increased pressure on pen, cocontraction and mild tremor of wrist muscles	None	9
F	M	65	?	Slow writing, increased pressure on pen, co-contraction of wrist muscles, overflow from lower to upper arm and shoulder muscles	Mild postural and action tremor bilaterally	3
H	M	63	?	Slow writing, increased pressure on pen, flexion of wrist, overflow from lower to upper arm and shoulder muscles	Difficulties with fine manual tasks	2
I	F	64	Over 30 ?	Slow writing, increased pressure on pen	None	2
J	F	30	4	Slow writing, increased pressure on pen	None	2

*Assessed using the Burke-Fahn-Marsden scale.

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EMG recordings

Electromyographic (EMG) recordings were obtained from pairs of surface electrodes (Delsys, Boston, MA, USA) placed on the skin, over the belly of the MD, the ECR and the FDI muscles. The skin was prepared for recording and electrodes were attached using double-sided tape. A large reference electrode was placed around the wrist. The electrodes were connected to the input of the EMG pre-amplifier (Delsys 2.1). The EMG signals were amplified (×1000) using high-pass filtering at 10 Hz and low-pass filtering at 1 kHz, before sampling at 2 kHz. The resulting EMG data were stored in a computer using a CED 1401 device and Spike2-4 software (CED, Cambridge, UK).

TMS protocol

A snugly fitting cap was positioned over the subject's head and a grid was drawn with stimulus sites spaced 1.5 cm from the vertex using the nasion-inion line and the interaural line as references. The TMS was delivered using a Magstim Pro (Dantec S.A., Skovlunde, Denmark) magnetic stimulator with a figure-of-eight coil. The coil was held tangentially to the skull and positioned at 45° in relation to the nasion-inion line with the handle held posteriorly. This coil position produced a posterior to anterior direction of the current induced in the brain to ensure optimal transsynaptic activation of the corticospinal pathways (Brasil-Neto *et al.* 1992, Sakai *et al.* 1997). The centre of the coil was placed over the site to be stimulated. The muscles were slightly activated at a constant level of 15% of the EMG obtained during maximal voluntary contraction. Prior to mapping, the active motor threshold (AMT) was determined by TMS at the scalp site, where the lowest stimulation intensity induced a MEP with a minimum amplitude of 200 μV for at least two out of five stimuli. Four stimuli were delivered to each site of the grid with time intervals that randomly ranged between 3 and 5 s. The number of scalp sites was increased until no MEP was evoked in all border sites. The stimulus intensity was adjusted to 1.2 × AMT of each muscle for mapping. MEPs were recorded from the three muscles separately and stored in a computer for offline analysis. The cortical representations of the MD, ECR and FDI muscles were computed on the dominant side in both groups.

Task

In each experimental condition, the subject grasped a handle mounted with a wire ring (Fig. 1). During TMS, the subject maintained the position of the handle relative to a convoluted wire that passed through the ring, without allowing the two metallic pieces to touch. In Task 1, the subject's elbow rested on an armrest, so that only the distal muscles (FDI and ECR) were slightly activated to maintain the stable position and the proximal muscle (MD) was relaxed (Fig. 1). Background MD EMG activity was displayed on the screen and constantly checked to ensure that the MD remained silent throughout Task 1. Data recording was interrupted if EMG activity was observed in the MD muscle and only resumed after complete relaxation of that muscle. The second condition (Task 2) was the same task but it involved the whole upper arm, so that the proximal MD muscle was co-activated with the ECR and FDI muscles (Fig. 1). The EMG activity of the MD muscle was carefully checked during Task 2 to ensure that the subjects maintained a constant level of activity. In Task 2, the distal muscles were activated at the same intensity as in Task 1. The subjects were instructed to adapt the arm position to maintain background EMG activity levels defined as 15% of the maximal voluntary contraction. The EMG activities were carefully monitored during the two tasks and for each muscle and were shown by traces on the screen to help keep the activity level constant.

Data analysis

To determine the cortical representation of each muscle, the four non-rectified EMG recordings were averaged for each cortical site (Fig. 1). The peak-to-peak amplitude of the MEPs was measured and plotted against each stimulus site. For each subject and for each muscle in both tasks, a contour plot (two-dimensional (2D) representation) was drawn to measure the cortical map area of each muscle representation in square centimetres. The largest MEP obtained during mapping was defined as the MEPmax and used to compare the cortical excitability during both tasks in the two groups.

To represent the shape of the cortical muscle representation, we have elaborated topographical maps of the cortical representations of the FDI and ECR muscles. The level maps were built with contour lines joining iso-MEPs of equal amplitudes above the given level of the MEPs of minimal amplitudes. Each contour line corresponded to an increase in the excitability level. These topographical maps provided information about the cortical distribution of the MEPs and their amplitudes to compare the cortical patterns between the control and the dystonic subjects.

To estimate the effect of co-activation, we compared the size of the cortical area of each muscle, the overlapping of cortical representations and the distances between the centres of cortical representation of the three muscles obtained during the two

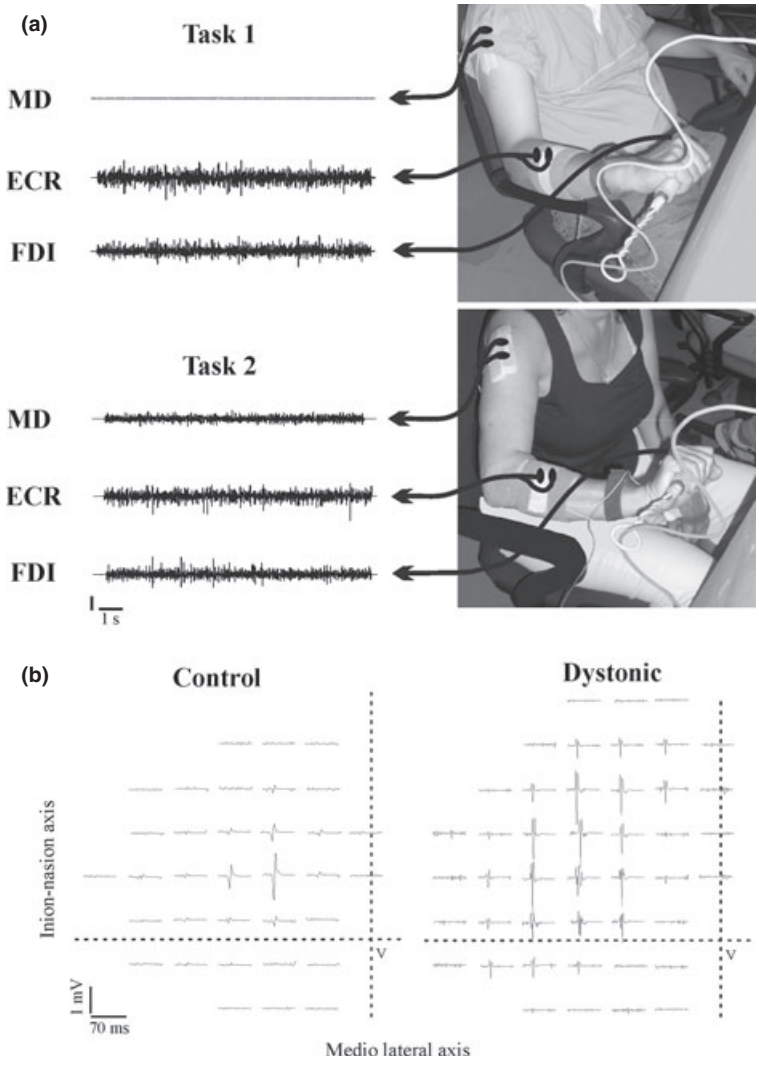

Figure 1 (a) Photographs showing the position of the arm during Task 1 and Task 2 and the placement of the electrodes on the MD, ECR and FDI muscles. The EMG traces obtained for the three muscles during the two tasks are shown. During Task 1, the elbow rested on an armrest and the MD muscle was inactive, and during Task 2, the elbow was up and the MD was co-activated (EMG vertical calibration bar = 2 mV for the FDI and 0.3 mV for the ECR and MD muscles). (b) Examples of mean MEPs obtained for one dystonic patient and one control subject on the FDI muscle. Each mean MEP was located at the site where TMS was applied. Part of (a) was published previously in Acta Physiol (Boyadjian *et al.* 2011).

tasks. For the overlapping, based on the 2D representations, the surfaces of the overlapping cortical representations of each pair of muscles (ECR-FDI, FDI-MD and ECR-MD) were measured. To estimate the centre of the cortical representation of each muscle in both tasks, we used the centre of gravity (CoG). The CoG of the cortical representation is the amplitude-weighted centre of the map (Wassermann *et al.* 1992, Wilson *et al.* 1993, Uy *et al.* 2002, Schabrun *et al.* 2009). The CoG was computed as follows: for each scalp position on a map, the amplitude-weight was computed as the mean MEP amplitude at that position divided by the sum of the mean MEP amplitudes recorded for the map using the formula:

$$\mathrm{CoG} = \sum V_i X_i / \sum V_i, \sum V_i Y_i / \sum V_i,$$

where V_i is the mean MEP amplitude at the scalp site with coordinates X_i and Y_i. The CoG of the map was calculated for each cortical muscle representation in both tasks. The distances between the CoG of each cortical representation of the different muscles were measured and compared between the two tasks and between the two groups.

Data for the FDI and ECR map areas, the inter-CoG distances and the MEP sizes were examined using two-way ANOVA ($\mathrm{Subject}_8 < \mathrm{Group}_2 > \times \mathrm{Tasks}_2$), with between-subject group factor and within-subject task factor, where appropriate, post hoc analyses were

performed for pairwise comparisons. Data for the MD muscle were obtained from one task condition, only the group factor was taken into account, and an unpaired t-test was used. The significance level was fixed at $P < 0.05$.

Results

The cortical mapping data of the three muscles showed differences between the two experimental groups. Cortical muscle representation areas and overlapping areas between the cortical muscle representations were larger in the patients with dystonia than in the controls (Fig. 2). Distances between the CoGs of the cortical representations of proximal and distal muscles were smaller in the patients with dystonia than in the controls (Fig. 3). On level maps, the dystonic cortical representations appeared to be patchy and inhomogeneous, with several hills (Fig. 4).

Active motor threshold and MEPmax

The AMTs for the FDI muscles were not different between the two groups. The ANOVA test did not show any simple effect of group factor ($F_{1,14} = 0.137$ $P < 0.71$) or task factor ($F_{1,14} = 1.000$ $P < 0.33$). The AMT values as a percentage of the maximal output of the stimulator were 40 ± 1.9% and 38 ± 2.5% (mean ± SEM) for the dystonic group during Task 1 and Task 2, respectively, and 39 ± 1.5% and 40 ± 1.0% for the control group during Task 1 and Task 2 respectively. An interaction appeared between group and task factors ($F_{1,14} = 6.53$ $P < 0.02$). The post hoc test showed that AMT was lower during Task 2 in the dystonic group ($t_7 = 2.43$ $P < 0.05$). This difference did not appear for the control group ($t_7 = 1.14$ $P < 0.29$). The ECR AMTs were not different between the patients with dystonia and the control subjects: 40 ± 1.6% and 38 ± 1.4% (mean ± SEM), respectively, for the maximum stimulator output. The

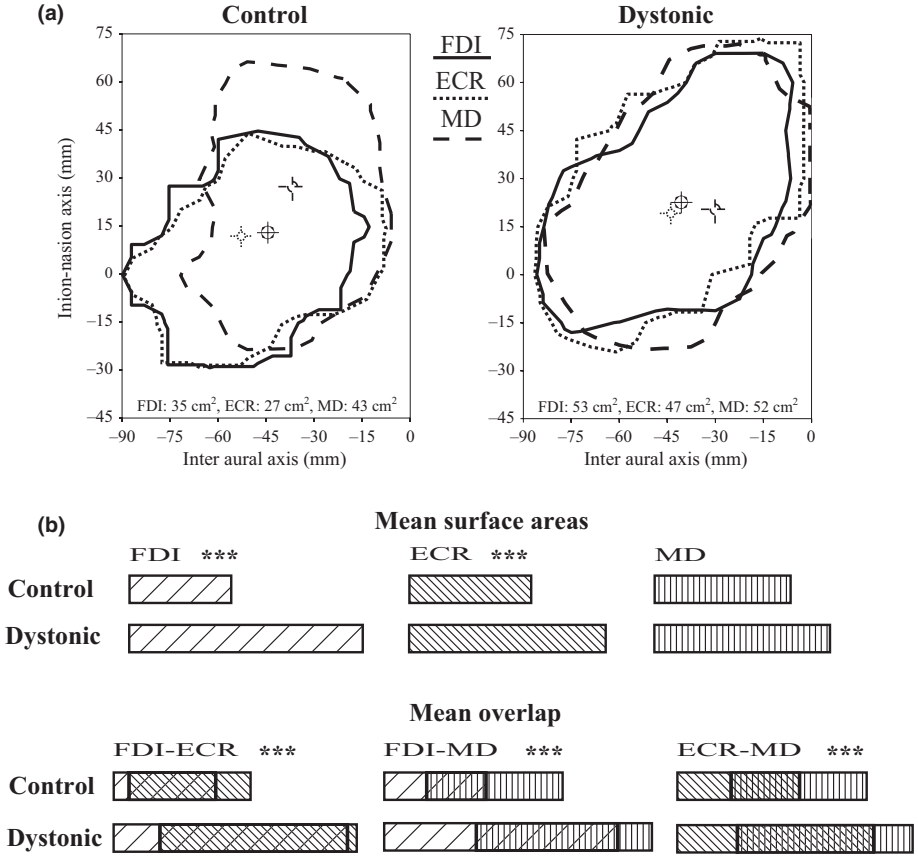

Figure 2 (a) 2D cortical map representation of the MD, ECR and FDI muscles obtained for one dystonic patient and one control subject based on the recorded MEPs. The symbols represent the positions of the theoretical hot spots for each muscle. (b) Graphical representation of the size of the mean cortical representation areas of each muscle in each group and the size of the overlap between the three pairs of muscles. The size of each bar is proportional to the surface area of the cortical muscle representation. ***indicate a significant difference in the cortical representation areas and overlaps in dystonics and controls.

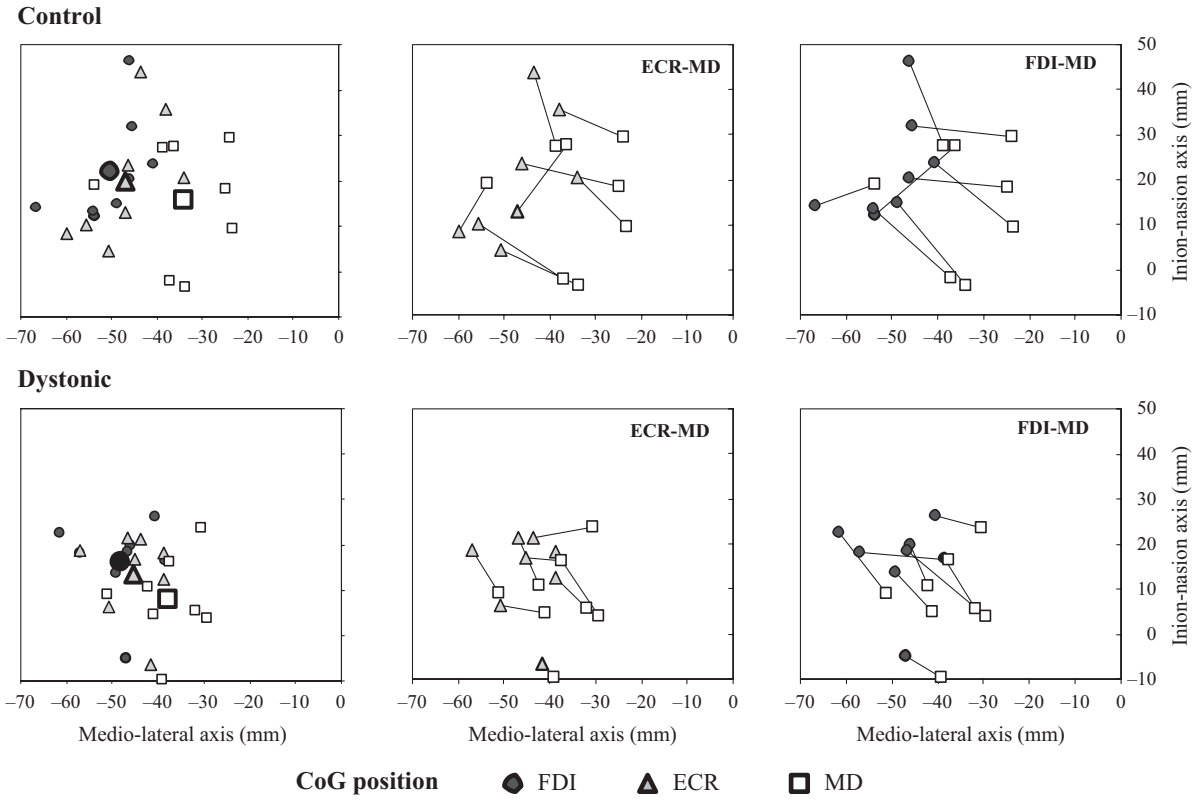

Figure 3 Representation of the CoG positions of the MD, ECR and FDI muscles in eight patients with dystonia and eight control subjects (left column). The mean CoG positions are indicated by large symbols. Note the grouping of the CoGs in the patients with dystonia compared with control subjects. Right columns: representation of the distance between the cortical representation CoG positions of pairs of muscles (ECR-MD and FDI-MD) for each subject in both groups. The inter-CoG distances were smaller in the patients with dystonia than in control subjects.

ANOVA test did not show any simple effect of group factor. The MD AMTs were different between the two groups ($t_7 = 0.02$). The mean MD AMT was higher in the dystonic group than in the control group, with 54 ± 3.4% and 44 ± 1.5% (mean ± SEM) for the patients with dystonia and the controls respectively.

The mean MEPmax values elicited in the FDI muscles were not different between the two groups or between the two tasks. The ANOVA test did not show any simple effect of group ($F_{1,14} = 0.36$ $P < 0.56$), task ($F_{1,14} = 0.29$ $P < 0.59$) or the group and task interaction ($F_{1,14} = 0.03$ $P < 0.85$). The mean MEPmax values in the FDI muscles were 1500 ± 218 μV and 1627 ± 339 μV (mean ± SEM) in the dystonic group for Task 1 and Task 2, respectively, and 1304 ± 222 μV and 1364 ± 372 μV for Task 1 and Task 2 in the control group respectively.

In the ECR, the mean MEPmax values were not different between the groups or between the tasks. The ANOVA test did not show any simple effect of the group factor ($F_{1,14} = 0.15$ $P < 0.71$), of the task factor ($F_{1,14} = 0.31$ $P < 0.58$) or any interaction between group and task factors ($F_{1,14} = 2.58$ $P < 0.13$). The mean MEPmax elicited in the ECR muscles were 558 ± 116 μV and 715 ± 187 μV (mean ± SEM) in the dystonic group for Task 1 and Task 2, respectively, and 889 ± 313 μV and 564 ± 95 μV in the control group for Task 1 and Task 2 respectively.

For the MD muscles, the mean MEPmax values were not different between the two groups ($P < 0.3$): 614 ± 126 μV and 782 ± 401 μV (mean ± SEM) for the patients with dystonia and controls respectively.

FDI cortical representation areas

The ANOVA test (two factors: one within and one between) showed a simple effect of the group factor ($F_{1,14} = 37.8$ $P < 0.000025$) and an absence of task effect ($F_{1,14} = 0.998$ $P < 0.33$). A significant interaction appeared between the group and the task factor ($F_{1,14} = 6.00$ $P < 0.03$). The cortical representation of the FDI muscles was larger in the dystonic group than in the control group (Fig. 2). A post hoc test showed a significant difference between the two tasks in the

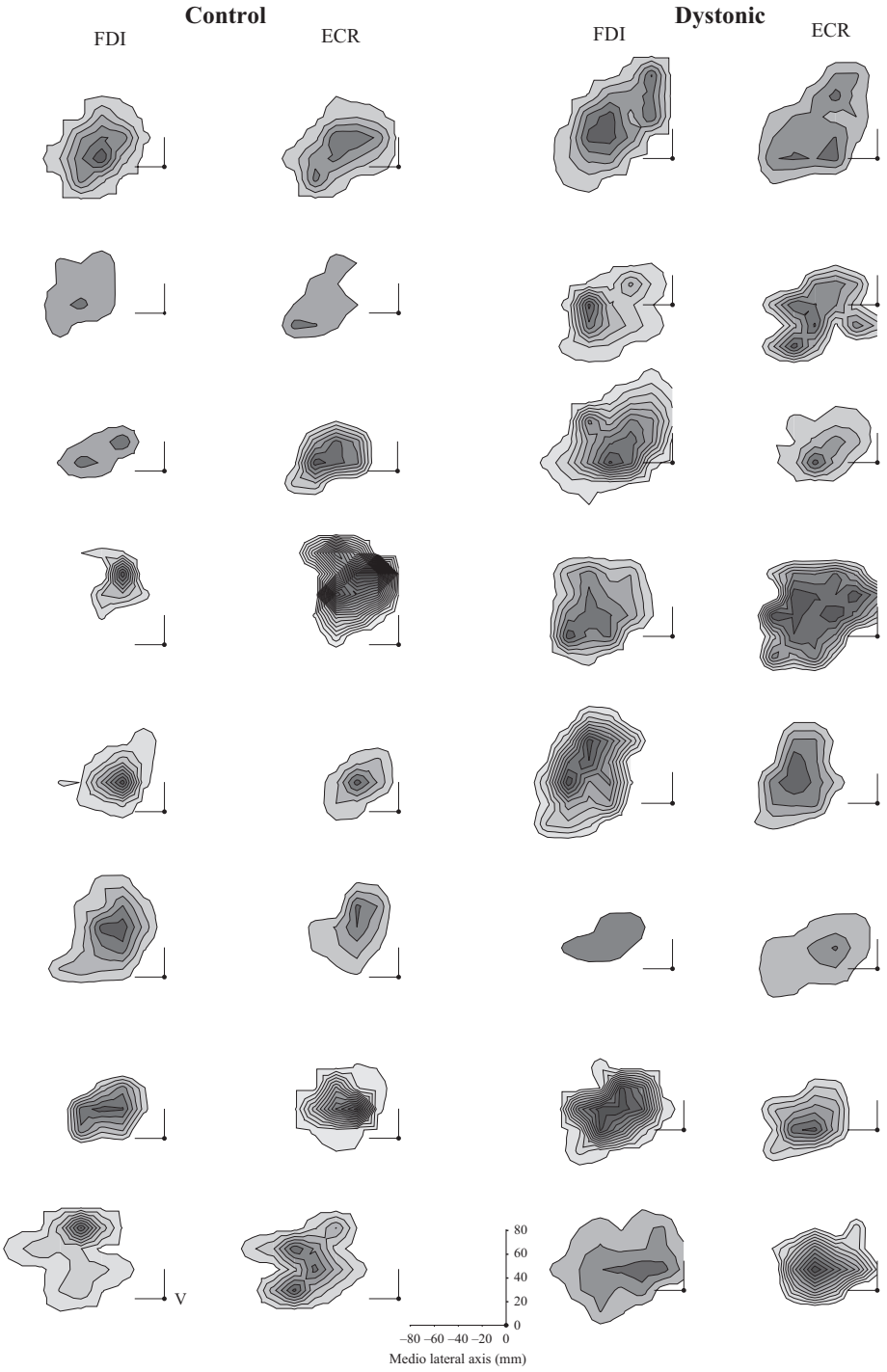

Figure 4 Level cards of ECR and FDI cortical muscle representations obtained for control subjects and the patients with dystonia. The successive contour lines represent steps of excitability of 200 μV for FDI and 80μV for ECR representations. This specific representation reveals that the cortical maps were patchy for the patients with dystonia compared with the more homogenous pattern observed for control subjects.

dystonic group ($t_7 = 2.69$ $P < 0.03$). The cortical representation areas obtained during Task 2 were larger than the cortical representation areas obtained during Task 1 (Table 2). Such a difference was not observed in the control group ($t_7 = 0.94$ $P < 0.38$).

ECR cortical representation areas

The ANOVA test (two factors: one within and one between) showed a simple group effect ($F_{1,14} = 7.00$ $P < 0.02$) and a simple task effect ($F_{1,14} = 5.50$

Table 2 Mean cortical representation areas (cm^2) of the three muscles measured in both groups and for both tasks. The FDI and ECR cortical map areas were significantly larger in the dystonic group than in the control group. Task 1: target muscle alone and Task 2: target muscle and MD co-activation

	Control		Dystonic	
	Task 1	Task 2	Task 1	Task 2
Areas (cm^2)				
FDI	24.6 ± 3.2	22.3 ± 3.1	45.7 ± 3.1	51.2 ± 3.0
ECR	26.5 ± 2.7	26.7 ± 3.0	36.5 ± 4.5	43.1 ± 4.1
MD		29.8 ± 4.7		38.5 ± 4.0

$P < 0.03$). An interaction appeared between the group and the task factors ($F_{1,14} = 5.07$ $P < 0.04$). The cortical representation areas of the ECR muscles were larger in the patients with dystonia than in the controls (Fig. 2, Table 2). A post hoc analysis showed that the ECR maps were different in the dystonic group for the two tasks ($t_7 = 2.76$ $P < 0.03$). The cortical representation of the ECR was larger during Task 2 when the MD was co-activated compared with the cortical representation obtained during Task 1. This effect was not observed in the control subjects, in whom the task did not influence the size of the ECR cortical representation areas ($t_7 = 0.09$ $P < 0.93$) (Table 2).

MD cortical representation areas

The ANOVA test (one between subject factor) did not show an effect of the group factor ($F_{1,14} = 1.97$ $P < 0.18$). The mean cortical representation areas for the dystonic and control groups were not significantly different (Fig. 2, Table 2).

Cortical representation overlaps

FDI-ECR overlap. The ANOVA test (two factors: one within and one between) for the size of the overlap between the FDI and ECR cortical representations showed an effect of the group factor ($F_{1,14} = 17.9$ $P < 0.001$) and an effect of the task factor ($F_{1,14} = 6.58$ $P < 0.02$). The overlapping area between the FDI and the ECR cortical representations was larger in the dystonic group than in the control group (Fig. 2). An interaction was observed between the group and the task factors ($F_{1,14} = 7.12$ $P < 0.02$). The post hoc tests showed that in the dystonic group, the size of the FDI-ECR overlapping area was larger in Task 2 when the MD was co-activated ($t_7 = 3.33$ $P < 0.01$) than in Task 1 (Table 3). This effect was not observed in the control group ($t_7 = 0.08$ $P < 0.94$).

Table 3 Mean overlapping areas of cortical representations of each pair of muscles in cm^2 (1) and the percentage of cortical representation of the ECR overlapped by FDI and MD cortical representation overlapped by the FDI and ECR muscles (2) for each group in the two tasks. The areas overlapped and the percentage of overlapping in FDI-ECR, FDI-MD and ECR-MD were significantly bigger in the patients with dystonia than in the controls

	Control		Dystonic	
	Task 1	Task 2	Task 1	Task 2
(1) Overlap (cm^2)				
FDI-ECR	19 ± 2.1	19 ± 2.9	34 ± 3.7	41 ± 3.8
FDI-MD	14 ± 2.0	13 ± 2	29 ± 3.3	31 ± 3.2
ECR-MD	15 ± 1.3	15 ± 2.1	27 ± 3.6	30 ± 3.7
(2) Overlap (%)				
ECR by FDI	74 ± 7	69 ± 5	94 ± 3	95 ± 2
MD by FDI	50 ± 6	46 ± 7	76 ± 4	81 ± 3
MD by ECR	57 ± 7	59 ± 9	69 ± 7	79 ± 5

In the dystonic group, 94% and 95% of the ECR cortical representation area was overlapped by the FDI cortical representation in Task 1 and Task 2 respectively (Table 3). This part of the ECR cortical representation that was overlapped by the FDI was smaller in the control group and represented 74% in Task 1 and 69% in Task 2. The ANOVA test showed a simple group effect ($F_{1,14} = 14.4$ $P < 0.002$), no task effect ($F_{1,14} = 0.245$ $P < 0.63$) and no interaction between group and task factors ($F_{1,14} = 0.55$). The percentage of the ECR cortical representation overlapped by the FDI cortical representation was greater for the dystonic group (Fig. 2).

FDI-MD overlap. The ANOVA test (two factors: one within and one between) for the size of the overlap between the FDI and MD cortical representations showed an effect of the group factor ($F_{1,14} = 20.0$ $P < 0.0005$). The overlapping areas between the FDI and the MD cortical representations were larger in the dystonic group than in the control group (Table 3). There was no task effect ($F_{1,14} = 0.073$ $P < 0.79$) and no interaction between the group and task factors ($F_{1,14} = 3.81$ $P < 0.07$).

The percentage of the MD cortical representation area overlapped by the FDI cortical representation was larger in the dystonic group than in the control group (Fig. 2). The ANOVA test showed a simple group effect ($F_{1,14} = 19.2$ $P < 0.0006$), no task effect ($F_{1,14} = 0.082$ $P < 0.78$) and no group or task interaction ($F_{1,14} = 1.91$ $P < 0.19$). In the dystonic group, the percentage of the MD cortical representation area that was overlapped by the FDI cortical representation area was 76% and 81% in Tasks 1 and 2 respectively (Table 3). In the control group, the area of the MD

cortical representation covered by the FDI cortical representation was smaller and represented 50% and 46% in Tasks 1 and 2 respectively.

ECR-MD overlap. The ANOVA test (two factors: one within and one between) showed an effect of the group factor ($F_{1,14} = 10.8$ $P < 0.005$). The overlapping areas of the ECR and the MD cortical representations were larger in the dystonic group than in the control group (Fig. 2, Table 3). We observed a task effect ($F_{1,14} = 6.37$ $P < 0.02$) and an interaction between the task and group factors ($F_{1,14} = 4.69$ $P < 0.05$). The post hoc analysis showed an increase in the overlapped area between the two cortical muscle representation areas when the MD was co-activated ($t_7 = 3.07$ $P < 0.02$). This effect was not observed in the control group ($t_7 = 0.28$ $P < 0.79$) (Table 3).

In the dystonic group, the MD cortical representation was covered by 69% and 79% of the ECR cortical representation in Tasks 1 and 2 respectively (Fig. 2). In the control group, the MD cortical representation area covered by the ECR cortical representation appeared to be smaller: 57% and 59% in Tasks 1 and 2 respectively (Table 3). The ANOVA test did not show a significant effect of the group factor, only a slight effect ($F_{1,14} = 2.36$ $P < 0.15$). The ANOVA test showed a simple task effect ($F_{1,14} = 6.22$ $P < 0.03$) and a slight group and task interaction effect ($F_{1,14} = 3.00$ $P < 0.10$). The post hoc analysis showed that the task effect on the percentage of overlap was attributed to the dystonic group, confirming the tendency towards a group effect and group and task interaction ($t_7 = 3.05$ $P < 0.019$ and $t_7 = 0.53$ $P < 0.61$ for the dystonic and control groups respectively).

Position of the centre of the cortical representation

The positions of the muscle CoG were different in the dystonic and the control groups. In the dystonic group, a grouping of the different muscle CoGs was revealed (Fig. 3). The normal lateral dispersion observed for the controls was not present in the dystonic group. The distances between the MD and ECR or FDI cortical muscle representation CoGs were reduced in the dystonic group compared with the control group (Fig. 3, Table 4). This difference was not observed for the distances between the FDI and ECR CoGs.

FDI-ECR CoG distances

The mean distances between the ECR and FDI CoGs were not different between the two groups or between the two tasks (Table 4). The ANOVA test (two factors: one within and one between) did not show an effect of the group or the task on the distance between the FDI and ECR CoGs (Group: $F_{1,14} = 0.02$ $P < 0.87$; Task: $F_{1,14} = 1.99$ $P < 0.18$; Group × Task: $F_{1,14} = 0.009$ $P < 0.92$).

Table 4 Mean distances in millimetre between the CoGs of the different muscles for each group in the two tasks. The distances between the FDI and MD CoGs and the distances between the ECR and MD CoGs were significantly smaller in the dystonic group than in the control group

	Control		Dystonic	
	Task 1	Task 2	Task 1	Task 2
Distances (mm)				
FDI-ECR	6.5 ± 0.9	5.6 ± 0.9	6.4 ± 1.1	5.4 ± 0.9
FDI-MD	20.1 ± 1	18.8 ± 2.8	14.3 ± 1.8	14.1 ± 1.2
ECR-MD	17.0 ± 1.1	16.1 ± 1.9	10.6 ± 1.3	11.5 ± 1.2

FDI-MD CoG distances

The mean distances between the FDI and MD CoGs were smaller in the dystonic group than in the control group (Table 4, Fig. 3). The ANOVA test (two factors: one within and one between) showed a simple group effect ($F_{1,14} = 5.40$ $P < 0.03$), no task effect ($F_{1,14} = 0.34$ $P < 0.57$) and no group or task interaction ($F_{1,14} = 0.24$ $P < 0.63$).

ECR-MD CoG distances

The ANOVA test (two factors: one within and one between) showed a simple group effect ($F_{1,14} = 8.65$ $P < 0.01$) but no task effect ($F_{1,14} = 0.000$ $P < 1.00$) and no group or task interaction ($F_{1,14} = 1.36$ $P < 0.26$). The mean distances between the ECR and MD CoGs were smaller in the dystonic group than in the control group in the two tasks (Fig. 3, Table 4).

Topographical maps of cortical muscle representations

Figure 4 shows the cortical representations of the FDI and ECR muscles on a level map. The topographical maps using contour lines provided specific information about the cortical location of the MEPs, their amplitudes and their spatial patterns, allowing a comparison of the cortical patterns between the control and dystonic groups. We used the contour lines joining iso-MEPs of equal amplitudes above the given level of the MEPs of minimal amplitudes. Each contour corresponded to an increase in the excitability level. The configuration of the contours revealed patchy patterns

in the dystonic group in contrast to the more homogeneous patterns in the control group. The dystonic representations showed several hills corresponding to higher excitability zones that were similarly present in the same zone for both muscle cortical representations.

Discussion

This study reveals a difference in the organization of cortical representation areas of the MD, ECR and FDI muscles between the patients with dystonia and normal subjects. In the patients with dystonia, (i) the ECR and FDI cortical representation areas were larger, (ii) the cortical representations of the three muscles largely overlapped, (iii) the CoGs of the ECR and FDI cortical muscle representations were closer to the MD muscle CoG and (iv) the level maps quantifying the cortical representations appeared to be patchier.

Several different approaches have supported the involvement of cortical centres in dystonia (Ridding *et al.* 1995, Chen *et al.* 1997, Di Lazzaro *et al.* 2009). Reorganization of the motor cortical representation of hand and forearm muscles (Byrnes *et al.* 1998, Thickbroom *et al.* 2003), modification of the representation of the hand in S1 (Byl *et al.* 1996, Blake *et al.* 2002) and the modification of cerebral activity have been observed (Ceballos-Baumann *et al.* 1995, De Vries *et al.* 2008). An abnormality in the inhibitory systems at the cortical level was most likely because no differences were seen in F-waves or in the ratio of H-reflex to maximum M-response (H/M ratio) in dystonia compared with control groups (Bour *et al.* 1991, Koelman *et al.* 1995, Sabbahi *et al.* 2003, Beck *et al.* 2008, Richardson *et al.* 2008). Moreover, paired associative stimulation (PAS), which were used to observe changes in the motor cortex, showed modifications of LTP- and LTD-like plasticity in WC (Quartarone *et al.* 2003, Weise *et al.* 2006). These results support the theory that the changes observed in our experiments could be ascribed to a cortical level, even though we could not exclude modifications at other levels of the cortico-spinal pathway. Noteworthy, our findings are reminiscent of those of Byl *et al.* (1997) in owl monkeys that were trained in a repetitive motor task for 12–25 weeks and developed signs of FHD. The authors found changes in the somatosensory cortex that resulted from the repetitive, highly articulated hand squeezing task. Motor changes were correlated with deterioration and dedifferentiation of the normally sharply segregated areas of the hand representation in area 3b. Further evidence for a role of abnormally synchronous sensory inputs in producing and maintaining dedifferentiation in the motor and somatosensory cortices in FHD has been provided by Schabrun *et al.* (2009). After 1 h of nonassociative stimulation of the abductor pollicis brevis (APB) and FDI muscles, a tendency to normalization of motor cortical maps in FHD subjects was observed. On the other hand, Quartarone *et al.* (2003) showed that PAS was able to induce increased cortical excitability even in muscles that were supplied by a different nerve (i.e. median nerve stimulation resulted in increased excitability for both APB and FDI). Although this effect occurred in normal subjects, it was more pronounced in the patients with dystonia. A possible contributory factor for this effect might be the decreased distance between the centres of gravity of FDI and APB cortical representation, as recorded in our subjects.

Functional links between proximal and distal muscles have been shown. Excitability of distal muscles controlling the elbow and the wrist was enhanced by co-activation of the proximal muscle (Dominici *et al.* 2005, Ginanneschi *et al.* 2005, Tyč & Boyadjian 2011). This modification could reveal a role of the M1 in muscle coordination during complex movements. In our experiments, the subjects executed a motor task that mobilized several joints and muscles. The simultaneous control of wrist, elbow and shoulder muscles involves common motor circuits. Such motor control could be sustained by a large overlap between the cortical representations of proximal and distal muscles performing the same movement (Tyč *et al.* 2005). Furthermore, the overlap between the cortical representations was shown to increase with training (Tyč & Boyadjian 2011). In monkeys, cortical microstimulation at one point can induce the simultaneous activation of two muscles (Nudo *et al.* 1996). It was observed that the total area of this dual response representation increased following digit training. In the patients with dystonia, we observed that the overlapping area for each pair of muscles was larger than in the controls and that this overlap increased during co-activation. As dystonic subjects display an expanded motor area as well as faulty surrounding inhibition (Beck *et al.* 2008), we assume that the mechanisms of proximo-distal facilitation might be exaggerated in these patients. The disorganization observed could be related to an abnormal plasticity (Bara-Jimenez *et al.* 1998, Elbert *et al.* 1998, Tinazzi *et al.* 2000, Quartarone *et al.* 2003, 2005) and impaired sensorimotor processing (Stinear & Byblow 2004, 2005, Weise *et al.* 2006). The changes in plasticity and processing of peripheral information could induce simultaneous activation of agonist and antagonist muscles and an overflow of muscles that was not involved in the tasks (Sheehy & Marsden 1982, Valls-Solé & Hallett 1995).

In the patients with dystonia, the proximo-distal facilitation observed involves the most distal, intrinsic

hand muscles, such as the FDI (Boyadjian *et al.* 2011). As muscle representations in M1 and S1 cortices are largely superimposed in the patients with dystonia, we hypothesize that such an overlap might be responsible for the excessive facilitation observed. The inadequate inhibitory processes described in the patients with dystonia may also play a role in over-facilitating networks dedicated to coordination (Nordstrom & Butler 2002, Stinear & Byblow 2004, Beck *et al.* 2008). During co-activation with MD muscles, the longer silent periods of FDI muscles that were observed in control subjects (Boyadjian *et al.* 2011) could reflect a task-specific change that failed to occur in the patients with dystonia. This 'abnormal' facilitation of the FDI during proximal muscle activation apparently could not be explained by impaired intracortical inhibition alone, because similar silent periods were observed in controls and the patients with dystonia during the task involving only the FDI muscle. This is in agreement with the fact that silent period durations were shorter during dystonic contractions than during voluntary contractions of similar strength performed with the same hand (Filipović *et al.* 1997). However, further studies with measurement of the degree of intracortical inhibition are necessary. Impaired inhibitory plasticity in focal dystonia has been described before even for muscles in limbs not affected by the dystonia (Allam *et al.* 2005, Weise *et al.* 2011).

The duality of 'positive' larger cortical representations observed in subjects after training and 'negative' larger cortical representations in the patients with dystonia is rather puzzling. One could assume that in the athletes, the cortical representations become re-organized and enlarged as a function of the specific motor task developed. In the patients with dystonia, the enlargement of cortical representations could be caused by unspecific and inappropriate global muscle activation.

In our experiment, the FDI muscle was similarly involved during the two tasks. The only change was the interaction between the joints controlling the arm position. Tinazzi *et al.* (2005) suggested that this task effect might depend on greater overflow activation of extraneous muscles while performing precision tasks. In our task, the 'extraneous' muscle, the MD, controlled a different joint than the FDI muscle. The excitability of one muscle could be modified by the activation of other muscles even though the muscle executed the same action. This operation was expressed differently in each group. The dynamic interaction between functional networks and their excitatory/inhibitory properties caused neuronal state patterns to produce different types of coordination during task performance.

The modification observed on the topographical maps could reveal a disorganization of the cortical muscle 'control'. Inhomogeneous maps with several hills of higher excitability were observed more frequently in the patients with dystonia. This observation could be interpreted as abnormal over-coupling of muscles and the common overflow activation.

A different spatial organization of the muscle representations in M1 was revealed in the patients with dystonia. This anomalous cortical organization has recently been reported for the FDI and APB muscle maps in the patients with FHD (Schabrun *et al.* 2009) and could be one of the factors responsible for the common, involuntary muscle activation patterns usually observed in the patients with dystonia. In addition, muscle activation strategies also seem to be abnormal in the patients with dystonia, as we recently reported in a study that demonstrated the abnormal facilitation of distal muscles when proximal muscles were activated in the patients with writer's cramp (Boyadjian *et al.* 2011). As a further confirmation of this abnormal interaction between cortical muscle representation areas, the present study also showed dynamic and acute changes in cortical muscle representation areas in tasks involving a proximal muscle in the patients with dystonia.

Not only did the cortical muscle representation areas increase in the FDI and ECR muscles of the patients with dystonia during the task involving a proximal muscle, but the degree of overlap of these areas also increased significantly; this might also increase the probability of the production of abnormal muscle activation patterns during voluntary movements in these patients. Further studies involving imaging techniques during the execution of proximo-distal tasks in FHD will improve our understanding of motor cortical dysfunction in these patients.

Conflict of interest

There are no conflicts of interest.

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