

Subthreshold low-frequency repetitive transcranial magnetic stimulation over the premotor cortex modulates writer's cramp

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Summary

Writer's cramp, or focal hand dystonia, is characterized by involuntary coactivation of antagonist or unnecessary muscles while writing or performing other tasks. Although the mechanism underlying this muscle overactivation is unknown, recent studies of changes in cerebral blood flow during writing have demonstrated a reduction in the activation of the primary motor cortex (MC) and hyperactivity of parts of the frontal non-primary motor areas. Therefore, any measures that decrease the activities of non-primary motor areas such as the premotor cortex (PMC) and the supplementary motor area (SMA) might improve dystonic symptoms. To explore this possibility, we studied nine patients with writer's cramp and seven age-matched control subjects, using subthreshold low-frequency (0.2 Hz) repetitive transcranial magnetic stimulation (rTMS), which exerts an inhibitory action on the cortex. Previous studies have demonstrated shortened

cortical silent periods in dystonia, suggesting deficient cortical inhibition in the MC. We compared the silent periods and computer-assisted ratings of handwriting before and after rTMS applied to the MC, SMA or PMC. We also used the sham coil for control runs. Stimulation of the PMC but not the MC significantly improved the rating of handwriting (mean tracking error from the target, $P = 0.004$; pen pressure, $P = 0.01$) and prolonged the silent period ($P = 0.02$) in the patient group. rTMS over the other sites or using a sham coil in the patient group or trials in the control group revealed no physiological or clinical changes. This increased susceptibility of the PMC in dystonia suggests that the lack of inhibition in the MC is secondary to the hyperactivity of PMC neurons. Inhibition of the PMC using rTMS could provide a therapeutic measure of writer's cramp.

Keywords: dystonia; rTMS; premotor cortex; motor cortex; silent period

Abbreviations: aMT = active motor threshold; EMG = electromyography; FDI = first dorsal interosseous; MC = motor cortex; MEP = motor evoked potential; PMC = premotor cortex; rMT = resting motor threshold; rTMS = repetitive transcranial magnetic stimulation; Sham = sham coil stimulation; SMA = supplementary motor area; TMS = transcranial magnetic stimulation

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Introduction

Dystonia is defined as a syndrome of sustained muscle contractions, frequently causing twisting and repetitive

movements or abnormal postures (Fahn, 1988). Writer's cramp is a task-specific form of focal dystonia (Sheehy and

Marsden, 1982); at the clinical onset it usually affects only writing (simple writer's cramp), but later it also involves other tasks (dystonic writer's cramp or hand dystonia). The task specificity is seen in other types of dystonia, such as pianist's cramp, typist's cramp and other cramps, collectively known as occupational cramps, which develop in workers who perform repetitive and demanding tasks. Abnormal muscle contractions are stereotyped in each patient, and are characterized by co-contractions of agonists and antagonists or contractions of unnecessary muscles nearby (overflow). Some patients report symptomatic relief in writing when they touch a part of the affected hand with their other hand (sensory trick). Although these features are also observed to one degree or another in other forms of dystonia, writer's cramp provides a unique opportunity to explore the motor control mechanism underlying specific tasks, mainly because of the ease of manipulating sensory input and motor output in the upper limb. Pathophysiological changes have been implicated at various levels of the nervous system, including the motor cortex (MC) (Ridding *et al.*, 1995), the sensory cortex (Byl *et al.*, 1996; Tinazzi *et al.*, 2000) or sensorimotor integration (Murase *et al.*, 2000; Abbruzzese *et al.*, 2001), the basal ganglia (Bhatia and Marsden, 1994; Vitek *et al.*, 1999, 2000), the thalamus (Lee and Marsden, 1994; Lenz *et al.*, 1999) and the spinal cord (Nakashima *et al.*, 1989). A common abnormality found in these structures is reduced inhibition (Berardelli *et al.*, 1998), which may result in excessive muscle contractions and overflow.

In the study using $H_2^{15}O$ PET (Ceballos-Baumann *et al.*, 1997), patients with writer's cramp exhibited hyperactivity of the lateral premotor cortex (PMC) during writing. Ibanez and colleagues, using $H_2^{15}O$ PET during writing, reported deficient activation of the PMC and decreased correlation between the premotor cortical regions and the putamen (Ibanez *et al.*, 1999). Based on this study, they suggested that a dysfunction of the PMC network in these patients arises because of the primary deficit in the basal ganglia. Indeed, focal lesions in the basal ganglia and their connections to the motor cortices and the thalamus (motor loop) were found in patients with dystonia affecting the contralateral limbs (hemidystonia; Marsden *et al.*, 1985). It is, however, unknown how the basal ganglia affect the excitability of the primary and non-primary motor areas in dystonia. Non-primary motor areas such as the supplementary motor area (SMA) and the PMC receive two to eight times as many thalamocortical projections as the MC (Porter and Lemon, 1993). Therefore, studies on the interactions between the primary and non-primary motor areas might provide important clues that would clarify the pathophysiology of dystonia.

Transcranial magnetic stimulation (TMS) has been applied not only to the MC but also to the PMC (Schluter *et al.*, 1998; Gerschlag *et al.*, 2001; Munchau *et al.*, 2002) and the SMA (Muri *et al.*, 1994, 1995; Cunnington *et al.*, 1996). This method has been useful for studying the functional connectivity between different cortical areas. In addition, repetitive TMS (rTMS) can produce excitatory or inhibitory effects

depending on the intensity and frequency of stimulation. High-frequency stimulation (>5 Hz) increases cortical excitability, and low-frequency rTMS (<1 Hz) decreases it for an extended period of time (Chen *et al.*, 1997; Chen, 2000). Using this inhibitory effect, low-frequency rTMS (1 Hz) over the MC was applied to patients with writer's cramp (Siebner *et al.*, 1999). This procedure improved their clinical symptoms and corrected the increased excitability of the MC, as evidenced by the paired-pulse TMS technique and cortical silent periods.

To address the question of the interaction between the motor cortices in writer's cramp, we first developed a sensitive and objective measure of handwriting using a digitizer pen connected to a computer. We then applied low-frequency (0.2 Hz) subthreshold rTMS, which is known to inhibit cortical function, over the MC, PMC and SMA in patients with writer's cramp. The motor output was analysed with the aid of computer-based scores for evaluating handwriting. The design was a single-blinded study in which the subjects were unaware of the site of stimulation in each session.

Subjects and methods

Subjects

We studied nine right-handed patients (three female and six male, mean age \pm SD, 38 ± 8 years) (Table 1). All of them had symptoms pertaining to their ability to write and in other tasks (dystonic writer's cramp) in at least one hand. Six patients switched from the right to the left hand for holding a pen after onset of the condition, and at the time of this study all of them also had dystonia in the left upper limb, which was simple in five and dystonic in one. The average duration of the condition was 7.7 years. Patients 2, 3, 4 and 8 were taking no medication. The other patients had been taking medications at least for 2 years, and the medication was not changed for this study. All patients except patients 2 and 3 had a history of treatment with local lidocaine injection (muscle afferent block; Kaji *et al.*, 1995a), and all studies were carried out 1 week or longer after the last injection. Patient 6 had a history of botulinum toxin injection 7 years prior to this trial and had not been treated since. The inclusion criteria for the present study were as follows: (i) adult onset with no family history; (ii) no response to l-dopa; (iii) proximal muscles affected in addition to distal muscles; and (iv) able to hold a pen and write the three selected Chinese characters (Fig. 2). Patients with drug-induced dystonia or tardive dystonia were excluded from the study.

All patients had rTMS at three stimulation sites (MC, PMC and SMA) or with a sham coil over the PMC, in random order, and each separated by 1 week from the other. Seven healthy volunteers participated in a group comparison (two females and five males, age 36 ± 6 years). None of the subjects was given any information about the stimulation site in any of the experiments.

All subjects gave their informed written consent to participation in the study, which was approved by the Institutional

Table 1 Clinical profiles of the patients with writer's cramp

Case no.	Age (years), sex	Disease course (years)	Type	Clinical characteristics
1	26, M	10	R: dystonic L: dystonic	I, II and III finger flexion, wrist tremor, shoulder elevation All finger extension, wrist flexion
2	31, M	2	R: dystonic L: simple	IV and V finger flexion, wrist flexion, shoulder elevation II finger elevation, wrist extension, forearm supination
3	33, M	3	R: dystonic L: simple	I, II and III finger flexion, wrist pronation, shoulder elevation Wrist flexion (sometimes)
4	33, F	7	R: dystonic L: simple	IV and V finger flexion, wrist flexion, shoulder elevation IV and V finger flexion (sometimes)
5	41, M	4	R: dystonic L: simple	I, II and III finger flexion, wrist flexion, shoulder elevation Abnormal sensation without abnormal contraction (sometimes)
6	41, M	15	R: dystonic L: simple	I, II and III finger extension, wrist extension, forearm supination, shoulder elevation I, II and III finger flexion, wrist flexion
7	42, F	14	R: dystonic	All finger flexion, wrist flexion, shoulder elevation
8	47, F	4	R: dystonic	I, II and III finger flexion, wrist flexion and pronation, shoulder elevation
9	51, M	10	R: dystonic	I, II and III finger flexion, wrist flexion, shoulder elevation

R = right; L = left; M = male; F = female.

Review Board, Tokushima University School of Medicine and the Committee of Medical Ethics, Graduate School of Medicine, Kyoto University.

Recording of motor evoked potentials (MEPs)

The subjects were seated comfortably in a reclining chair and were told to relax. They were instructed to keep their eyes open and fix their attention on a target placed 1 m in front of them. MEPs were recorded with silver chloride disc electrodes, 1 cm in diameter, placed over the muscle belly and tendon of the right first dorsal interosseous (FDI). Electromyography (EMG) signals were amplified, analogue-filtered (50 Hz to 1 kHz) by an amplifier (Neuropack MEP; Nihon Koden, Tokyo, Japan), and acquired at a sampling rate of 5 kHz. Data were stored for off-line analysis. During the experiments, EMG activity was monitored continuously with visual and auditory feedback.

rTMS

We applied rTMS at 0.2 Hz, and 250 stimuli were delivered to each of the three cortical areas: the MC, PMC and SMA. The frequency of 0.2 Hz was chosen for two reasons. First, other studies have reported suppressive effects on cortical excitability at frequencies as low as 0.3 Hz (Cincotta *et al.*, 2003). In addition, stimulation at this frequency can be performed with a monophasic stimulator pulse rather than the biphasic pulse used in many other rTMS studies. Recent work has suggested that monophasic rTMS may be more effective than biphasic rTMS (Antal *et al.*, 2002).

MC stimulation

A figure-of-eight stimulation coil (outside diameter of one half-coil, 8.7 cm) connected to a Magstim 200 stimulator (2.2 tesla at coil surface when connected to the Magstim

200; Magstim, Whitland, UK) was placed over the area 2 cm anterior to a point that was 3.5 cm lateral to Cz (international 10–20 system), with the handle pointing backwards and parallel to the midline. The intensity of stimulation was increased from 30% of the maximum output of the stimulator in 5% steps until an MEP became just visible. The coil was then moved in 0.5 cm steps in four directions (medial, lateral, posterior and anterior) until the maximum MEP was found. The coil was then removed and the position was marked on the subject's scalp (hotspot). The resting motor threshold (rMT) was defined by decreasing or increasing the stimulus intensity in 1% steps, as the minimum intensity (as a percentage of the maximal stimulator output) that produced MEPs greater than 50 V. The stimuli were applied over the hotspot with the figure-of-eight coil at the stimulus intensity set to 85% of the rMT.

PMC stimulation

The stimulation site for the PMC was determined to be 2 cm anterior and 1 cm medial to the hotspot (Schluter *et al.*, 1998). This was estimated from the dorsal PMC established in a previous PET study (Fink *et al.*, 1997). Stimuli were applied with the figure-of-eight coil, and the stimulus intensity was set to 85% of rMT for the MC.

Additional sham coil stimulation (Sham) was performed over the PMC using a figure-of-eight sham coil (a placebo system; Magstim; outside diameter of one half-coil, 8.7 cm, the same shape as that of a true coil) connected to the Magstim 200 stimulator (0.44 tesla at coil surface when connected to the Magstim 200).

SMA stimulation

The SMA stimulation site was determined to be 2 cm anterior to the leg representation of the MC (Muri *et al.*, 1994; Fink

et al., 1997). Because of its relatively deep location, we used a double-cone coil (Magstim; outside diameter of one half-coil, 12.5 cm; angle of the two surfaces, 95°) connected to the Magstim 200 stimulator (1.4 tesla at coil surface when connected to the Magstim 200). We first searched for the leg motor area during active contraction of the leg muscles. Subjects were asked to continuously contract the right tibialis anterior (TA) muscle with a constant force of approximately 50% of the maximum EMG output, which was fed back to the subject by sound. The double-cone coil was then placed 2 cm anterior to Cz. The stimulus intensity was increased from 20% of the maximum output in 5% steps until an MEP larger than 200 V became just visible. The coil was then moved in 0.5 cm steps in the posterior or anterior direction and, if needed, medially or laterally, until the point of maximum MEP was reached (hotspot for the leg). The active motor threshold (aMT) was then determined, and was defined as the lowest stimulus intensity at which five out of 10 consecutive stimuli elicited reliable MEP larger than 200 V. We applied rTMS over the SMA on the sagittal midline (Muri *et al.*, 1994; Cunnington *et al.*, 1996; Fink *et al.*, 1997) at the intensity of the aMT for the leg motor area (see above). We confirmed that no MEP was elicited in any of 10 consecutive stimulation trials. The reason why the stimulus intensity given for SMA was determined relative to aMT, rather than rMT, for pre-motor stimulation, was that rMT is often proportionately much higher than aMT in leg muscles compared to the difference of these thresholds in hand muscles. Since aMT in the hand is approximately 85% of rMT, we chose the aMT for stimulation of the SMA in order not to overestimate the intensity required.

TMS for the evaluation of MC excitability

As a measure of cortical excitability, we examined rMT, MEP amplitude and the cortical silent period before and after rTMS. MEP amplitudes were measured by averaging four successive responses evoked at the intensity of 120% rMT.

For recording cortical silent periods, subjects were asked to perform a maximum voluntary abduction of the right index finger with the aid of auditory EMG feedback. The rectified EMG amplitude from the FDI muscle was displayed on a monitor, 40–60% of the maximum rectified EMG amplitude being marked by the examiner. After subjects had learned how to maintain the level of contraction, single-pulse TMS was given 3–5 s after the start of contraction, which lasted more than 10 s. To avoid spreading of the stimuli to the PMC, they were applied at a minimum level, at an intensity of 20% of the maximum stimulator output above rMT. Stimuli were delivered at frequencies of no more than once every 20 s to avoid fatigue or habituation. Four single stimuli were delivered, and responses were added when the intertrial variability of the silent period was more than 40 ms, as assessed by on-line inspection. EMG traces were rectified off-line, and the mean length of the silent period was determined on the basis of measurements from each individual trial. The silent period

was measured from the onset of the MEP to the recurrence of at least 50% of the EMG background activity, which was determined during the 50-ms epoch preceding the stimulation.

Evaluation of handwriting

Handwriting was assessed using a system designed for measuring voluntary movements of the upper limbs (Human Technology Laboratory, Japan), which consisted of a pressure-sensitive digitizing tablet with a crystal display and personal computer-based movement analysis software. First, a target (1 cm in diameter) appeared on the crystal display and subjects were asked to track it with a stylus pen, which drew a circle 4 cm in diameter three times at a fixed speed (42°/s). The position data of the tip of the stylus pen on the digitizing tablet were stored on a personal computer at a sampling frequency of 40 Hz. The spatial resolution was 0.05 mm, and the distance (positioning lag component) and phase difference (delay time component) between the target and tip were calculated continuously. The axial pressure at the tip (pen pressure component) was also measured with 256 steps up to the maximum value of 204 N (2 kg). For each trial, 1028 points were subjected to off-line analysis.

Subjects were asked to avoid contact between their elbows and the desk while they were being examined. Data from those subjects who could not meet this condition were excluded from the analysis. In a preliminary study, we found that the distance from the target (tracking error) and the pen pressure were most significantly abnormal in patients with writer's cramp. We therefore focused on these two parameters in the present study.

We also asked the patients to report the subjective rating of their symptoms after rTMS into five grades: improvement; slight improvement; no change; slight deterioration; and deterioration.

Statistical analysis

The data were analysed in two stages. First, we estimated whether there was a site-specific effect in the patient group. Secondly, we evaluated whether, if significant, this effect was any different to what we saw in normal subjects.

All data were first tested for a normal distribution (Shapiro–Wilk test of normality) and for homogeneity of variance (Levene's test). Since the tracking error and silent period were normally distributed data, a two-way analysis of variance (ANOVA) with repeated-measures design was performed for the patient data using the following two factors: stimulation site (PMC versus MC versus SMA versus Sham) and intervention (before and after rTMS); for group comparisons we used the two factors of group (patient versus control group) and intervention (before and after rTMS) in the same stimulation site. For *post hoc* pairwise comparisons, the Newman–Keuls procedure was performed for the patient

data, and paired or unpaired two-way *t* statistics for group differences.

The Shapiro–Wilk test of normality and Levene’s test indicated the writing pressure was better analysed as non-parametric data. We therefore used the Friedman two-way ANOVA by ranks to access the patient data using the main effect of site (PMC versus MC versus SMA versus Sham) and intervention (before and after rTMS), and for group comparison using the two factors of group (patient versus control group) and intervention (before and after rTMS). *Post hoc* pairwise comparisons were carried out using the Wilcoxon signed rank test with correction for multiple comparisons for the data within the patient group. A *post hoc* pairwise comparison for group comparisons was performed using the Mann–Whitney *U* test or the Wilcoxon signed rank test.

Unless stated otherwise, results are expressed as the mean \pm SD. Results were considered significant at a level of $P < 0.05$. All data were analysed with the aid of the commercial statistical program Statistica (StatSoft, USA).

Results

Clinical evaluation

Subjective rating revealed that the most effective site of stimulation was the PMC. Improvement or slight improvement was reported in 78% (seven out of nine patients) for stimulation of the PMC, in 37% (three out of nine patients) for stimulation of the MC, 56% (five out of nine patients) for stimulation of the SMA, and 11% (one out of nine patients) for sham stimulation. Surface EMG recordings made during writing revealed that the co-contraction and overflow decreased after rTMS over the PMC in patient 5 (Fig. 1). Figure 2 shows traces of handwriting made by patient 5 (male, 41 years old; Table 1) and by a healthy control (male, 47 years old) before and after rTMS over the PMC. Normal control subjects reported no subjective changes in handwriting after rTMS over any site.

Effect of TMS site in patients

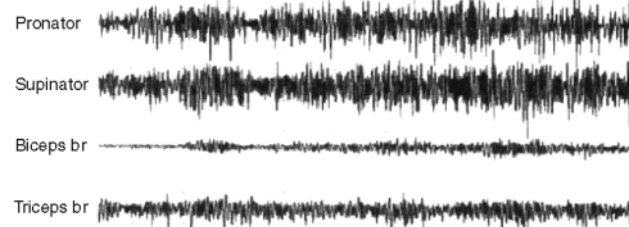
Computer-aided ratings

For quantitative measurements of tracking error, an initial two-way ANOVA with a repeated measures design was made using (i) stimulation sites (PMC versus MC versus SMA versus Sham) and (ii) intervention (before and after rTMS) as components. The site \times intervention interaction was significant [$F(3,24) = 3.85$, $P = 0.02$], as was the component of rTMS intervention [$F(1,8) = 6.85$, $P = 0.03$]. *Post hoc* analysis revealed a significant change for PMC stimulation after rTMS compared with the other stimulation sites and rTMS intervention ($P < 0.05$). Tracking error significantly changed after rTMS over the PMC in patients (paired *t* test, $P = 0.004$; Fig. 3 and Table 2).

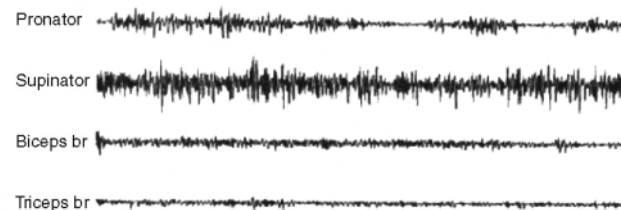
The pen-pressure data were found to be non-parametric, so Friedman two-way ANOVA by ranks was performed using

PATIENT

BEFORE



AFTER



HEALTHY VOLUNTEER

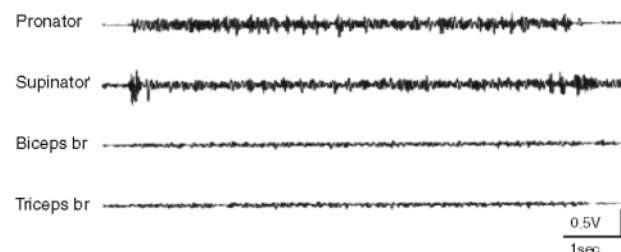


Fig. 1 Surface EMG of patient 5 (a 41-year-old male) recorded while writing Chinese characters before and after rTMS over the PMC. At the bottom is shown corresponding data from a healthy volunteer (a 44-year-old female). Co-contraction and overflow decreased after rTMS over the PMC.

(i) stimulation sites (PMC versus MC versus SMA versus sham) and (ii) intervention (before and after rTMS) as components. The site \times intervention interaction was significant [$\chi^2(7) = 14.7$, $P < 0.04$]. *Post hoc* analysis revealed a significant decrease for stimulation of the PMC after rTMS compared with before stimulation ($P = 0.01$), although there was no difference in effect for stimulation site after rTMS. Pen pressure was significantly changed after rTMS over the PMC in patients (Wilcoxon signed rank test, $P = 0.01$; Table 2).

MC excitability

rMT and MEP amplitudes did not change significantly after stimulation at any site in the patients; no group differences were seen. Statistical analysis revealed significant prolongation of the TMS-induced silent period after rTMS over the PMC in the patient group (Figs 4 and 5). The initial two-way ANOVA with a repeated measures design was made using (i) stimulation sites (PMC versus MC versus SMA versus

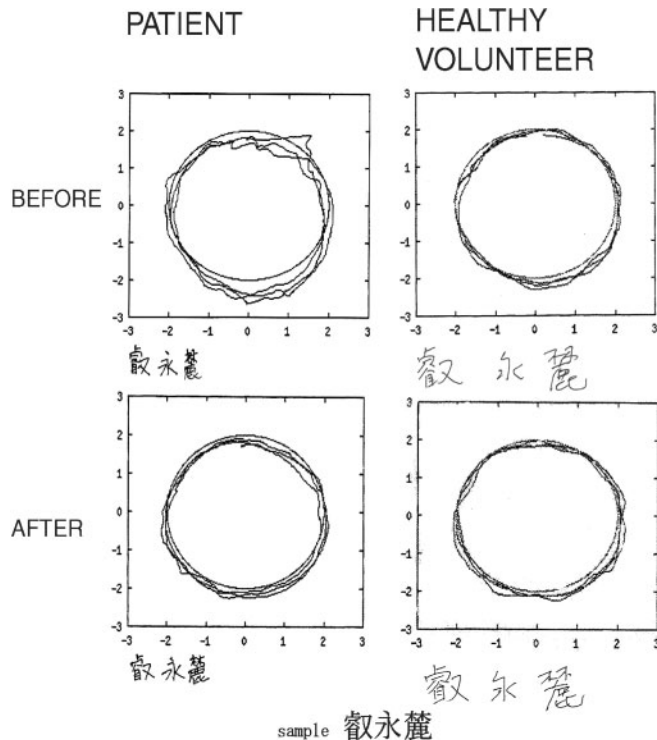


Fig. 2 Handwriting of patient 5 (a 41-year-old male) and a healthy control (a 47-year-old male) before and after rTMS over the PMC. The mean tracking error from the target recorded by computer-assisted ratings of handwriting improved after rTMS in the patient. The speed of writing the three Chinese characters improved. It took 142 s for the patient to complete this task before rTMS, and he needed to touch the right wrist with his left hand (sensory trick). After rTMS, it took him 98 s and required no touching. On the contrary, it took 22 s for the normal subject to complete the task, and no clear change was observed after rTMS.

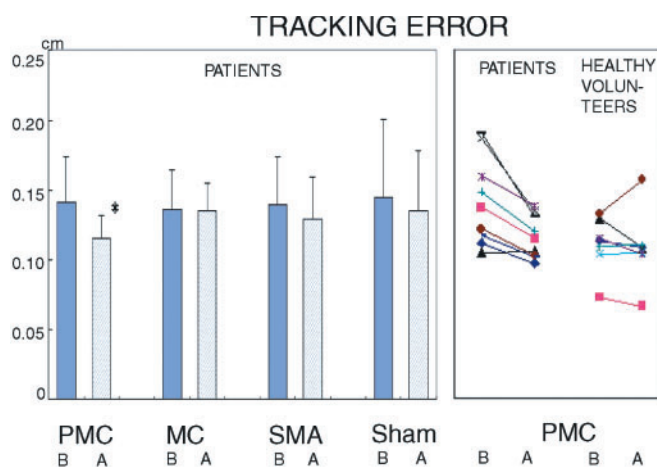


Fig. 3 Mean tracking error from the target before (dark column, B) and after (light column, A) rTMS over the PMC, MC and SMA, or with a sham coil (Sham) in the patient group (left panel), and individual data before (B) and after (A) rTMS over the PMC in patients and healthy volunteers (right panel). In the patient group, tracking error was significantly reduced after PMC stimulation.

Sham) and (ii) intervention (before and after rTMS) as components. The sites \times intervention interaction was significant [$F(3,24) = 3.40$, $P = 0.03$], although there was no significant effect of component. *Post hoc* analysis revealed significant changes for stimulation of the PMC after rTMS compared with the other stimulation sites, and rTMS intervention ($P < 0.05$). The silent period was significantly changed after rTMS over the PMC in patients (paired t test, $P = 0.02$; Fig. 5 and Table 2). By contrast, after rTMS we did not find any significant change in the amplitudes of MEPs preceding the silent period compared with those before rTMS (Fig. 4).

Comparison of patients and healthy volunteers with PMC stimulation

Computer-aided ratings

The group comparison of tracking errors for rTMS over the PMC between patient and control groups using two-way ANOVA with a repeated measures design revealed that the group \times intervention interaction was significant [$F(1,14) = 7.09$, $P = 0.02$], as was the component of rTMS intervention [$F(1,14) = 10.2$, $P = 0.01$]. *Post hoc* analysis revealed a significant difference between two groups before rTMS over the PMC ($P = 0.04$), and this difference disappeared after rTMS.

The group comparison of pen pressure for rTMS over the PMC between the patient and control groups revealed that the group \times intervention interaction was significant [$\chi^2(1) = 6.25$, $P < 0.02$]. *Post hoc* analysis revealed a significant difference between two groups before rTMS over the PMC ($P = 0.01$).

MC excitability

The group comparison of the TMS-induced silent period for rTMS over PMC between the patient and control groups using two-way ANOVA with a repeated measures design revealed that the group \times intervention interaction was significant [$F(1,14) = 5.59$, $P = 0.03$], and *post hoc* analysis revealed a significant effect of rTMS over the PMC in patients ($P = 0.02$). No correlation was observed between the silent period and either tracking error or pen pressure.

Discussion

The present study showed that low-frequency subthreshold rTMS over the PMC significantly prolonged cortical silent periods, and decreased tracking error and pen pressure in patients with writer's cramp. Although the study design was not double-blind, the results obtained here cannot be explained by any placebo effects but reflect the physiological action of rTMS that is specific to the stimulation sites, for the following two reasons. First, rTMS over the other areas or with a sham coil over the PMC produced no significant changes in these parameters in the patient group. Secondly, the patients were not informed of the different sites or of the significance of different stimulation sites for any of the

Table 2 Tracking error, pen pressure and silent period in each group for each stimulation site in patients and normal subjects

Component	Group	Site	Before rTMS	After rTMS	Before – after <i>P</i> value
Tracking error (cm)	Patient	PMC	0.142 ± 0.032	0.116 ± 0.016	0.004*
		MC	0.137 ± 0.028	0.135 ± 0.020	n.s.
		SMA	0.140 ± 0.034	0.130 ± 0.030	n.s.
		Sham	0.144 ± 0.056	0.135 ± 0.043	n.s.
	Normal	PMC	0.110 ± 0.020	0.108 ± 0.026	n.s.
		MC	0.117 ± 0.021	0.110 ± 0.020	n.s.
		SMA	0.114 ± 0.021	0.107 ± 0.015	n.s.
		Sham	0.114 ± 0.021	0.107 ± 0.015	n.s.
Pen pressure (N)	Patient	PMC	98.7 ± 37.9	84.8 ± 26.0	0.01†
		MC	102.8 ± 38.2	89.6 ± 33.5	n.s.
		SMA	100.7 ± 46.3	72.0 ± 10.3	n.s.
		Sham	82.4 ± 33.1	81.1 ± 34.0	n.s.
	Normal	PMC	65.6 ± 11.8	64.1 ± 7.3	n.s.
		MC	80.8 ± 23.6	76.1 ± 22.7	n.s.
		SMA	74.6 ± 23.5	79.8 ± 30.0	n.s.
		Sham	108.8 ± 36.9	113.1 ± 31.0	n.s.
Silent period (ms)	Patient	PMC	111.2 ± 33.5	126.7 ± 42.0	0.02*
		MC	116.4 ± 39.7	111.9 ± 38.5	n.s.
		SMA	111.4 ± 39.4	112.8 ± 42.4	n.s.
		Sham	108.8 ± 36.9	113.1 ± 31.0	n.s.
	Normal	PMC	125.7 ± 42.1	121.8 ± 37.8	n.s.
		MC	103.7 ± 18.2	95.3 ± 18.3	n.s.
		SMA	118.0 ± 25.7	119.2 ± 34.6	n.s.
		Sham	108.8 ± 36.9	113.1 ± 31.0	n.s.

Values are mean ± SD. n.s., not significant. *Paired *t* test; †Wilcoxon signed rank test.

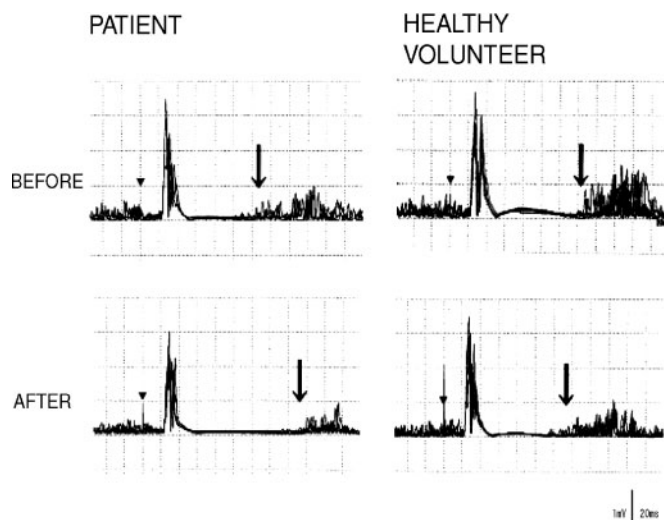


Fig. 4 TMS-induced silent period before and after rTMS over the PMC in patient 5 (a 41-year-old male) and a healthy volunteer (a 47-year-old male). Rectified EMG signals from four trials are superimposed in each panel. The triangle indicates the stimulus artefact caused by the test stimulation, and the arrow shows the average end-point of the silent period. Although the two subjects exhibited almost the same active MEP amplitude, the silent period became longer after rTMS only in the patient.

experimental sessions. In addition, objective measures, such as TMS-induced silent periods and computer-aided ratings of handwriting, could not be biased by the examiner knowing the stimulation site.

Given the proximity of PMC and MC and the size of the stimulating area of the coil used in these experiments, it is

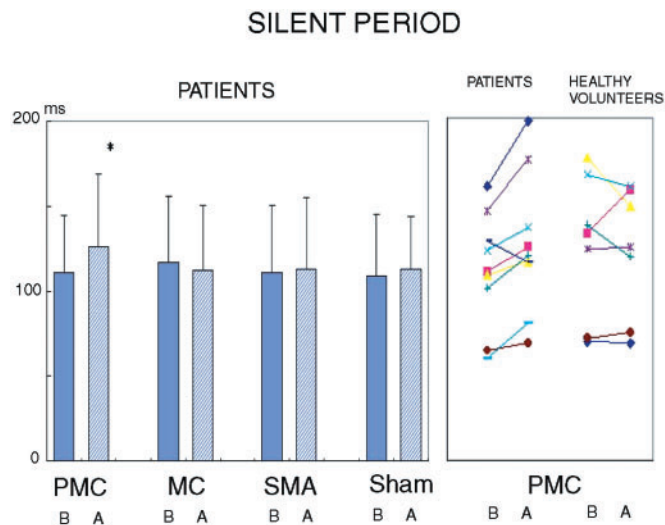


Fig. 5 Silent period before (dark column, B) and after (light column, A) rTMS over the PMC, MC and SMA, or with a sham coil (Sham) in the patient group (left panel), and individual data before (B) and after (A) rTMS over the PMC in patients and healthy volunteers (right panel). The silent period after PMC stimulation increased significantly in the patient group.

possible that MC may have been stimulated in addition to the PMC. If this were the case, the improvement observed in the present study might have been due to MC rather than PMC stimulation. This possibility is unlikely, however, because stimulation over the MC did not change the silent period or handwriting.

It is also possible that the stimulus could have spread to the SMA. Other workers have shown that rTMS over SMA at

intensities lower than those we used in the present experiments [Serrien and colleagues (Serrien *et al.*, 2002) used 90% aMT] can lead to behavioural changes consistent with activation of this structure. However, since direct rTMS over SMA in the present study did not lead to any effects, we conclude that this is an unlikely possibility. This does not mean that rTMS over SMA at a higher intensity would not produce effects on patients' symptoms. Indeed, given the positive effects that Serrien and colleagues observed after stimulation of SMA at a lower intensity (Serrien *et al.*, 2002), it is highly likely that our higher-intensity stimulation activated at least some part of the SMA. Nevertheless, since we do not know the relative thresholds for TMS activation of SMA or PMC, we do acknowledge that SMA stimulation might have been relatively less powerful, given its larger distance from the coil. Further experiments would be needed to address this point. We conclude that, under the circumstances of our present experiments, the effect of rTMS over PMC was specific and not due to the spread of SMA.

Thus, clinical improvement by functional inhibition of the PMC using rTMS, as shown in this study, suggests that hypersensitivity of the PMC is either directly or indirectly involved in the pathophysiology of writer's cramp or hand dystonia.

Impaired inhibition in the motor cortices in dystonia

An increasing number of studies using brain stimulation have reported hyperexcitability or loss of inhibition of the MC in dystonia (Berardelli *et al.*, 1998). The relationship between MEP amplitudes and background muscle activity was studied (Mavroudakis *et al.*, 1995; Ikoma *et al.*, 1996); MEP amplitudes increased more steeply with increasing muscle activation in dystonia than in normal subjects. These characteristics of MC disinhibition may result from an abnormality in the MC itself or be the result of changes in input to the MC from other areas.

Experiments using a conditioning–test pulse design have revealed the existence of intracortical inhibition and facilitation (Kujirai *et al.*, 1993), and that dystonia patients show less intracortical inhibition at rest (Ridding *et al.*, 1995) or during voluntary muscle activation (Chen *et al.*, 1997) than normal subjects. Abnormal corticocortical interactions, as studied by conditioning with a sensory input (Abbruzzese *et al.*, 2001) or stimulation of the contralateral MC (Niehaus *et al.*, 2001), have been reported. In the sensorimotor cortex and lentiform nucleus, decreased levels of the inhibitory neurotransmitter GABA were suggested from the study of MR spectroscopy (Levy and Hallett, 2002).

Neuroimaging studies during some tasks provide another line of evidence with respect to metabolic changes, with more detailed special information. H₂¹⁵O PET studies (Ceballos-Baumann *et al.*, 1995, 1997; Playford *et al.*, 1998; Ibanez *et al.*, 1999) have revealed a reduction in the

activation of the MC and an increase in the activation of the PMC during movement in idiopathic dystonia. These abnormally activated areas were not corrected by treatment with botulinum toxin (Ceballos-Baumann *et al.*, 1997), which suggests that these are the primary pathophysiological aspects of these cortices.

A functional MRI study carried out on patients with writer's cramp during writing revealed that activation of the primary sensorimotor cortex extends caudally and anteriorly towards the premotor association area, and involves the thalamus and cerebellum (Preibisch *et al.*, 2001). A similar functional MRI study involving patients with guitar-induced hand dystonia showed the occurrence of a greater activation of the contralateral primary sensorimotor cortex and underactivation of the premotor areas (Pujol *et al.*, 2000). Although the abnormality of the activation patterns in these frontal non-primary motor areas is different among experiments, probably because of differences in the tasks employed, patient selection and the imaging method used, abnormal activation of the frontal non-primary motor areas is a common finding of these studies.

All of these findings support the idea that not only the MC but also the thorough functional connectivity of the frontal non-primary MCs to the primary MC may play an important role in the pathophysiology of dystonia. Our finding that there is a clinical improvement and prolonged silent period after rTMS over the PMC in patients with dystonia is compatible with the involvement of the non-primary motor cortices in dystonia.

rTMS over the PMC in normal subjects and in patients with dystonia

The recent development of rTMS has made it possible to produce transient modulation of cortical excitability in the intact human brain. Studies using rTMS applied over the frontal non-primary motor areas in healthy volunteers have been reported by several groups. Subthreshold 1 Hz rTMS over the PMC has been shown to either decrease the MEP amplitude obtained by test stimulation to the MC (Gerschlagner *et al.*, 2001) or alter the time course of the intracortical inhibition/facilitation, as revealed by paired-pulse testing (Munchau *et al.*, 2002). Subthreshold 0.9 Hz rTMS over the PMC reduced the task-related power decrease in the alpha and beta bands and the EEG–EMG coherence, suggesting the suppression of voluntary activation of cortical motor areas (Chen *et al.*, 2003). When rTMS was applied over either the MC or the PMC, the subsequent activation of areas remote from the stimulation site, as studied by PET, was wider in the case of PMC stimulation than for MC stimulation, although both rTMS over the MC and PMC decreased MEP amplitudes (Chouinard *et al.*, 2003). Thus, subthreshold and low-frequency rTMS over the PMC can result in inhibition of wide areas, leading to suppression of the MC in healthy volunteers, probably through the strong interconnections between these two brain regions (Matelli *et al.*, 1986; Porter and Lemon, 1993). Our results from healthy volunteers showing

that rTMS over the PMC, MC or SMA did not exert any effect on MEP amplitudes, handwriting or the silent period suggest that either our stimulus condition was too weak to change the excitability of the MC or the sensitivity for evoking such a remote effect was too low in healthy volunteers. Patients exhibited a change of MC excitability only after rTMS over the PMC. While the stimulation paradigm was not effective in normal subjects, the cortical changes occurring in dystonia might have rendered the PMC particularly susceptible to the same stimulation paradigm. It is possible that the PMC is responsible for the abnormal excitability of the MC in dystonia. Subthreshold stimulation of the PMC may activate inhibitory neurons or reinforce inhibitory synaptic connections in the MC. Dysfunction of the final common pathway in dystonia might, at least in part, be attributable to loss of inhibition of the PMC, which itself may play an important role in its pathophysiology.

Subthreshold 1 Hz rTMS over the MC exerted a clinical effect as well as prolonging the silent period (Siebner *et al.*, 1999). However, a recent study of 1 Hz rTMS over the PMC failed to show any obvious clinical effect even though it evoked a more prominent decrease in PET activation in patients with dystonia than in healthy volunteers (Siebner *et al.*, 2003). There are several possible reasons for the lack of clinical effect in that study. First, the frequency was different from that used here; secondly, the TMS pulses were biphasic rather than monophasic. Finally, it is most likely that patients could not be tested clinically in detail until after the PET scan had been performed, which was some time after the end of rTMS. This meant that shorter-lasting clinical changes would have been missed.

Silent period in dystonia

The silent period produced by TMS of suprathreshold intensity was either shorter in dystonia than in normal subjects (Mavrouidakis *et al.*, 1995; Filipovic *et al.*, 1997; Rona *et al.*, 1998; Curra *et al.*, 2000; Niehaus *et al.*, 2001) or was compatible with that of healthy volunteers (Schwenkreis *et al.*, 1999). The patients in the present study did not exhibit a shorter silent period than the healthy volunteers, although there was a tendency (not significant) for it to be shorter in the patient group. This is probably because we stimulated MC at a relatively low intensity (20% of the maximum stimulator output above rMT) in order to avoid stimulus spread to the PMC. Chen and colleagues reported the shorter silent period in writer's cramp when stimulated with the intensity of 110% above the rMT (Chen *et al.*, 1997). In their study they used a round coil, whereas we used a figure-of-eight coil. It is known that the former activates a much wider area bilaterally as well as different elements within the motor cortex (Di Lazzaro *et al.*, 2002) than the figure-of-eight coil. Thus, direct comparison with our results may not be justified.

Several authors have reported that short-interval intracortical inhibition is reduced in patients with dystonia affecting the arm. Indeed, it might have been useful to measure short-

interval intracortical inhibition in addition to the silent period in the present group of patients, since these two phenomena are thought to reflect excitability in separate inhibitory pathways (GABA_A and GABA_B, respectively; Werhahn *et al.*, 1999). However, the result of short-interval intracortical inhibition is critically dependent on the level of ongoing muscle activity at the time of evaluation, and thus can be influenced by patients' difficulty in relaxing their muscles completely. Because of this, we preferred to use the silent period, which is measured during voluntary contraction and is relatively independent of the absolute level of muscle contraction (Kukowski and Haug, 1992; Inghilleri *et al.*, 1993). Similar reasoning has been employed by other workers in studies of patients with dystonia (Mavrouidakis *et al.*, 1995).

It should be noted that, although rTMS lengthened the silent period in patients, the statistical analysis showed no difference in silent period duration between patients and healthy subjects, either before or after treatment. Effectively, the change seen in our dystonia patients fell within the range of normal between-subjects variation. The difference between the groups lay specifically in the fact that the patients were more susceptible to the effects of rTMS than healthy subjects. Since neither MT nor MEP changed after rTMS, we suggest the following two possibilities in terms of excitatory and inhibitory circuits intermingled and interconnected in the PMC (Porter and Lemon, 1993; Tokuno and Nambu, 2000). First, this increased susceptibility might be due to the fact that dystonia patients have a lower threshold for inducing inhibitory effects after rTMS of the PMC. Alternatively, rTMS might have resulted in the suppression of a tonic facilitation from the PMC to the MC. The latter is compatible with recent work in monkeys showing that there is a powerful facilitatory output from the ventral PMC to the MC (Shimazu *et al.*, 2004). The more the PMC is excited, the more easily detected the inhibitory effect of rTMS might be. Further study is warranted to test these hypotheses.

Although the H reflex was not examined in the present study, the finding of a prolonged silent period indicates the possibility that the PMC changed the level of spinal excitability indirectly by changing the excitability of the MC. In fact, a recent study revealed that the later part of the time course of spinal reciprocal inhibition was potentiated after 1-Hz rTMS over the PMC in DYT1 dystonia (Huang *et al.*, 2004). This suggests that rTMS over the PMC can change spinal excitability and normalize the decreased reciprocal inhibition characteristic of dystonia (Nakashima *et al.*, 1989).

The role of PMC abnormality in dystonia

The PMC plays an important role in the preparation for and the sensory guidance of movements (Wise, 1985; Kurata and Wise, 1988a, b; Di Pellegrino and Wise, 1993a, b), motor sequence organization (Mushiake *et al.*, 1996), determining movement direction (Kakei *et al.*, 2001; Cisek and Kalaska, 2002), inhibiting automatic responses (Praamstra *et al.*, 1999) and motor learning in the time domain (Lucchetti and Bon,

2001). The set-related activity, characteristic of the PMC (Wise, 1985; Kurata and Wise, 1988a, b; Di Pellegrino and Wise, 1993a, b; Matsumoto *et al.*, 2003) may be disrupted in a specific movement (Kaji *et al.*, 1995b; Hamano *et al.*, 1999) if the PMC is functionally abnormal. This may explain some of the characteristics of dystonia: task-specificity and stereotypy.

The PMC is important not only in terms of its own function, but also of its anatomical connections with three different systems: both the PMC and SMA are densely and reciprocally interconnected with area 4 and are topographically adjacent to it (Porter and Lemon, 1993; Matelli *et al.*, 1986), and the PMC and SMA have direct projections to the spinal segments (Dum and Strick, 1991). Furthermore, the PMC and caudal SMA receive input projections from the rostral superior parietal lobule (Mufson and Pandya, 1984), which is hyperactive during writing before and after botulinum toxin injections, as revealed by PET (Ceballos-Baumann *et al.*, 1997). Although the nature of the precise interactions between the second sensory association areas and the primary sensory cortex or the frontal non-primary motor areas is not well known, these connections might also be essential with regard to the sensory aspects of dystonia (Hallett, 1995; Kaji *et al.*, 1995a, 2004). What the PMC hypersensitivity seen in our results means in relation to the role of the PMC in motor programming and sensory guidance remains unknown and is a topic that requires further study.

Conclusions

rTMS over the PMC gave rise to significant prolongation of the cortical silent period, and improved handwriting in the patients with writer's cramp. rTMS over either the MC or the SMA did not exert any change. No change was seen in the normal control group or when using a sham coil over the PMC in the patient group. This increased susceptibility of the PMC in dystonia suggests that the hyperactivity of the PMC plays an important role in the pathophysiology of dystonia, and the inhibitory effect on the MC induced by rTMS over the PMC modulates excitability of the MC, providing a therapeutic strategy for patients with writer's cramp.

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