ACTA PHYSIOLOGICA

Acta Physiol 2011, **203**, 321–330

Writer's cramp: cortical excitability in tasks involving proximo-distal coordination

A. Boyadjian,[1] F. Tyč,[1] N. Allam[2,3] and J.P. Brasil-Neto[2]

1 *Laboratoire de Plasticité et Physio-Pathologie de la Motricité, CNRS UMR 6196, Marseille, France*

2 *Laboratório de Neurociências e Comportamento, Universidade de Brasilia (UnB), Brasilia, Brazil*

3 *Unidade de Distúrbios do Movimento, Hospital de Base do Distrito Federal, Brasília, Brazil*

Received 6 November 2010,
revision requested 10 January 2011,
final revision received 28 March 2011,
accepted 13 April 2011

Correspondence: F. Tyč, Laboratoire de Plasticité et Physio-Pathologie de la Motricité, CNRS UMR 6196, 31 Chemin Joseph Aiguier, 13402 Marseille, France.
E-mail: tycfr@free.fr

Abstract

Aim: The aim of this work was to analyse how writer's cramp patients coordinate each element of the proximal to distal upper arm muscle chain during voluntary movement.

Methods: Using transcranial magnetic stimulation, we have assessed motor cortex excitability properties in patients by recording motor-evoked potentials and silent periods in both the extensor carpi radialis (ECR) and the first dorsal interosseus muscles (FDI), activated either in isolation, or in conjunction with voluntary medial deltoid (MD) co-activation during performance of precise tasks. Ten dystonic patients and ten healthy controls were tested.

Results: In both test groups, the ECR muscle displayed a similar active motor threshold, but the excitability curves reached higher plateau values, when the proximal MD muscle was co-activated. In the dystonic group, the FDI muscle excitability curves reached higher plateau values when the MD was co-activated, whereas co-activation had no effect on the control group. In the control group, silent periods, in both the ECR and the FDI were longer when the MD was co-activated. This effect was not observed in the dystonic group.

Conclusion: In the dystonic group, facilitation of the FDI was observed during a task involving proximo-distal coordination. No differences in silent periods were observed when the muscle was activated alone. Our results suggest that such abnormal facilitation is not only an impairment of the central inhibitory mechanisms reported for dystonic patients, but, in addition, represents true abnormality in cortical muscle activation strategies.

Keywords dystonia, motor control, muscle coordination, silent period, transcranial magnetic stimulation.

Writer's cramp (WC) is a focal hand dystonia (FHD) of the fingers, hand and/or forearm, and is a task-specific form of primary dystonia. WC often occurs in patients with a long history of repetitive, stereotyped writing movements before the onset of dystonia. Repetitive movement seems to be one of the triggering factors in the onset of focal dystonias, as observed in other subjects exposed to repetitive motor activity, such as musicians, who spend many hours per day practising on a musical instrument and may develop the so-called musician's dystonia. However, Rosenkranz *et al.* (2005) have recently shown that this is not necessarily the only trigger for WC. In fact, many patients with WC have a history of average hand use.

In an animal model of FHD, Byl *et al.* (1996) observed in extensively trained monkeys unequivocal breakdown of the normally separate cortical representations of the fingers. Thus, dystonia may reflect a

maladaptative response of the brain to repetitive performance of stereotyped movements. In humans, imagery and somatosensory-evoked potentials have been used to show spatial de-differentiation of somatosensory representations (Bara-Jimenez *et al.* 1998, Elbert *et al.* 1998, Tinazzi *et al.* 2000). Weise *et al.* (2006) suggested that spatial de-differentiation and increased gain were intimately related to abnormalities of neuronal inhibition that have been identified previously both in motor and somatosensory systems. Studies using paired-pulse transcranial magnetic stimulation (TMS) and single pulse TMS have shown that both $GABA_A$ and $GABA_B$ inhibitory processes seem to be abnormal in FHD. Stinear & Byblow (2004) have suggested that FHD is associated with impaired modulation of intracortical inhibition (ICI) during performance of precise manual tasks, which may contribute to a lack of specificity in M1 output and the development of dystonic symptoms. These findings support the hypothesis that there is a temporal pattern of ICI and corticospinal excitability modulation during phasic muscle activation. In contrast, Nordstrom & Butler (2002) observed both ICI and intracortical facilitation (ICF) changes in healthy musicians. The authors found these changes rather puzzling, because ICI is considered to be useful in the production of fine-tuned individual finger muscle contractions. Quartarone *et al.* (2003) have shown an increase in motor evoked potentials (MEPs) with paired associative stimulation (PAS) when using a 25-ms inter-stimulus interval on healthy controls and WC patients. However, the MEP increases in WC patients substantially exceeded that observed in healthy controls. Furthermore, dystonic patients also exhibited an increase in MEP recorded from control muscles. Responses to PAS are thus exaggerated in WC patients and their spatial specificity is reduced.

Other TMS studies have shown that cortical representations of forearm muscles largely overlap (Wassermann *et al.* 1992, Wilson *et al.* 1993), and in particular, cortical representations of proximal and distal muscles simultaneously involved in coordinated movements (Tyč *et al.* 2005, Devanne *et al.* 2006, Tyč & Boyadjian 2011). Devanne *et al.* (2002) have shown that extensor carpi radialis (ECR) muscle MEPs are facilitated when this muscle is co-activated with the anterior deltoid. We observed that both the size of the cortical representation and the excitability of the brachioradialis muscle are enhanced during co-activation of a proximal muscle (Tyč & Boyadjian 2011). Notably, MEP facilitation was not observed in finger muscles during co-activation of proximal muscles (Devanne *et al.* 2002, Dominici *et al.* 2005). Although proximal muscles do not influence finger muscles involved in fine motor tasks, they do influence less distal muscles to reduce degrees of freedom and aid in hand stabilization (Schieber 2001, 2002, Schieber & Santello 2004). One might speculate that a pathological process that causes finger muscles to behave like more proximal muscles could significantly impair manual dexterity during proximal muscle activation. To test whether this could be the case in hand dystonias, we have studied proximo-distal facilitation mechanisms in patients with WC. As it has been shown that both ICI and ICF appear to be altered in WC, it is conceivable that faulty proximo-distal facilitation might also be present in these patients.

Part of this work has been previously presented in abstract form (Boyadjian *et al.* 2008).

Materials and methods

Subjects

Ten dystonic patients and ten healthy subjects, all right-handed, participated in this study (53 ± 15 and 56 ± 7 years respectively, $P = 0.58$). All subjects signed a free informed consent form for this study, which was approved by the local ethics committee. Healthy subjects did not report any neurological diseases. WC patients showed slight variability in clinical characteristics, such as dystonic posture of the wrist. The clinical features of the WC patients are shown in Table 1.

Electromyographic recordings

Electromyographic (EMG) recordings were obtained from pairs of surface electrodes (Delsys 2.1, Boston, MA, USA) placed on the skin, over the belly of the medial deltoid (MD), the ECR and the first dorsal interosseus (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. Electrodes were connected to the input of the EMG's pre-amplifier (Delsys 2.1, Boston, MA, USA). EMG signals were amplified (×1000) using high-pass filtering at 10 Hz and low-pass filtering at 1 kHz, before sampling at 2 kHz. Resulting EMG data was stored on a computer using a CED 1401 device and Spike2-4 software (CED, Cambridge, UK).

Transcranial magnetic stimulation protocol

Transcranial magnetic stimulation was delivered using a Magstim Pro® (Dantec S.A., Skovlunde, Denmark) magnetic stimulator with a figure-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 posterior to anterior direction of the current induced in the brain to ensure optimal trans-synaptical activation of the corticospinal pathways (Brasil-Neto *et al.* 1992, Sakai

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

Patient	Sex	Age (years)	Duration (years)	Sign during writing	Other symptoms	Score*
A	F	52	3	Slow writing. Extension of fourth and fifth fingers, ulnar deviation of wrist, overflow from lower to upper arm and shoulder muscles	Sign of dystonic posture in both arms, mirror movement	2
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, cocontraction of wrist muscles, overflow from lower to upper arm and shoulder muscles	Mild postural and action tremor bilaterally	3
G	M	32	3	Slow writing, increased pressure on pen, overflow from lower to upper arm and shoulder muscles	Writing and keyboard	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

F, female; M, male.
*Assessed using the Burke–Fahn–Marsden scale.

et al. 1997). The centre of the coil was placed over the site to be stimulated. The ECR muscle was slightly activated at a constant level of 15% of the maximal voluntary contraction. The active motor threshold (AMT) was determined by TMS at the scalp site where the lowest stimulation intensity induced a MEP with amplitude of at least 200 μV for at least two of five stimuli. Seven increasing stimulation intensities, relative to the ECR AMT, were applied on the optimal scalp position for ECR activation (0.9, 1.1, 1.3, 1.4, 1.5, 1.7, 1.9 × AMT), and EMG recordings were obtained from MD, ECR and FDI muscles. At each intensity level, four stimuli with intervals randomly ranging between 3 and 5 s were applied and four EMG recordings were stored on a computer for offline analysis.

Task

For each experimental condition, the subject grasped a handle mounted with a wire ring (Fig. 1). In both experimental conditions, during TMS the subject maintained the position of the handle fixed relative to a convoluted wire 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). MD EMG activity was displayed on the screen and checked constantly to ensure that MD remained silent all over Task 1. Data recording was interrupted if EMG activity was observed in MD and restarted only after complete relaxation of that muscle. The second condition (Task 2) involved the same task but used the whole upper arm, so that the proximal MD muscle was co-activated with ECR and FDI (Fig. 1). MD EMG activity was carefully checked during Task 2 to ensure that subjects maintained a constant activity. In Task 2, the distal muscles were activated with the same intensity as in Task 1. Subjects were instructed to adapt the arm position to maintain the 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 as indicated by traces on the screen in order to keep the activity level constant.

Data analysis

For subsequent analysis, we excluded two dystonic patients. The first, Subject E, did not exhibit a classic sigmoidal excitability curve, but instead displayed an erratic response shape. Subject E scored 9 on the

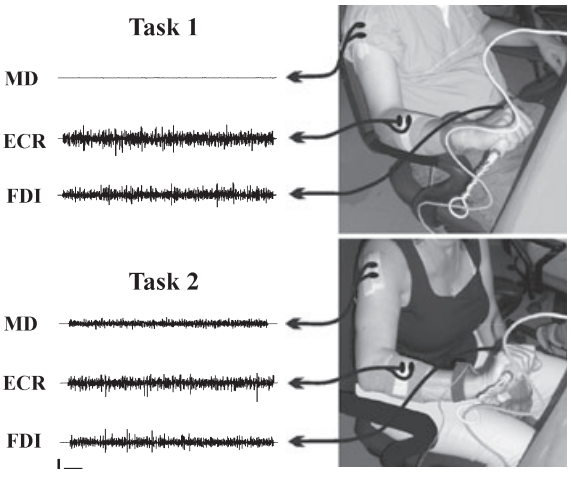

Figure 1 Photographs showing the position of the arm during Task 1 and Task 2 and the place of the electrodes on medial deltoid (MD), extensor carpi radialis (ECR) and first dorsal interosseus (FDI) muscles. The EMG traces obtained on the three muscles during the two tasks are shown. During Task 1 the elbow rests on an armrest with the MD inactive and during Task 2 the elbow is up with the MD co-activated. Calibration bars: horizontal = 1 s, vertical = 2 mV for FDI and 0.3 mV for MD and ECR.

dystonia scale, which was significantly different from the other WC subjects, who all scored between 2 and 4. The second, Subject J, did not perform the required tasks correctly. Therefore, eight subjects were included in the statistical analysis.

The peak-to-peak values of MEP amplitudes were measured from non-rectified EMG signals. For excitability curve fitting, based on MEP size, we used the following Boltzmann sigmoidal function, as reported in other studies (Devanne *et al.* 2002):

$$\mathrm{MEP} = \frac{\mathrm{MEP}_{\max}}{1 - \mathrm{e}^{-(S - S_{50}/k)}}, \quad (1)$$

where $\mathrm{MEP}_{\max}$ is the plateau level, S_{50} is the stimulus intensity required to obtain a 50% plateau value and k is the slope of the curve.

We performed a two-way ANOVA $S_8 < \mathrm{Group}_2 > \times \mathrm{Task}_2$ with repeated measures on Task factor on plateau values.

The silent period (SP) was defined as the time elapsed between the beginning of the MEP and the resumption of EMG activity (Wilson *et al.* 1993, Byrnes *et al.* 1998). We analysed the SP for each group for the two tasks with a partially repeated ANOVA, because no mathematical model fit the SP data. For some subjects, no SPs appeared for the first intensity of stimulation (1.1 × AMT) and therefore we excluded this intensity from the ANOVA. A three-way ANOVA was designed as $S_8 < \mathrm{Group}_2 > \times \mathrm{Task}_2 \times \mathrm{Intensities}_5$. We defined three independent factors: one between factors (Group) and two within factors (Tasks and Intensities). If no interaction appears, a two-way ANOVA was performed.

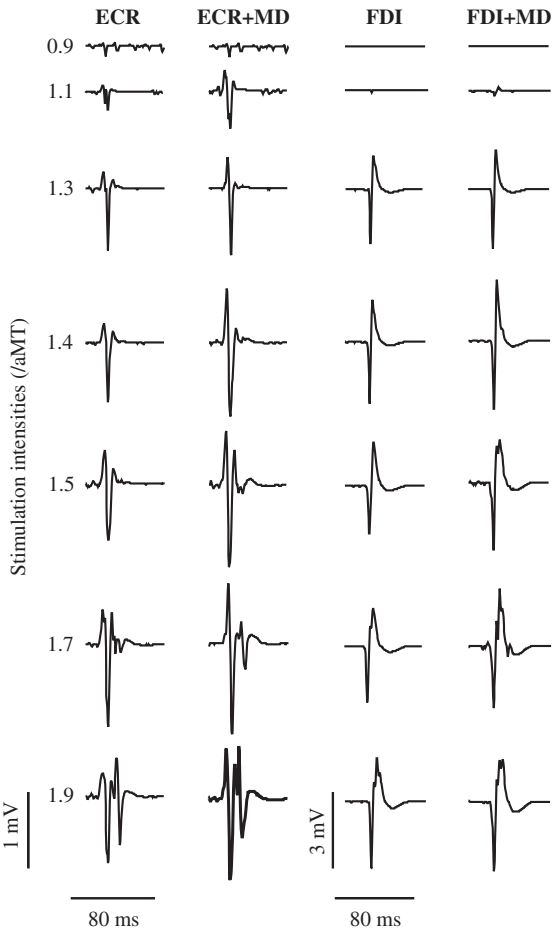

Figure 2 Mean motor-evoked potentials (MEPs) obtained for one dystonic patient at different transcranial magnetic stimulation (TMS) intensities from extensor carpi radialis (ECR) (left) and first dorsal interosseus (FDI) (right) muscles in the two conditions. Task 1: muscle activated alone (ECR, FDI); Task 2: muscle co-activated with medial deltoid (MD) (ECR+MD, FDI+MD). In both muscles, the MEP amplitudes were higher in Task 2 than in Task 1.

Results

Active motor threshold

An ANOVA on AMT did not show any simple effect of group factor or muscle factor. The AMT for the ECR was not different between dystonic patients and control subjects: 40 ± 5% and 38 ± 3.9% (mean ± SD), respectively, of the maximum stimulator output. No correlation was observed between age and AMT in either group.

The FDI AMT was calculated on the regression curves for each subject. In the dystonic group the FDI

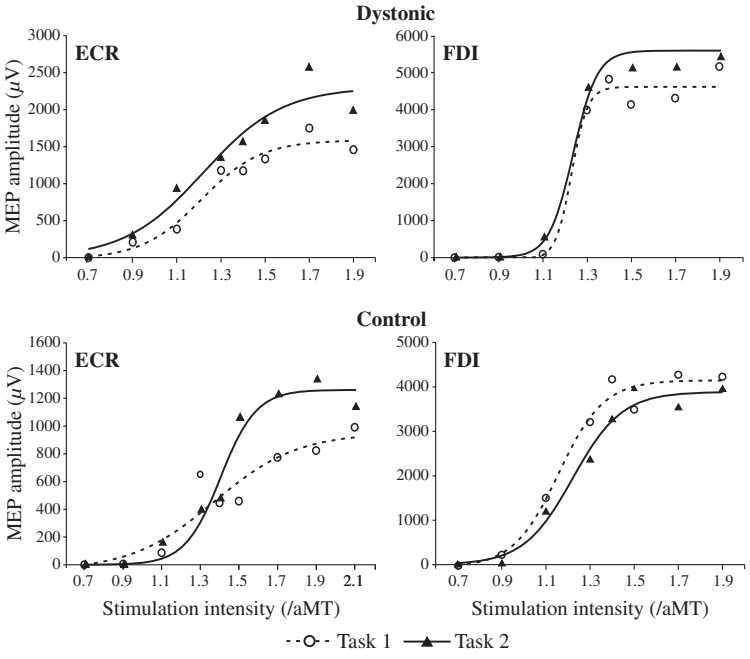

Figure 3 Mean motor-evoked potential (MEP) amplitude excitability curves as a function of stimulation intensity in a dystonic patient and a control subject. MEPs were recorded from extensor carpi radialis (ECR) and first dorsal interosseus (FDI) muscles during both conditions: Task 1: target muscle alone (empty symbols); Task 2: target muscle and medial deltoid (MD) co-activated (filled symbols). Note that MEP facilitation was present for both muscles in the dystonic patient in Task 2. In contrast, MEP facilitation was observed on the ECR but not on the FDI in the control subject. The two subjects selected for illustration are representative examples of the results obtained in the two groups.

AMT did not statistically differ between Task 1 and Task 2 – 37 ± 7% and 37 ± 12% (mean ± SD), respectively of the maximum stimulator output; neither in the control group, with a FDI AMT of 38 ± 9% and 42 ± 13% during Task 1 and Task 2 respectively. No statistical differences on the FDI AMT were observed between the two groups.

Extensor carpi radialis excitability properties

An example of MEP recordings obtained for one dystonic subject during completion of the two tasks is shown in Fig. 2. The ANOVA did not show a Group factor effect ($F(1,14) = 1.19$, $P < 0.29$). The ANOVA showed a simple effect due to the Task factor ($F(1,14) = 12.7$, $P < 0.003$). During Task 2, MEP amplitudes were higher compared with MEP amplitudes during Task 1 (Fig. 3). The ANOVA test failed to reveal a Group × Task interaction ($F(1,14) = 1.47$, $P < 0.26$). *Post hoc* test showed significant difference between Task 1 and Task 2 for the control group (unilateral, $t = 0.005$), and only a tendency for the dystonic group (unilateral, $t = 0.07$). The mean plateau values for the ECR were 929 μV for Task 1 and 1141 μV for Task 2 in the dystonic group, and 1146 μV and 1683 μV for Task 1 and Task 2, respectively, in the control group (Table 2).

First dorsal interosseus muscle excitability properties

The ANOVA did not show a Group effect, despite a tendency ($F(1,14) = 3.18$, $P < 0.09$). A Task factor effect appeared ($F(1,14) = 5.63$, $P < 0.03$) and a tendency to interaction between Group × Task ($F(1,14) = 3.54$ $P < 0.08$). *Posthoc* tests revealed a Task effect in the dystonic group (paired t, $P < 0.04$) and no Task effect in the control group. FDI MEP amplitudes were significantly higher in the dystonic group during Task 2 compared with Task 1: the mean plateau values were 3230 μV and 4409 μV for Task 1 and Task 2, respectively. In the control group, the mean plateau values were 2566 μV for Task 1 and 2637 μV for Task 2 (Table 2). As no interaction appeared, we did a one-way ANOVA on the MEP with one factor group. The ANOVA showed an effect of the Group factor ($F(1,30) = 5.57$ $P < 0.02$). The excitability of the FDI was higher in the dystonic group than in the control group. Fig. 3 shows excitability curves obtained during completion of the two tasks for one dystonic patient and one control subject. Interestingly, no correlation was observed between the clinical score for each dystonic subject and the observed facilitation during completion of Task 2.

Table 2 Sigmoidal regression (equation 1) plateau values (μV) obtained in ECR and FDI for each subject from the two groups and the two conditions. Task 1: target muscle alone (ECR, FDI); Task 2: target muscle and medial deltoid (MD) co-activated (ECR+MD, FDI+MD). The % column shows the coefficient of variation of the plateau value using Task 1 as a baseline

	Control							Dystonic					
	ECR			FDI				ECR			FDI		
Sub	Task 1	Task 2	%	Task 1	Task 2	%	Sub	Task 1	Task 2	%	Task 1	Task 2	%
1	1153	1390	21	318	273	−14	A	1447	1227	−15	820	4820	488
2	800	1577	97	3955	4264	8	B	338	605	79	3542	3550	0
3	1338	1388	4	3928	3610	−8	C	843	658	−22	1470	1430	−19
4	2076	1318	−37	4891	4691	−4	D	438	810	85	4471	4843	8
5	1301	1376	6	619	435	−30	E*	(576)	(517)	(−10)	(200)	*	
6	941	1260	34	4209	3888	−8	F	1397	1387	−1	3063	3321	8
7	814	1170	44	2156	3832	78	G	1439	2301	60	4672	5593	20
8	1205	2270	88	1408	860	−39	H	607	1077	77	4920	7090	44
9	1146	3913	241	1524	1334	−12	I	924	1069	16	2885	4632	61
10	690	1174	70	2657	3179	20	J*	(815)	(1146)	(42)	(3613)	*	
Mean	1146	1683		2566	2637		Mean	929	1141		3230	4409	

ECR, extensor carpi radialis; FDI, first dorsal interosseus muscles.
*Note that data from patients E and J in bracket have been excluded from statistical analysis.

Extensor carpi radialis silent period

The three-way ANOVA (S_8 < $Group_2$ > × $Task_2$ × $Intensities_5$) on SP showed a simple Group effect ($F_{(1,14)} = 9.07$, $P < 0.01$), a simple Task effect ($F_{(1,14)} = 12.1$, $P < 0.004$) and a simple stimulation Intensity effect ($F_{(4,56)} = 6.49$, $P < 0.0002$). For both groups, SPs were longer when the stimulation intensity was increased. A tendency to interaction was revealed between Group and Task ($F_{(1,14)} = 2.68$, $P < 0.12$). SPs were longer during completion of Task 2 than Task 1 (Fig. 4, Table 3). The *post hoc* tests showed a Task effect ($P < 0.01$) only in the control group, e.g. the paired comparisons at each stimulation intensity revealed longer SPs in Task 2 than in Task 1. In contrast, in the dystonic group, no task effect was observed (Fig. 4), and paired comparisons in *post hoc* tests failed to show any difference between SPs in Task 2 and Task 1. As no interaction appeared between Task and Group a two-way ANOVA to test the task effect between the groups (S_8 < $Group_2$ > × $Intensities_5$) was performed. In Task 1 the SPs were shorter for the dystonic group than control ($F_{(1,7)} = 12.5$, $P < 0.01$). In Task 2, a group effect was observed ($F_{(1,14)} = 10.5$, $P < 0.005$); SPs were longer in the control group than in the dystonic group.

First dorsal interosseus muscles silent period

The three-way ANOVA (S_8 < $Group_2$ > × $Task_2$ × $Intensities_5$) revealed no Group effect on FDI SPs ($F_{(1,14)} = 0.28$ $P < 0.60$), a simple Task factor effect ($F_{(1,14)} = 5.64$, $P < 0.03$) and a simple Intensity factor effect ($F_{(4,56)} = 26.1$, $P < 0.0001$). SPs were longer in both groups when stimulation intensities were increased (Fig. 4). As no interaction was observed between Group × Task we did a repeated ANOVA (S_8 × $Task_2$ × $Intensities_5$) to test the task effect in each group. For the dystonic group, no Task effect was found ($F_{(1,7)} = 0.981$, $P < 0.35$). There was no difference between SP durations for the two tasks. For the control group, a simple Task effect was revealed ($F_{(1,7)} = 6.68$, $P < 0.03$). The SPs in Task 2 were longer than in Task 1 (Fig. 4, Table 3).

Discussion

This study revealed proximo-distal facilitation of all muscles tested in dystonic patients. The cortical networks involved in the control of FDI and ECR muscles were more excitable when proximal MD muscle was voluntarily co-activated along with these target muscles. Although no difference was observed in AMT between the two groups, cortical excitability was higher in dystonic patients compared with control subjects when their proximal muscle was co-activated. In both groups we observed an increase in ECR excitability when the proximal muscle was activated, as evidenced by the ECR MEP increase recorded upon MD co-activation during completion of the experimental task.

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).

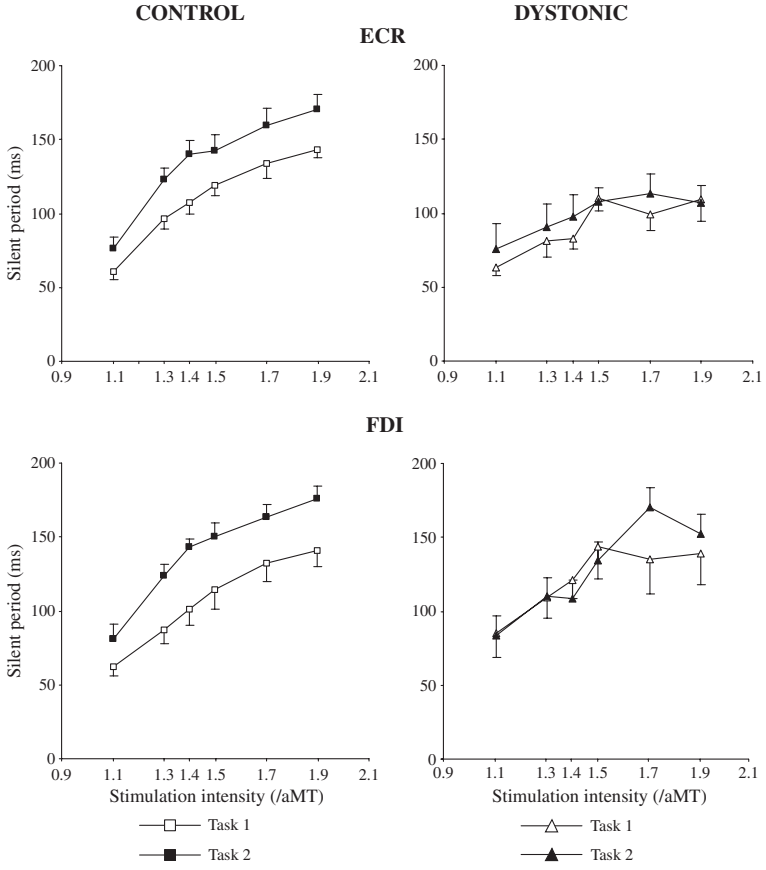

Figure 4 Mean silent period (SP) durations as a function of stimulation intensity for the two groups. SPs were measured on extensor carpi radialis (ECR) and first dorsal interosseus (FDI) muscles under both conditions: Task 1: target muscle alone (empty symbols); Task 2: target muscle co-activated with medial deltoid (MD) (filled symbols). Vertical bars represent the SEM. In the two groups, a stimulation intensity effect was observed. Note that, for the control group, there was a task effect for SP duration in both muscles: SPs were longer in Task 2 than in Task 1. For the dystonic group, there was no task effect on SP duration in both muscles.

Table 3 Mean silent period (SP) duration (ms ± SEM) measured from ECR and FDI muscles at each stimulation intensity level for control and dystonic groups. SP was measured for the two conditions. Task 1: target muscle alone (ECR, FDI); Task 2: target muscle and medial deltoid (MD) co-activated (ECR+MD, FDI+MD)

	ECR				FDI			
	Control		Dystonic		Control		Dystonic	
Stim	Task 1	Task 2	Task 1	Task 2	Task 1	Task 2	Task 1	Task 2
1.1	61 ± 5	76 ± 8	64 ± 5	76 ± 17	62 ± 6	81 ± 10	85 ± 16	83 ± 13
1.3	97 ± 7	123 ± 9	82 ± 11	90 ± 16	87 ± 9	124 ± 7	109 ± 14	110 ± 15
1.4	107 ± 8	140 ± 11	83 ± 7	97 ± 15	101 ± 11	143 ± 5	121 ± 12	108 ± 14
1.5	119 ± 7	143 ± 12	110 ± 9	108 ± 9	114 ± 13	150 ± 9	143 ± 22	134 ± 19
1.7	134 ± 11	159 ± 10	99 ± 11	113 ± 14	132 ± 12	163 ± 9	135 ± 23	171 ± 22
1.9	143 ± 5	170 ± 9	109 ± 15	107 ± 12	141 ± 11	176 ± 8	139 ± 21	153 ± 14

Stim, stimulation intensity/active motor threshold; ECR, extensor carpi radialis; FDI, first dorsal interosseus muscles.

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) as well as modification of cerebral activity have been observed (Ceballos-Baumann *et al.* 1995, De Vries *et al.* 2008).

Abnormality in the inhibitory systems was attributed most likely to a cortical level as no differences were seen in F-waves and in ratio of H-reflex to maximum M-response (H/M ratio) in dystonia compared to control (Bour *et al.* 1991, Koelman *et al.* 1995, Sabbahi *et al.* 2003, Beck *et al.* 2008, Richardson *et al.* 2008). Moreover, PAS protocols, which were used to observe changes in the motor cortex, have shown modification of long-term potentiation-like plasticity and long-term depression-like plasticity in WC (Quartarone *et al.* 2003, Weise *et al.* 2006). These results support that the changes observed in our experiments could be ascribed to a cortical level even though we cannot exclude modifications at other levels of the cortico-spinal pathway.

Our subjects were required to execute a motor task that mobilizes several joints and muscles, and to select a solution from abundance/redundance known as the 'control of degrees of freedom' (Bernstein 1967). In turn, these degrees of freedom are reduced in coordinated movements, when motor networks are functionally coupled to operate different muscles. Similar studies suggest that functional links between elements of the neuromotor system, organized into task-specific flexible structural units, are at the root of motor control (Gelfand & Tsetlin 1967, Latash *et al.* 2003). Assuming that simultaneous control of wrist, elbow and shoulder muscles involves common motor circuits, their coordinated operation should be controlled in an integrated manner. TMS studies have proposed that such motor control could be sustained by large overlap between the cortical representations of proximal and distal muscles performing the same movement (Tyč *et al.* 2005, Tyč & Boyadjian 2011). In monkeys, Nudo *et al.* (1996) have shown that cortical microstimulation at one point can induce simultaneous activation of two muscles. They observed that this dual response representation increased in total area following digit training. As dystonic subjects display an expanded motor area as well as faulty surround inhibition (Beck *et al.* 2008), we assume that normal mechanisms of proximo-distal facilitation might be exaggerated in these patients. In support of this assumption, the proximo-distal facilitation observed in the dystonic group involves the most distal intrinsic hand muscles, such as the FDI. Moreover, this facilitation was not observed in control subjects. As muscle representations in M1 and in S1 cortices are largely superimposed in dystonic patients, we hypothesize that such overlap might be responsible for the observed excessive facilitation. Inadequate inhibitory processes described in dystonics may also play a role in over facilitating networks dedicated to coordination (Stinear & Byblow 2004, Beck *et al.* 2008).

In both groups, SP durations increased with an increase in stimulation intensity. In ECR muscles, each stimulation intensity level evoked shorter SPs in the dystonic patients than in control subjects, confirming the observation by Rona *et al.* (1998). We did not find a difference between groups in SP duration for the FDI when activated alone, as described previously (Byrnes *et al.* 1998, Quartarone *et al.* 2003, Stinear & Byblow 2005). In our experiment, no differences in inhibitory processes were observed between the two groups, whereas cortical excitability properties were different.

During co-activation with MD, SP durations observed in the FDI were longer in control subjects. This could reflect a task-specific change in the control subjects, which failed to occur in dystonics. This 'abnormal' facilitation of the FDI, during proximal muscle activation, could not be explained by only impaired intracortical inhibition, because similar SPs were observed in the two groups during the task involving only the FDI muscle.

In our experiment, the FDI muscle was similarly involved during the two tasks. The only change was the interaction between joints controlling arm position. Tinazzi *et al.* (2005) have suggested that this task effect might depend on greater overflow activation of extraneous muscles while performing precision tasks involving different coordinated movements. 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 its action remained the same. These dynamical neural properties were expressed differently in each group. The dynamic interaction of functional networks and excitatory/inhibitory properties operated neuronal state patterns to produce different coordinations during task performance.

Our study shows that dystonia in WC patients is not simply a problem of changes in the cortical excitability properties of individual muscles. Abnormal proximo-distal facilitation and modifications of the balance between excitatory and inhibitory processes are factors which should be considered together before recommending different rehabilitation protocols, e.g. therapeutic repetitive TMS (rTMS) or botulin toxin injections (Byrnes *et al.* 1998, Allam *et al.* 2005, Schabrun *et al.* 2008). To the best of our knowledge, this is the first report of a more subtle abnormality, abnormal proximo-distal facilitation, in distal hand muscle motor control in dystonic patients.

Conflict of interest

There are no conflicts of interest.

References

Allam, N., Fonte-Boa, P.M., Tomaz, C.A. & Brasil-Neto, J.P. 2005. Lack of effect of botulinum toxin on cortical excitability in patients with cranial dystonia. *Clin Neuropharmacol* **28**, 1–5.

Bara-Jimenez, W., Catalan, M.J., Hallett, M. & Gerloff, C. 1998. Abnormal somatosensory homunculus in dystonia of the hand. *Ann Neurol* **44**, 828–831.

Beck, S., Pirio Richardson, S., Shamim, E.A., Dang, N., Schubert, M. & Hallett, M. 2008. Short intracortical and surround inhibition are selectively reduced during movement initiation in focal hand dystonia. *J Neurosci* **28**, 10363–10369.

Bernstein, N. 1967. *The Coordination and Regulation of Movements*. Pergamon, London.

Bour, L.J., Ongerboer de Visser, B.W., Koelman, J.H.T.M., van Bruggen, G.J. & Speelman, J.D. 1991. Soleus H-reflex tests in spasticity and dystonia; a computerized analysis. *J Electromyogr Kinesiol* **1**, 9–19.

Boyadjian, A., Tyč, F., Allam, N. & Brasil-Neto, J.P. 2008. Joint coordination studied by TMS in focal hand dystonia. 3rd International Conference on TMS and tDCS, Göttingen, Germany, October 1–4, 2008.

Brasil-Neto, J.P., Cohen, L.G., Panizza, M., Nilsson, J., Roth, B.J. & Hallett, M. 1992. Optimal focal transcranial magnetic activation of the human motor cortex: effects of coil orientation, shape of the induced current pulse, and stimulus intensity. *J Clin Neurophysiol* **9**, 132–136.

Byl, N.N., Merzenich, M.M. & Jenkins, W.M. 1996. A primate genesis model of focal dystonia and repetitive strain injury: I. Learning-induced dedifferentiation of the representation of the hand in the primary somatosensory cortex in adult monkeys. *Neurology* **47**, 508–520.

Byrnes, M.L., Thickbroom, G.W., Wilson, S.A., Sacco, P., Shipman, J.M., Stell, R. & Mastaglia, F.L. 1998. The corticomotor representation of upper limb muscles in writer's cramp and changes following botulinum toxin injection. *Brain* **121**, 977–988.

Ceballos-Baumann, A.O., Passingham, R.E., Warner, T., Playford, E.D., Marsden, C.D. & Brooks, D.J. 1995. Overactive prefrontal and underactive motor cortical areas in idiopathic dystonia. *Ann Neurol* **37**, 363–372.

Chen, R., Wassermann, E.M., Caños, M. & Hallett, M. 1997. Impaired inhibition in writer's cramp during voluntary muscle activation. *Neurology* **49**, 1054–1059.

De Vries, P.M., Johnson, K.A., de Jong, B.M., Gieteling, E.W., Bohning, D.E., George, M.S. & Leenders, K.L. 2008. Changed patterns of cerebral activation related to clinically normal hand movement in cervical dystonia. *Clin Neuro Neurosurg* **110**, 120–128.

Devanne, H., Cohen, L.G., Kouchtir-Devanne, N. & Capaday, C. 2002. Integrated motor cortical control of task-related muscles during pointing in humans. *J Neurophysiol* **87**, 3006–3017.

Devanne, H., Cassim, F., Ethier, C., Brizzi, L., Thevenon, A. & Capaday, C. 2006. The comparable size and overlapping nature of upper limb distal and proximal muscle representations in the human motor cortex. *Eur J Neurosci* **23**, 2467–2476.

Di Lazzaro, V., Oliviero, A., Profice, P., Dileone, M., Pilato, F., Insola, A., Della Marca, G., Tonali, P.A. & Mazzone, P. 2009. Reduced cerebral cortex inhibition in dystonia: direct evidence in humans. *Clin Neurophysiol* **120**, 834–839.

Dominici, F., Popa, T., Ginanneschi, F., Mazzocchio, R. & Rossi, A. 2005. Cortico-motoneuronal output to intrinsic hand muscles is differentially influenced by static changes in shoulder positions. *Exp Brain Res* **164**, 500–504.

Elbert, T., Candia, V., Altenmuller, E., Rau, H., Sterr, A., Rockstroh, B., Pantev, C. & Taub, E. 1998. Alteration of digital representations in somatosensory cortex in focal hand dystonia. *Neuroreport* **16**, 3571–3575.

Gelfand, I.M. & Tsetlin, M.L. 1967. On mathematical modeling of the mechanisms of the central nervous system. In: I.M. Gelfand, V.S. Gurfinkel, S.V. Fomin & M.L. Tsetlin (eds). *Models of the Structural-Functional Organization of Certain Biological Systems*, pp. 9–26. MIT Press, Cambridge, MA, USA.

Koelman, J.H., Willemse, R.B., Bour, L.J., Hilgevoord, A.A., Speelman, J.D. & Ongerboer de Visser, B.W. 1995. Soleus H-reflex tests in dystonia. *Mov Disord* **10**, 44–50.

Latash, M.L., Yarrow, K. & Rothwell, J.C. 2003. Changes in finger coordination and responses to single pulse TMS of motor cortex during practice of a multifinger force production task. *Exp Brain Res* **151**, 60–71.

Nordstrom, M.A. & Butler, S.L. 2002. Reduced intracortical inhibition and facilitation of corticospinal neurons in musicians. *Exp Brain Res* **144**, 336–342.

Nudo, R.J., Miliken, G.W., Jenkins, W.M. & Merzenich, M.M. 1996. Use dependent alterations of movement representations in primary motor cortex of adult squirrel monkeys. *J Neurosci* **16**, 785–807.

Quartarone, A., Bagnato, S., Rizzo, V., Siebner, H.R., Dattola, V., Scalfari, A., Morgante, F., Battaglia, F., Romano, M. & Girlanda, P. 2003. Abnormal associative plasticity of the human motor cortex in writer's cramp. *Brain* **126**, 2586–2596.

Richardson, S.P., Bliem, B., Lomarev, M., Shamim, E., Dang, N. & Hallett, M. 2008. Changes in short afferent inhibition during phasic movement in focal dystonia. *Muscle Nerve* **37**, 358–363.

Ridding, M.C., Sheean, G., Rothwell, J.C., Inzelberg, R. & Kujirai, T. 1995. Changes in the balance between motor cortical excitation and inhibition in focal, task specific dystonia. *J Neurol Neurosurg Psychiatry* **59**, 493–498.

Rona, S., Berardelli, A., Vacca, L., Inghilleri, M. & Manfredi, M. 1998. Alterations of motor cortical inhibition in patients with dystonia. *Mov Disord* **13**, 118–124.

Rosenkranz, K., Williamon, A., Butler, K., Cordivari, C., Lees, A.J. & Rothwell, J.C. 2005. Pathophysiological differences between musician's dystonia and writer's cramp. *Brain* **128**, 918–931.

Sabbahi, M., Etnyrea, B., Al-Jawayeda, I. & Jankovicc, J. 2003. Soleus H-reflex measures in patients with focal and generalized dystonia. *Clin Neurophysiol* **114**, 288–294.

Sakai, K., Ugawa, Y., Terao, Y., Hanajima, R., Furubayashi, T. & Kanazawa, I. 1997. Preferential activation of different I waves by transcranial magnetic stimulation with a figure-of-eight-shaped coil. *Exp Brain Res* **113**, 24–32.

Schabrun, S.M., Stinear, C.M., Byblow, W.D. & Ridding, M.C. 2008. Normalizing motor cortex representations in focal hand dystonia. *Cereb Cortex* **19**, 1968–1977.

Schieber, M.H. 2001. Constraints on somatotopic organization in the primary motor cortex. *J Neurophysiol* **86**, 2125–2143.

Schieber, M.H. 2002. Motor cortex and the distributed anatomy of finger movements. *Adv Exp Med Biol* **508**, 411–416.

Schieber, M.H. & Santello, M. 2004. Hand function: peripheral and central constraints on performance. *J Appl Physiol* **96**, 2293–2300.

Stinear, C.M. & Byblow, W.D. 2004. Impaired modulation of intracortical inhibition in focal hand dystonia. *Cereb Cortex* **14**, 555–561.

Stinear, C.M. & Byblow, W.D. 2005. Task-dependent modulation of silent period duration in focal hand dystonia. *Mov Disord* **20**, 1143–1151.

Thickbroom, G.W., Byrnes, M.L., Stell, R. & Mastaglia, F.L. 2003. Reversible reorganisation of the motor cortical representation of the hand in cervical dystonia. *Mov Disord* **18**, 395–402.

Tinazzi, M., Priori, A., Bertolasi, L., Frasson, E., Mauguiere, F. & Fiaschi, A. 2000. Abnormal central integration of dual somatosensory input in dystonia. Evidence for sensory overflow. *Brain* **123**, 42–50.

Tinazzi, M., Farina, S., Edwards, M., Moretto, G., Restivo, D., Fiaschi, A. & Berardelli, A. 2005. Task-specific impairment of motor cortical excitation and inhibition in patients with writer's cramp. *Neurosci Lett* **11**, 378.

Tyč, F. & Boyadjian, A. 2011. Plasticity of motor cortex induced by coordination and training. *Clin Neurophysiol* **122**, 153–162.

Tyč, F., Boyadjian, A. & Devanne, H. 2005. Motor cortex plasticity induced by extensive training revealed by transcranial magnetic stimulation in human. *Eur J Neurosci* **21**, 259–266.

Wassermann, E.M., McShane, L.M., Hallett, M. & Cohen, L. 1992. Non-invasive mapping of muscle representations in human motor cortex. *Electroencephalogr Clin Neurophysiol* **85**, 1–8.

Weise, D., Schramm, A., Stefan, K., Wolters, A., Reiners, K., Naumann, M. & Classen, J. 2006. The two sides of associative plasticity in writer's cramp. *Brain* **129**, 2709–2721.

Wilson, S.A., Thickbroom, G.W. & Mastaglia, F.L. 1993. Transcranial magnetic stimulation mapping of the motor cortex in normal subjects. *J Neurol Sci* **118**, 134–144.