Repetitive TMS of the somatosensory cortex improves writer's cramp and enhances cortical activity

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Abstract

OBJECTIVE: Since the somatosensory system is believed to be affected in focal dystonia, we focused on the modulation of the primary somatosensory cortex (SI) induced by repetitive transcranial magnetic stimulation (rTMS) in order to improve symptoms of writer's cramp.

PATIENTS AND METHODS: Patients with writer's cramp (N=9 in the pilot study and N=11 in the advanced study) were treated with 30-minute 1 Hz real- or sham-rTMS of the SI cortex every day for 5 days. Before and after rTMS, 1.5 T fMRI was examined during simple hand movements. While in the pilot study the rTMS coil was navigated over the SI cortex with a maximum of blood oxygenation-level dependent (BOLD) signal induced by passive movement, patients in the advanced study had the coil above the postcentral sulcus.

RESULTS: After real-rTMS, 4 pilot study patients and 10 advanced study patients experienced subjective and objective improvement in writing, while only minimal changes were observed after sham-rTMS. Patients involved in the active movement task exhibited a rTMS-induced BOLD signal increase bilaterally in the SI cortex, posterior parietal cortex and in the supplementary motor area ($p<0.001$ corrected). After sham-rTMS, no BOLD signal changes were observed.

CONCLUSIONS: 1 Hz rTMS of the SI cortex can improve writer's cramp while increasing the cortical activity in both hemispheres. Handwriting improved in most patients, as well as the subjective benefit, and lasted for 2–3 weeks. The beneficial effects of rTMS paralleled the functional reorganization in the SI cortex and connected areas, reflecting the impact of somatosensory system on active motion control.

ORIGINAL ARTICLE

INTRODUCTION

Writer's cramp (graphospasm) is the most frequent form of task-specific dystonia and is manifested as excessive involuntary co-contractions of the agonists and antagonists in the forearm and hand, and experienced mainly in writing (Marsden & Sheehy 1990). Conventional treatment consists of local botulinum toxin induced denervation of the dystonic muscles (Cohen *et al.* 1989). In addition to the local effects of botulinum toxin, motor system changes have also been demonstrated at a central level (Byrnes *et al.* 1998; Ceballos-Baumann *et al.* 1997; Senkarova *et al.* 2009). Other treatment techniques are rather experimental in nature and comprise of special rehabilitation procedures using sensory (Zeuner & Hallett 2003) or motor training (Zeuner *et al.* 2008; Zeuner *et al.* 2005). Successful use of deep brain stimulation has also been reported (Fukaya *et al.* 2007).

Another approach involves repetitive transcranial magnetic stimulation (rTMS) based on a series of high-energy magnetic pulses applied to the cerebral cortex. While botulinum toxin affects the brain indirectly through neuromuscular junction chemodenervation causing a change in proprioceptive feedback (Trompetto *et al.* 2006), rTMS interacts with motion control directly at a cortical level. After the application of 1 Hz rTMS to the contralateral motor cortex, several patients showed subjective improvement of writer's cramp (Siebner *et al.* 1999). When rTMS was focused on the contralateral premotor cortex, PET revealed functional changes in the premotor cortex, basal ganglia and cerebellum. However no positive therapeutic effect was observed (Siebner *et al.* 2003). In contrast, another study produced quite opposite results. Therapeutic improvement of dystonia was achieved by rTMS of the premotor rather than the motor cortex (Murase *et al.* 2005).

As follows from the choice of the rTMS targets made in previous studies, these efforts focused on therapeutic intervention in the motor system. Although focal dystonia is primarily considered to be a movement disorder, a number of authors have also suggested the possible involvement of the somatosensory system. Besides the positive effects of somatosensory tricks – *geste antagoniste,* long-term somatosensory training (Zeuner & Hallett 2003), or percutaneous somatosensory electric stimulation of the hand (Tinazzi *et al.* 2005), this is also supported by other findings. Writer's cramp also affects the somatosensory spatial (Sanger *et al.* 2001), temporal (Bara-Jimenez *et al.* 2000; Fiorio *et al.* 2003) and somatognostic (Fiorio *et al.* 2006) discrimination of the hand.

Furthermore, abnormal somatotopy and abnormal size of the receptive fields of the fingers (Bara-Jimenez *et al.* 1998; Braun *et al.* 2003; Elbert *et al.* 1998; Meunier *et al.* 2001; Nelson *et al.* 2009) and significant changes in somatosensory gating (Murase *et al.* 2000) have been observed. As documented by imaging studies, the somatosensory cortex of patients with writer's cramp exhibits bilateral thickening (Garraux *et al.* 2004), various functional abnormalities (Butterworth *et al.* 2003; Hu *et al.* 2006; Lerner *et al.* 2004; Peller *et al.* 2006; Sanger *et al.* 2002) and changes in its subcortical connectivity (Delmaire *et al.* 2009).

Co-responsible for the development of focal dystonia may be disordered sensorimotor integration in long-term motor learning or a somatosensory system abnormity due to overlearning a specific motion (Abbruzzese *et al.* 2001; Roze *et al.* 2009; Tinazzi *et al.* 2000; Vidailhet *et al.* 2009). Historically speaking, the name writer's cramp lends support to the theory. Originally, the term referred to a cramp experienced by professional individuals who performed a specific activity (writing) for several hours per day. Long-term motor learning is being associated with hyperactivation, disintegration, enlargement and overlapping of the receptive fields of the contralateral somatosensory cortex (Candia *et al.* 2003; Elbert *et al.* 1995; Floyer-Lea & Matthews 2005; Karni *et al.* 1995). Such manifestations have also been found in animal models based on long-term repetition of active limb movements (Blake *et al.* 2002; Byl *et al.* 1997). Some animals developed dystonia-like movements even after prolonged execution of repetitive movements in a passive way (Byl 2007). This suggests that in predisposed individuals dystonia can develop by overloading the somatosensory or proprioceptive input leading to an abnormal rebuilding of first the somatosensory and then the motor cortices.

All this led us to the hypothesis that focal dystonia might be therapeutically influenced through the somatosensory system. Patients with writer's cramp underwent rTMS focused on the contralateral primary somatosensory cortex of the hand (SI) as part of a sham-controlled, single-blind study. High-frequency rTMS of the SI cortex had previously been used on healthy subjects, in whom an increase in cortical activation was observed (Pleger *et al.* 2006; Tegenthoff *et al.* 2005). We chose low-frequency (1 Hz) rTMS for its known interference with tactile discrimination (Knecht *et al.* 2003; Satow *et al.* 2003) and for its assumed interaction with inhibitory mechanisms observed in healthy subjects (Ogawa *et al.* 2004). It has also been shown, that low-frequency rTMS may affect somatosensory integration in patients with writer's cramp. After 1 Hz exposure of the SI cortex there was a reduction of short-latency afferent inhibition not seen after rTMS of the primary motor cortex (Baumer *et al.* 2007).

Besides the clinical effects, we searched for any functional changes in the cerebral cortex that may have occurred from applying the 30-minute sessions of rTMS over a 5 day period. For this purpose, event-related functional magnetic resonance imaging (fMRI) was employed during the execution of a simple movement – closing and opening of the palm of the affected hand. For better understanding of the rTMS-related effects on

somatosensory circuits, the movement was executed actively and passively. Active and passive movements are known to be accompanied by activation of similar cortical areas even if those are controlled by different mechanisms (Dinomais *et al.* 2009; Guzzetta *et al.* 2007; Mima *et al.* 1999; Reddy *et al.* 2001; Weiller *et al.* 1996). While active movement has to be planned, controlled, executed and perceived; passive movement is associated primarily with kinesthetic perception and voluntary muscle relaxation. In our assumption, if the motor system function is influenced by SI rTMS, fMRI change will be manifest exclusively in active movement task. On the other hand, if SI rTMS mostly affects the kinesthetic perception, we should notice similar fMRI changes in the execution of active and passive movements because proprioceptive feedback is common to both types of movement. Assuming that SI rTMS interferes with the clinical manifestation of dystonia, i.e., with functional modulation of motor circuits, we predict to see more pronounced rTMS-related changes in fMRI with active movement rather than with passive movement task.

MATERIAL AND METHODS

Fifteen patients with writer's cramp in the right hand participated in two experimental protocols *(pilot study* and/or *advanced study).* Nine patients (all women) of mean age 42.5 ± (SD) 9 years were enrolled in the *pilot study*. The *advanced study* comprised 11 patients (8 women, 3 men; mean age 40.3 ± 3 years), five of whom had taken part in the *pilot study* (Table 1). All patients were right-handed, and their hand dystonia had first occurred between 2 and 11 years before entering the study. Four patients in the *pilot study* and five patients in the *advanced study* had cramps which were manifested only during writing (simple dystonia), while the others were affected during other hand movements as well (complex dystonia). Four patients in both studies had already been treated with botulinum toxin in the past, the last injection having been received at least four months prior to the study. No clinical effect of botulinum toxin was detectable in any of the patients during enrollment. Only patients with adult-onset dystonia were enrolled and all were otherwise healthy. All confirmed their participation in the study by signing their informed consent. The study received the approval of the local ethics committee.

Design of the study

Each patient completed two four-week treatment blocks – one with real-rTMS, the other with sham-rTMS, in random order. Each (real- or sham)-rTMS lasted 30 minutes and was administered every day for the first five consecutive days of each block. In order to minimize the effect of placebo, all patients were informed that both would be therapeutical blocks differing only in technical details. The severity of dystonia was assessed subjectively and objectively before the first (real- or sham)-rTMS block (day 0, visit V1), after its termination (day 5, visit V2), and subsequently

Tab. 1. A group of 11 patients with writer's cramp enrolled in the *Advanced study*.

									real-rTMS						sham-rTMS					
									SEW			OEWQ			SEW			OEWQ		
N	M/F	age	dur.	type	btx.	ord.	MT	R/N	V2	V3	V4	V2	V3	V4	V2	V3	V4	V2	V3	V4
1	F	53	3	s	n	1	43	R	+25	+25	+30	+42	+33	+25	+25	+25	0	–17	0	–8
2	F	42	3	s	y(4)	1	35	R	+50	+50	+50	+25	0	+17	0	–25	–25	0	0	–8
3	F	43	8	c	y(24)	2	43	R	+25	+25	0	+50	+50	+25	0	0	0	0	–8	–25
4	F	58	11	c	y(5)	1	34	R	+75	+25	0	+58	+58	+50	+25	+25	0	+17	+8	+8
5	F	42	10	c	n	1	35	R	+25	+25	+25	+8	0	+25	0	0	0	–25	–33	–42
6	F	47	2	s	n	2	35	R	+25	+50	+25	+25	+25	+17	0	0	0	–8	–8	–8
7	F	38	2	c	n	2	47	R	+25	+25	+25	+33	+17	+25	0	0	0	0	0	0
8	F	51	6	s	y(4)	2	39	N	0	0	0	+25	+25	+33	0	0	0	–17	–25	–25
9	M	57	10	c	n	1	47	R	+25	+25	+25	+33	+8	+33	0	0	0	0	0	0
10	M	58	6	c	n	2	43	R	+25	+25	+25	+17	+17	–8	0	0	0	0	0	–17
11	M	42	4	s	n	1	42	R	+25	+25	+25	+25	+25	+25	0	–25	0	–17	–8	–17

SEW – subjective effect of rTMS on writing (%); OEWQ – objective effect of rTMS on writing quality (%); V2, V3, V4 – state at end of real- or sham-rTMS (visit V2), at a week afterwards (visit V3), at another two weeks (visit V4) in comparison with state prior real- sham-rTMS (visit V1). M/F – male/female; dur. – duration of writer's cramp (yrs); type – type of writer's cramp: simple/complex; btx – previous treatment with botulinum toxin: yes/no – if yes, period of time from last injection in months; MT – motor threshold (% of maximal output of stimulator); R/N – responder/non-responder

one week (day 14, visit V3) and three weeks (day 28, visit V4) after the end of the treatment block. Patients were then re-tested before and after the second (real- or sham)-rTMS block in the same intervals as in the first treatment block (repeated visits V1, V2, V3, V4). Continuing in the second block was conditional upon a phone call in which each patient reported the ineffectiveness or extinction of the effect of the first rTMS block.

The hot-spot coil position was defined in two ways (for more detail see rTMS procedure):

In the *pilot study*, the SI cortex of each patient was visualized using fMRI. The coil was then navigated on the local maximum of the activated cluster within the SI cortex contralateral to the affected hand.

In the *advanced study*, the coil position was determined using the results of the *pilot study*. The position was calculated by averaging the normalized coordinates of the coil positions obtained from patients-responders, i.e., only from those who manifested clinical improvement in the *pilot study*. Rated as responders were patients showing post-real-rTMS subjective as well as objective improvement of writer's cramp of at least 25% while their dystonia changed only little or not at all after sham-rTMS. Four fMRI sessions were held in the a*dvanced study*: before and after real-rTMS and before and after sham-rTMS.

Clinical assessment

The severity of writer's cramp was evaluated during all eight visits. For *objective* assessment, the Burke-Fahn-Marsden dystonia scale (BFMDS) and the 2M-Writing test in which transcribing a text within a 2-minute time limit were used. For *subjective* assessment, self-evaluation of hand function (HF) and pain intensity (PI) using visual analogue scales were employed. The subjective effect of treatment on writing (SEW) and the objective effect of treatment on writing quality (OEWQ) were assessed during visits V2, V3 and V4, after real- or sham-rTMS. While the SEW was rated by the patients themselves, OEWQ was assessed by three independent blinded raters (F.R., P.D. and S.H.). While objective measures for evaluation of writing is difficult to define, qualitative change in tidiness of writing (improvement or worsening) of the same subject is easier to recognize. To avoid bias, the raters were instructed to assess a change in quality of writing without knowledge of rTMS state (real or sham). A semi-quantitative scale was used for SEW and OEWQ rating (maximal (+100%), large (+75%) , moderate (+50%) or mild (+25%) improvement; no change (0%); mild (–25%), moderate (–50%), large (–75%) or maximal (100%) worsening) against the state before real- or sham-rTMS at visit V1. Agreement among raters was calculated by Spearman's correlation analysis. For subsequent evaluation we used the average OEWQ scores from all three raters.

The clinical data was evaluated using SPSS 11.5 software (SPSS Inc., Chicago, IL). While the results of the *pilot study* were assessed with descriptive statistics only, those of the *advanced study* were tested for normality of distribution and then rated with nonparametric tests. Each of the subjective and objective clinical measures was tested with the Fridman test for all visits, for the effect of order and for either of the two rTMS techniques (real- or sham-) corrected for muliple comparisons (Bonferroni). Significant results were further analyzed post hoc with the Wilcoxon signed ranks test, in which each parameter was compared relative to real- and sham-rTMS for each visit separately (e.g., SEW (visit V2) after real-rTMS was compared with the SEW (visit V2) after sham-rTMS).

rTMS procedure

rTMS was performed using a figure-eight 70-mm air-cooled double coil attached to a Magstim Rapid stimulator (Magstim, Whitland, UK). Biphasic stimulation was used at a frequency of 1 Hz and at 90% intensity of the active motor threshold. The threshold was based on the intensity of motor cortex stimulation during 30% isometric contraction of the abductor pollicis brevis muscle, in which only 50% of the motor responses reached an amplitude of 150 μV. Over the five-day block, a total of 9 000 stimuli were delivered (each day a series of 1 800 stimuli were applied within a 30-minute period). The position of the coil was reached with the frameless stereotaxy navigation system Brainsight (Magstim, Whitland, UK) using the co-registered fMRI results obtained prior to rTMS. For real-rTMS, the coil was positioned tangentially to the skull surface with its handle directed posteriorly. For sham-rTMS, the coil was tilted by 90 degrees, and the rest of the stimulation parameters being identical. Throughout real- or sham-rTMS, the coil was firmly fixed in the required position using a gripping arm.

In the *pilot study*, the coil was focused on the SI cortex contralateral to the affected hand with the hot-spot placed above the postcentral sulcus or posterior bank of the postcentral gyrus near the local maximum of the activated cluster of each individual fMRI elicited by passive hand movements.

In the *advanced study*, a relatively identical position of the coil was used in all patients. The position was defined in a standardized stereotactic space (Montreal Neurological Institute) by means of averaging the normalized coordinates of the positions of the coil hot-spot in the responders from the *pilot study*. The averaged position was then transformed through reverse normalization back into the native space of each patient enrolled in the *advanced study*. The SPM5 software (The Wellcome Department of Imaging, London, UK) was employed for forward and reverse normalization procedures.

fMRI procedure

During fMRI, each patient performed a simple movement with the fingers of the right (dystonic) hand. The *active movement* task required voluntary flexion and

extension of the 2nd–5th fingers in the metacarpophalangeal and proximal interphalangeal joints. During the six-minute task, each subject was instructed to execute about ten such motions, each lasting approximately 5 seconds, and to avoid counting the movements performed or the intervals between them. The motion during the *passive movement* task was performed in the same manner as in the *active movement* task except that the subject's hand was moved passively by the investigator. In the resting phase, the investigator held the subject's fingers mildly semiflexed. Each subject was asked to keep the hand relaxed throughout the investigation without assisting or hampering the execution of the movements. To standardize the procedure, all of the passive movements were executed by the same investigator wearing a rubber glove. The investigator watched for any muscle tone variation caused by voluntary co-activation or passive resistance from insufficient muscle relaxation. Since great emphasis was laid on practicing relaxation in the training phase, the investigator never noticed any voluntary or dystonic contraction of the hand muscles during fMRI.

The investigation was made with a 1.5 T MR Siemens Symphony scanner (Erlangen, Germany). The blood oxygenation-level dependent (BOLD) signal was detected using gradient echo–planar T2*–weighted sequence of the following parameters: TR=2 900 ms; TE=56 ms; FA=90 deg. During each fMRI session, lasting 6 minutes and 11 seconds, 128 dynamic scans were obtained consisting of 27 axial slices 4-mm thick. For morphological imaging, a T1-weighted sequence was added (TR=2 140 ms; TE=3.93 ms; FA=15 deg; TI=1 100 ms) to obtain 160 axial 1.6-mm thick slices.

For exact hand movement detection, we developed a method of video-monitoring using a digital video camera (Canon MV20i) linked to the fMRI scanner. A detail of each subject's right hand was taken during each fMRI session. The video recording was synchronized during the course of fMRI using a light emitting diode (LED) placed in the camera visual field. The video records were then analyzed using our own software permitting automatic LED flash detection as well as timing for any videotaped event with a 40 ms time resolution. The beginning and the end of the hand movement were detected visually by the investigator during slowed-down frame-by-frame projection. This procedure enabled us retrospectively to exclude any incorrectly executed movements.

fMRI data preprocessing and statistical analysis were made in the SPM5. The preprocessing involved realignment of images distorted by motion artifacts, slice-time correction, normalization into standardized stereotactic space (Montreal Neurological Institute), and isotropic smoothing with a 8-mm Gaussian FWHM (full-width at half-maximum) filter. For stereotactic navigation over the SI cortex, the source image data for individual fMRI analysis of passive movement was left in the native space.

Only active and passive movements lasting for close to 5 seconds were selected for analysis. Hence, there was no statistical difference in the average duration of the selected movements before and after rTMS. The vectors containing the beginning and duration of each single movement were subsequently convolved with the expected haemodynamic response function as an input to the general linear model using an event-related design. Four regressors of active movements and four regressors of passive movements (i.e. one from each fMRI session) were used for individual analyses. Random-effect analysis was employed for group results processing, in which contrasts between the condition before real- or sham-rTMS (visit V1) and after real- or sham-rTMS (visit V2) were calculated for active and passive movements separately. The results of group analyses were at a threshold of $p<0.001$ level of significance and corrected at non-isotropic adjusted cluster-level.

Dynamic Causal modeling

Connectivity between active movement-related brain regions was analyzed in an *advanced study* using Dynamic Causal Modeling (DCM). Whether or not this connectivity could be changed by exposure to rTMS was also analyzed. DCM analysis makes it possible to estimate intrinsic connectivity between brain regions, the modulation of connectivity induced by experimental conditions and the influence of direct external input on regional brain activity (Friston *et al.* 2003). Local cluster maxima of group-level fMRI analysis showing the impact of real-rTMS on execution of active movement (i.e. contrast: after vs. before real-rTMS treatment) with a threshold of $p<0.001$ corrected at cluster level were selected for DCM analysis. To make the model as simple as possible, we chose from among the four cerebral areas known to be involved in movement control or perception and to be anatomically interconnected. In the left hemisphere, we chose the SI cortex (defined by the rTMS coil position), the posterior parietal cortex (PPC), and the supplementary motor area (SMA). In the right hemisphere, we chose the SI cortex. The coordinates of those areas are given in Table 3 and Figure 4. Cluster-specific time series were extracted from each patient for each of the four fMRI sessions at the uncorrected threshold of $p<0.01$. The time series were the first eigenvariate from all voxels within a 4-mm diameter centered on each position of the above mentioned regions.

First, we defined the model which reflected the brain areas behavior before exposure to rTMS. Using Bayesian model selection, we selected the best from among 11 models, which reflected various connections between all four brain regions (Stephan *et al.* 2007). The DCM module in SPM5 was used for the Bayesian model estimation and selection. All the tested models are described in Figure 4. While model 1 made use of reciprocal connections between the areas, each of the

Tab. 2. *Advanced study*: mean clinical results (±SD) of subjective and objective parameters in 11 patients with writer's cramp before and after real/sham-rTMS.

		real-rTMS				sham-rTMS			
Subjective measures	***p*-value**	**V1**	**V2**	**V3**	**V4**	**V1**	**V2**	**V3**	**V4**
SEW	10^{-5}		+29(18)**	+27(13)**	+21(15)**		+5(10)	0(16)	–2(8)
Function of the hand (FH)	n.s.	3.7(2)	4.4(2)	4.0(2)	3.8(2)	4.1(2)	3.7(2)	3.8(2)	3.6(2)
Pain intensity (PI)	n.s.	2.9(3)	2.0(3)	2.2(3)	2.1(3)	2.6(3)	1.9(2)	2.4(2)	2.9(3)
Objective measures									
OEWQ	10^{-6}		+31(14)**	+23(19)**	+24(14)**		–6(12)	–7(12)	–13(14)
2M-Writing test	n.s.	170(68)	174(70)	172(74)	189(73)	178(73)	178(71)	173(69)	174(71)
BFMDS	n.s.	3.0(1.2)	2.5(0.5)	2.5(0.5)	2.5(0.5)	2.8(1.2)	2.8(1.2)	2.8(1.2)	2.7(1.2)

SEW – Subjective Effect on Writing and OEWQ – Objective Effect on Writing Quality give per-cent rating at end of real- or sham-rTMS (V2), at a week thereafter (V3), and at another two weeks (V4) in comparison with the state before real- or sham-rTMS (V1). FH – Function of the hand and PI – Pain intensity in the hand are subjective visual analogue scales (0 – worst, 10 – best). 2M-Writing test – number of letters written within 2 min. interval; BFMDS – Burke-Fahn-Marsden dystonia scale; *p* – corrected significance level of Friedman test; ** ($p<0.01$) – significance level of Wilcoxon signed ranks test comparing corresponding visits between real- and sham-rTMS.

Tab. 3. *Advanced study*: regions with significantly increased BOLD signal in patients with writer's cramp (N=9) exposed to real- or sham-rTMS ($p<0.001$ corrected at non-isotropic adjusted cluster level) with the coil positioned on the left postcentral sulcus.

	BA	**x**	**y**	**z**	**k**	**T**	***p* uncorr.**
hot spot of the coil: left postcentral sulcus •	2, 5	-44	-42	60			
real-rTMS:							
right hand active movement: after vs. before treatment							
left postcentral sulcus	2, 5, 7	-32	-48	60		10.3	*0.00001*
+ left superior parietal lobule	7				697		
left inferior parietal lobule •	40	-46	-52	42		6.5	*0.0001*
left precuneus	7	-6	-58	62	245	5.7	*0.001*
medial frontal gyrus (SMA) •	6	4	-22	68	173	6.9	*0.0001*
right postcentral gyrus •	3, 1, 2	26	-36	64	3842	9.4	*0.00001*
right postcentral sulcus	2, 5, 7	46	-40	58		6.4	*0.0001*
+ right superior parietal lobule	7				805		
right inferior parietal lobule	39, 40	50	-58	40		10.0	*0.00001*
right insula		32	18	6	400	8.9	*0.0001*
right hand passive movement: after vs. before treatment							
left superior parietal lobule	7	-36	-56	60	160	5.3	*0.001*
right superior parietal lobule	7	40	-54	58	166	6.2	*0.001*
sham-rTMS:							
right hand active movement: after vs. before treatment							
no activation							
right hand passive movement: after vs. before treatment							
no activation							

The table shows results of the contrast: after vs. before real-rTMS, i.e. state after real-rTMS (visit V2) as compared to the state before real-rTMS (visit V1) for active and passive movements separately. No significant results were found for the contrast: before vs. after real-rTMS. For sham-rTMS treatment, no clusters have been detected for any contrasts. • – region used for DCM analysis; BA – Brodmann area; x, y, z – coordinates in standardized stereotactic space (Montreal Neurological Institute – MNI); k – cluster size; T – t-score, P uncorr. – uncorrected significance at voxel level.

other models preferred connections in a particular direction. The general assumption was that the driving inputs directly influenced the SMA (voluntary movement initiation) and the left SI (performed movement perception) in all the models.

In DCM analysis, we followed the conservative model comparison strategy (Penny *et al.* 2004). Evidence for each model, based on Akaike's and Bayesian information criterion, was analyzed by Bayes Factors (BF) for each pair of models and each patient separately. BF is the ratio between the estimated evidences of the two models and indicates which between the two better explains the data. The best model was finally chosen by using a Group Bayes Factor (GBF) and Positive Evidence Ratio (PER). The GBF was computed as a product of the individual Bayes factors. The PER counts the number of comparisons which the BF passed the threshold for positive evidence for either of the compared models.

During the second step, we analyzed the rTMS modulatory effects at the group-level for the best model only. The Wilcoxon signed ranks test was carried out to compare individual intrinsic connections before and after real-rTMS. The same procedure was applied to analyze the effects related to sham-rTMS. These tests were used separately for each connection. The results were thresholded at the $p<0.05$ significance level with correction (Bonferroni).

RESULTS

Pilot Study

On the day of visit V2, i.e. after the end of the 5th series of real-rTMS, four of the nine patients noted a subjectively positive effect on writing (SEW). Subjective improvement was present in all four a week after (V3), and in two of them for three weeks after real-rTMS ended (V4). After sham-rTMS, only one patient noted a mild deterioration in writing one week after the series (V3), while the rest reported no change in writing. The objective quality of writing (OEWQ) showed clear improvement in response to real-rTMS in these four responders. After sham-rTMS, the quality of writing showed no visible improvement.

The actual coil positions for each patient were plotted in a standardized stereotactic space (Figure 1). Unlike the non-responders, the coil hot-spot positions of these four responders were remarkably close to each other. Their averaged position with coordinates x=–44, y=–42, z=60 was then used for coil navigation in the *advanced study*.

Advanced Study

Clinical results

Subjective parameters: The group of patients enrolled in the *advanced study* exhibited significant SEW improvement ($\chi^2=36$, $p<10^{-5}$ corrected) (Figure 2) which was observed at every visit (V2, V3, V4) after exposure to real-rTMS. The best result was noted during visit V2 (an improvement of 30% ± (SD)18%, variance 0–75%, $p<0.01$) when 8 patients showed maximal effect. Another patient reached maximum SEW improvement during visit V3 and another one at V4. SEW was unaffected in one patient.

None of the patients showed SEW worsening in response to real-rTMS (Table 1 and 2), and there was also no effect caused by the order of treatment blocks. After sham-rTMS, only non-significant SEW changes of SEW were noted. Hand function (HF) and its pain intensity (PI) expressed by means of visual analogue scales showed no differences between real- and sham-rTMS.

Objective parameters: OEWQ improvement was noted in all patients during every visit (V2, V3, V4) in response to real-rTMS ($\chi^2=44$, $p<10^{-6}$ corrected). The best effect was found at visit V2 (improvement of 31% ± (SD)14%, variance 8–58%, $p<0.01$), when 9 patients showed maximum improvement (Table 1 and 2). Maximum OEWQ improvement was seen in two patients at V4. Only one patient experienced slight worsening after real rTMS (visit V4, 8% worsening) despite improvements seen during two previous visits. Both sham-rTMS and the order of treatment blocks resulted in only non-significant OEWQ changes. As follows from the inter-rater variability analysis, the QEWQ parameter can be considered a reliable measure of tidy handwriting (correlation F.R. vs. P.D.: $\rho=0.62$, $p<10^{-6}$; correlation P.D. vs. S.H.: $\rho=0.44$, $p<0.001$; correlation F.R. vs. S.H.: $\rho=0.36$, $p<0.01$). After real-rTMS, the largest number of letters written (2M-Writing test) was noted during visit 4 in 9 out of 11 patients. After correction, however, no statistical significance was reached. In response to sham-rTMS, the maximum number of written letters occurred

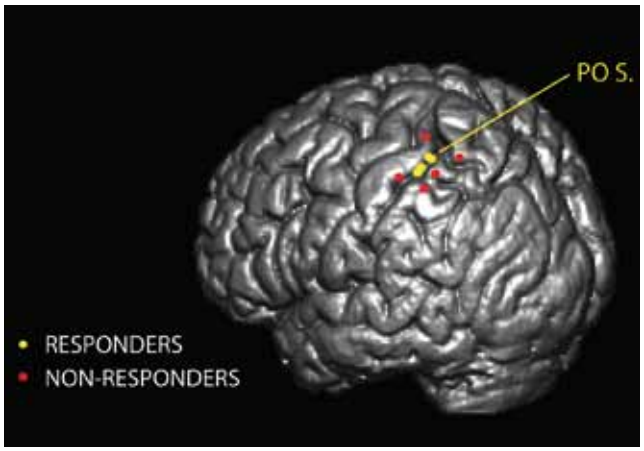

Fig. 1. *Pilot study* – positions of the coil hot-spot in 4 responders with real-rTMS-related improvement and in 5 patients with no effect. Only the responders had the hot-spot (yellow dots) positioned over the postcentral sulcus (PO S.). In non-responders, the hot-spot was entirely outside this area (red dots). An averaged hot-spot position of responders from pilot study has been used for coil targeting in advanced study.

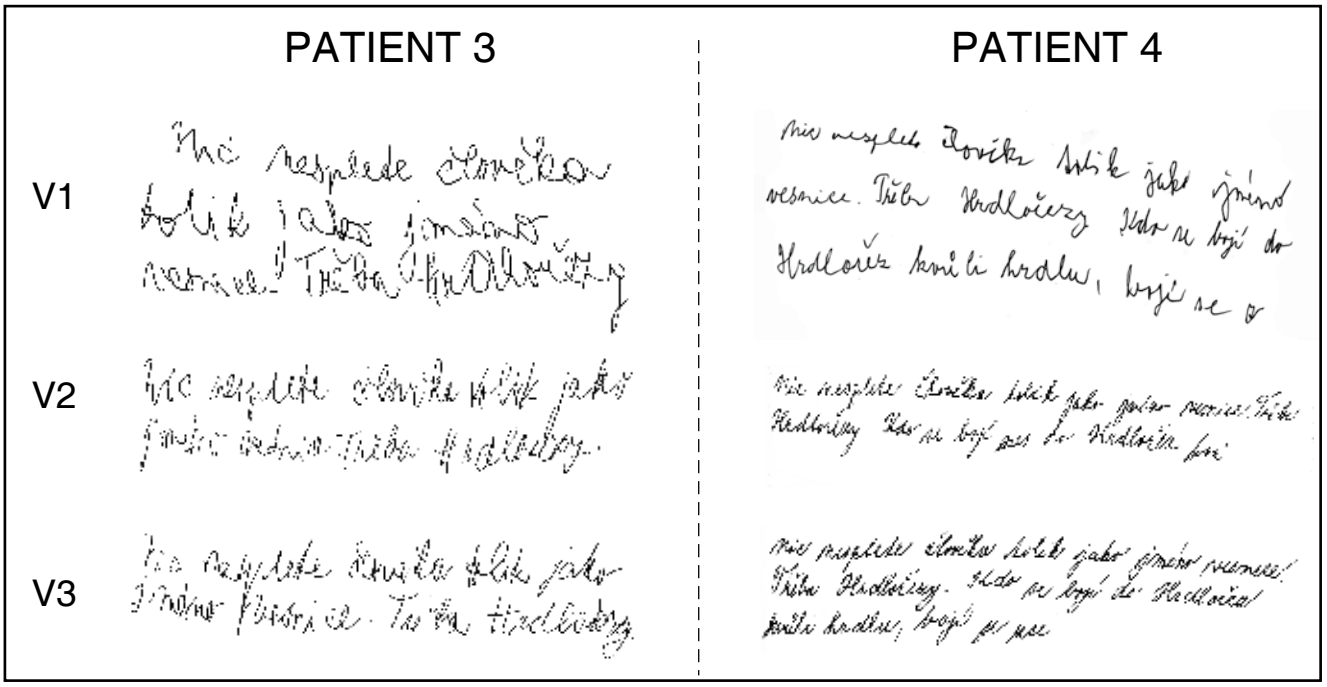

Fig. 2. Improved quality of writing after real-rTMS of the primary somatosensory cortex in two responders with writer's cramp in *Advanced study*. The handwriting of patient 3 (left column) and patient 4 (right column) before rTMS (V1), immediately after the last session of rTMS (V2), and one week later (V3).

during different visits (at V1 in 5 patients, V2 in 1, V3 in 3 and V4 in 2 patients).

The BFMDS score dropped in 5 out of 11 patients after real-rTMS but after sham-rTMS remained unaltered in 10 of them. Nonetheless, the BFMDS change was not significant.

fMRI results

Nine responders out of the 11 patients in the *advanced study* were enrolled in the group-level fMRI analysis. Patient 5, also a responder, had to be excluded for high contamination with head motion artifacts. Patient 8 was withdrawn due to failure of subjective improvement, thus falling short of the criteria for responders.

Group-level fMRI results showed that the active movements performed after the end of real-rTMS (visit V2) were associated with greater activation in several regions of both hemispheres as compared to the period before rTMS (visit V1), in particular the left SI cortex near the site of stimulation but also the SI cortex in the right hemisphere (Table 3 and Figure 3). In response to real-rTMS there was a bilateral BOLD signal increase in the posterior parietal cortex, SMA and in the right anterior insula. No rTMS-related hypoactivation was noted in any area.

Real-rTMS effect on the cortex during passive movement was manifested by bilateral BOLD signal increase in a small part of the superior parietal lobule (Table 3 and Figure 3). Conversely, sham-rTMS caused no change in cortical activation in either motor task.

DCM results

Pairwise Bayesian model comparisons of 11 models shown in Figure 4 suggested model M8 as the best option. This model which describes the behavior of the activated brain areas before the rTMS was given showed clear preference on the basis of parameter GBF in all patients: M8 vs. M1 (GBF>10^7); M8 vs. M2 (GBF>10^3); M8 vs. M3 (GBF>10^4), M8 vs. M4 (GBF>10^3), M8 vs. M5 (GBF>10^4); M8 vs. M6 (GBF>10^3); M8 vs. M7 (GBF>10^4); M8 vs. M9 (GBF>10^1); M8 vs. M10 (GBF>10^0); M8 vs. M11 (GBF>10^2). With respect to parameter PER, the M8 model was found to be more advantageous than models M1–M7 in all nine patients (PER 9:0). The models M10 and M11 were better for two patients (PER 7:2) and the model M9 was better in one patient only (PER 8:1).

Statistical analysis of model M8 showed the modulatory effect of real-rTMS solely on connectivity from the SMA to the left SI which, after exposure to real-rTMS increased from (mean) $0.02 \pm (SD) 0.02 s^{-1}$ to $0.06 \pm 0.05 s^{-1}$ ($Z=2.3$, $p<0.05$ corrected). In contrast, it was found that sham-rTMS had no modulatory effect on any of the connections.

DISCUSSION

Clinical effects

Real-rTMS of the contralateral SI cortex had a positive subjective and objective effect on the manifestations of writer's cramp in four patients (out of nine)

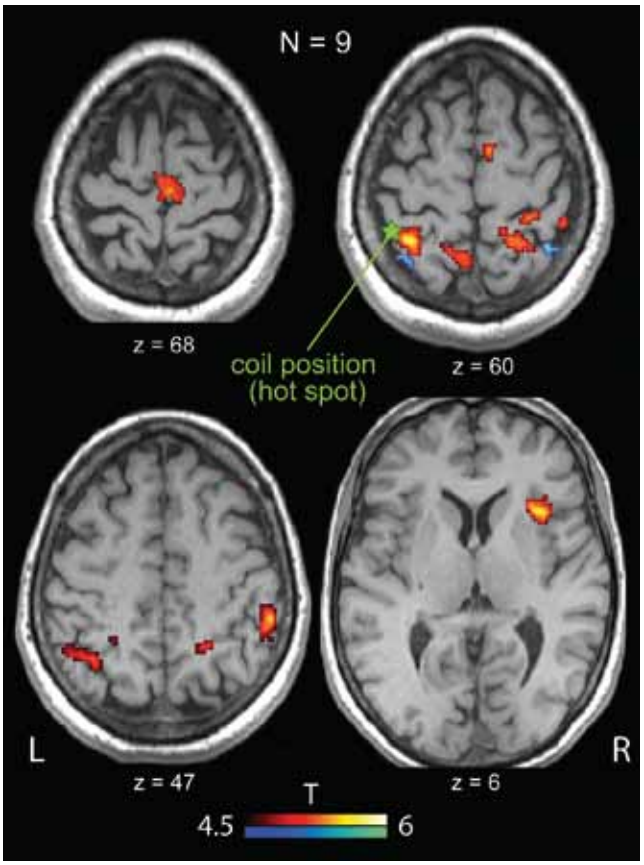

Fig. 3. *Advanced study* – group-level analysis of real-rTMS effects on execution of active and passive movements in patients with writer's cramp (N=9). Figure represents increase of the BOLD signal after real-rTMS (visit V2) as compared to state before real-rTMS (visit V1). Results are shown independently for active (red-yellow scale) and passive (blue-green scale) movements. The coil hot-spot has been positioned in the relatively same location (postcentral sulcus) in all patients (green star). Results are corrected at non-isotropic adjusted cluster-level ($p<0.001$) and projected on the normalized brain image of patient 1.

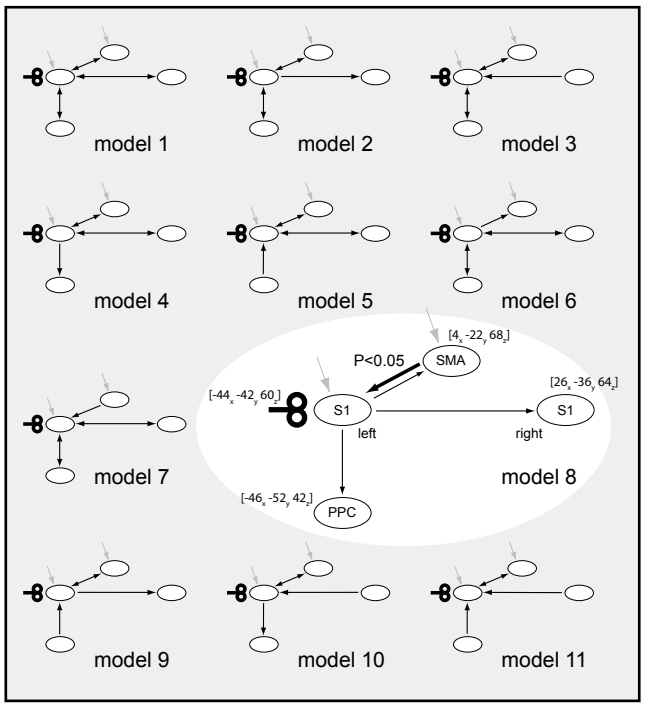

Fig. 4. Dynamic Causal Modeling in *Advanced study*. In responders, Model 8 was found as the best among 11 models. Connection from the SMA to the left SI cortex (i.e. area of stimulation) became stronger after real-rTMS ($0.06\pm(SD)0.05\ s^{-1}$) as compared to state before rTMS ($0.02\pm0.02\ s^{-1}$, $p<0.05$ corrected). On the contrary, no changes in connectivity were noted after sham-rTMS. SI – primary sensory cortex; PPC – posterior parietal cortex; SMA – supplementary motor area.

in the *pilot study* and in ten of eleven in the *advanced study*. This improvement reached an average of 30% and was already noticeable, after the five-day block of real-rTMS, and persisted for the next three weeks. The patients themselves rated the improvement after real rTMS as either mild or moderate. As confirmed by all three blinded-raters, objective effect of rTMS on writing quality (OEWQ) was noted in all *advanced study* patients and lasted with the exception of one patient for three weeks (Table 1 and 2).

Other parameters appeared to be insufficiently sensitive. Hand function and pain intensity expressed in visual analog scales showed non-significant improvement because of higher variability. The number of letters written within two minutes or the BFMDS subscore (Burke *et al.* 1985) remained almost unchanged after real- or sham-rTMS (Table 2). The result of the BMFDS subscore analysis was not surprising as the scale is too broad and is intended for rating generalized dystonia.

Like pharmacological studies, those with rTMS are limited by the placebo effect arising from the expectation of the positive impact of treatment. Alternation of blocks of effective and ineffective therapies is one way of suppressing this phenomenon. However, patients may still subconsciously expect one of the blocks to be naturally ineffective. To avoid this, our patients were not told that placebo treatment would be used in this study. Before the study was launched, they received information that both blocks would be therapeutically effective. With the exceptions of two patients, one patient (8) who could feel no changes in either block and another (1) who showed partial improvement in both blocks, the rest of the cohort experienced subjective improvement exclusively after real rTMS. Similar conclusions were reached by blinded raters: qualitative improvement of handwriting after real rTMS was noted in all patients whereas after sham rTMS improvement was seen in only one patient (4), who notably showed even more improvement after real rTMS. We thus believe that positive effects on SEW and OEWQ in our study cannot be attributed to placebo effect or bias since, sham-rTMS produced no or minimal changes.

Studies, in which real- and sham-rTMS alternate, are limited by the cross-over effect, whereby the therapeutical block effects may persist into the subsequent sham-

rTMS block. We tried to prevent this in two ways: firstly by administering the blocks in reverse order so that nearly half the patients were exposed to sham-rTMS first. Statistical analysis failed to prove that the order of the blocks would have significant effect on any clinical parameter. The second prevention was to continue with the second block only after any possible clinical effects of the previous block had disappeared. A period of 4–10 weeks had passed between the last visit of the first block (V4) and the first visit of the second block (V1). We considered this to be a sufficiently long interval taking into account that the longest after-effect due to motor cortex rTMS in patients with writer's cramp lasted only a few hours or days (Siebner *et al.* 1999). Moreover, as well as a different rTMS target, there were differences in the total dose of low-frequency rTMS pulses aplied. Each patient received a dose five times higher in our study. We expected that the more stimuli applied the greater chance of inducing long-lasting plasticity changes in the brain. This apparently holds true not only for rTMS. Electric somatosensory stimulation of the muscles of the forearm applied repeatedly for a period of ten days also improved writer's cramp for as long as three weeks (Tinazzi *et al.* 2005).

Several other attempts to treat writer's cramp using rTMS have been made previously. Whereas low-frequency rTMS of the motor cortex was accompanied by temporary improvement in some patients with writer's cramp (Murase *et al.* 2005; Siebner *et al.* 1999), stimulation of the premotor cortex produced rather inconsistent results. According to one study, rTMS of the premotor cortex exceeded the clinical effects of motor cortex stimulation (Murase *et al.* 2005), and according to another (Siebner *et al.* 2003) no positive effect was observed at all. As pointed by Hosono *et al.*, these varying effects may result from different frequencies and phases (monophasic/biphasic) of rTMS used in the previous studies (Hosono *et al.* 2008).

rTMS-related improvement in certain aspects of writing as observed in our study suggests that maladaptive plasticity of the sensorimotor system may be temporarily overcome by forced reorganization of the SI cortex. Accordingly, our clinical results further support the involvement of the somatosensory cortex in the pathophysiology of writer's cramp which is in agreement with many previous clinical and electrophysiological observations, which suggested that dystonia is also a sensory disorder (Hallett 1995) with dysfunction of the peripheral and/or central somatosensory systems (Abbruzzese *et al.* 2001; Baumer *et al.* 2007; Berardelli *et al.* 1998; Kanovsky 2002; Quartarone *et al.* 2006; Tinazzi *et al.* 2000; Tinazzi *et al.* 2003).

Importance of stimulation coil positioning

The *pilot study* revealed the critical importance of accurate coil positioning above the SI cortex. As is known from our experience with TMS of the primary motor cortex, even a slight displacement of the stimulation coil can cause a dramatic decrease in the amplitude or even loss of motor evoked potential. In the *pilot study* it was necessary to navigate the coil on the SI cortex of the contralateral dystonic hand. This was done using fMRI with the passive movement task. Admittedly, the SI occupies a relatively large part of the cortex and, like the primary motor cortex, has a clear somatotopic organization (Hluštík *et al.* 2001) and is organized into various reception fields (Bara-Jimenez *et al.* 1998; Braun *et al.* 2003; Meunier *et al.* 2001). Evidently then, different parts of the SI may respond to rTMS in different manners. Therefore, we retrospectively evaluated the normalized positions of the coil hot-spot for all patients involved in the *pilot study*. After their simultaneous visualization (Figure 1), we noticed that an almost identical position of the coil had been reached in four responders along the postcentral sulcus. Conversely, the coil was positioned in different locations in five non-responders.

Consequently, a narrow strip of the SI cortex along the postcentral sulcus seemed to be the optimal target for rTMS. This proved to be the correct assumption. Targeting the coil hot-spot at exactly the postcentral sulcus, i.e., relatively the same place in the brain for all of the patients, accounted for substantially better clinical results in the *advanced study*. Since TMS induces currents in a plane parallel to the coil (Rothwell 1997), it is likely that the cortex deep inside the sulcus was exposed to stimulation. This includes the Brodmann area (BA) 2 constituting the anterior wall of the posterior sulcus, as well as BA 40 forming its posterior wall. While the BA 2 is still a part of the SI cortex, the BA 40 belongs to the parietal association cortex. As known from animal studies, the BA 2 combines information on finger position with tactile somesthetic information (Kaas 2004) and receives complex projections from skin receptors and muscle spindles (Pons & Kaas 1986). The BA 40 adjoining the postcentral sulcus participates in somatosensory discrimination by providing a mental model of the extremity function (Kaas 2004) and having connections with the BA 2 as well as with the motor and premotor cortices (Pons & Kaas 1986).

rTMS-induced cortical activation

Clinical improvement of writer's cramp paralleled functional reorganization of several cortical regions in both hemispheres. As follows from comparison between fMRI performed before and after the end of the five-day series of real-rTMS, there was an activation in the bilateral SI cortex including the adjacent posterior parietal cortex (PPC), in the supplementary motor area (SMA) and in the right insula. In addition, one cluster of activation in the contralateral postcentral sulcus (SI cortex) was localized close to the hot-spot of the coil (Figure 3). All these changes were seen in the *advanced study* responders, and solely during the active movement task (Table 3). In contrast, no cortical activity changes were found after sham-rTMS. The increased activity in the

somatosensory and in adjacent areas is likely to have been directly related to the effects of real-rTMS and thereby to writer's cramp improvement.

Focal dystonia may develop in predisposed individuals by "overlearning" the repetitive complex movement. This may lead to SI cortex enlargement and maladaptive reorganization accompanied by aberrant behavior of the motor cortex and subsequently by clinical manifestation of dystonia (Byl 2007; Guehl *et al.* 2009; Nelson *et al.* 2009; Sanger & Merzenich 2000). However, enlargement and hyperactivation of the primary sensorimotor cortex is also seen in long-term motor learning which does not lead to dystonia (Floyer-Lea & Matthews 2005; Karni *et al.* 1995; Rioult-Pedotti *et al.* 1998). In these cases, the primary sensorimotor cortex is also subject to functional reorganization resulting in functional integration of the new complex movement in already existing motor patterns. In this process, the areas of perception grow in size, differentiating better and overlapping less, leading to their more specialized interaction with the motor cortex and more accurate movement execution. From this perspective, any plastic reorganization of the SI cortex – positive as well as maladaptive – may be conditional upon its enlargement and increased activation. Our results are in agreement with this concept. Presumably enough, long-term repetitive exposure by rTMS may have been another way of inducing plastic reorganization of the SI cortex as manifested by the local BOLD signal enhancement and improved writing.

As documented by previous studies, the SI cortex can be greatly influenced by rTMS. The SI cortex of patients with writer's cramp manifested plastic changes in response to low-frequency (1 Hz) rTMS by increasing its excitability due to reduced short-latency afferent inhibition (Baumer *et al.* 2007). In healthy subjects, increased SI cortex excitability was observed with high-frequency rTMS (Ragert *et al.* 2004) accompanied by local hyperactivation in fMRI (Tegenthoff *et al.* 2005) and by improved tactile discrimination (Pleger *et al.* 2006; Ragert *et al.* 2003).

As expected, rTMS in our study influenced the SI cortex activity during active and passive movements in different ways. While rTMS produced wide cortical activations during active movements we noticed only limited rTMS-related enhancement found in a small portion of PPC during passive movements (Figure 3). This then means that the effect on the SI cortex was related to more than just proprioception, otherwise, rTMS would have produced a similar fMRI pattern regardless of whether the movement was active or passive since the process of proprioception is common for both types of movement (Mima *et al.* 1999; Reddy *et al.* 2001; Weiller *et al.* 1996). We considered this finding as one of the main results of our study, suggesting that SI rTMS selectively influences somatosensory processing especially in relation to active motion control and not just to mechanisms of kinesthetic perception. This is perhaps possible due to rich cortico-cortical connections arising from the SI and represents the main input into the primary motor cortex (Asanuma *et al.* 1968).

Unlike our study, authors of previous PET and fMRI studies focused mainly on differences between patients with writer's cramp and healthy controls. They reported variable findings concerning the SI cortex and some of them evaluated the SI area together with the primary motor cortex because of poor spatial resolution. Displacement of the reception fields of the dystonic hand on the SI cortex (Butterworth *et al.* 2003) and abnormal SI activation dependence on the intensity of somatosensory stimulation were observed (Sanger *et al.* 2002). The average intensity of SI activation was either reduced (Tempel & Perlmutter 1993) or the same as in healthy subjects (Peller *et al.* 2006). On voluntary contraction of the muscles of the forearm the level of SI activation was significantly lower in patients with writer's cramp than in the controls (Ibanez *et al.* 1999; Islam *et al.* 2009; Oga *et al.* 2002). In contrast, writing was accompanied by a distinct increase in SI activation (Ceballos-Baumann *et al.* 1997; Hu *et al.* 2006) which was positively correlated with the duration of the task (Lerner *et al.* 2004; Odergren *et al.* 1998). It has then been suggested that for patients with writer's cramp, increased SI activation is mostly related to situations provoking dystonia. Conversely, other authors found no such SI activity increase in patients during writing (Ibanez *et al.* 1999; Preibisch *et al.* 2001).

In our study, real-rTMS was found to lead not only to local BOLD signal changes in the SI cortex close to the coil hot-spot but also to hyperactivation of a number of cortical areas. This supports the idea that rTMS effects were spreading from the SI cortex to remote cortical regions. Apart from increased SI cortex activation contralateral to the dystonic hand, we observed rTMS-induced co-activation of the neighbouring PPC and mirror areas in the ipsilateral hemisphere. This was not surprising because there are rich cortico-cortical and transcallosal connections (Killackey *et al.* 1983; Pons & Kaas 1986). The PPC is part of the somatosensory association cortex participating in the integration and comprehensive processing of somesthetic stimuli (Knecht *et al.* 1996). Its aberrant involvement in writer's cramp was reported previously (Butterworth *et al.* 2003).

Cortical areas co-activated after real-rTMS are known to be anatomically interconnected. We studied the relevance of those connections using the DCM (Friston *et al.* 2003). As previously confirmed by DCM analysis, the primary motor cortex is strongly influenced by the SI cortex (Pleger *et al.* 2006) and SMA (Kasess *et al.* 2008). In our study we tested 11 models with connections between four activated cortical regions belonging to the sensorimotor system. As we found out, the behavior of those areas before the beginning of rTMS could best be explained by model 8 suggesting forward connection pointing from SI to PPC and from SI to the contralateral SI, and containing

reciprocal connection between SI and SMA (Figure 4). Consequently, in patients with writer's cramp, the SI cortex modulates ipsilateral PPC, SMA and the contralateral SI cortex while being itself under SMA control. As expected, rTMS improved not only the clinical manifestations of writer's cramp but also changed the functional connectivity of model 8.

After real-rTMS we observed enhancement of connections projecting from the SMA to the left SI cortex whereas in response to sham-rTMS no functional connections were modulated (Figure 4). SI rTMS-related strengthening of functional connectivity from the SMA implies that the SI cortex was more influenced by the SMA, which may explain some of the therapeutic mechanisms of the treatment suggesting better voluntary control of ongoing movements. The SMA is involved in the preparation of self-initiated voluntary motion (Deiber *et al.* 1999) and in correct sequential movement timing (Tanji 2001). Its function is associated with motor learning and apparently with the cognitive control of movement (Nachev *et al.* 2008). In addition, the SMA probably participates in the development of dystonia. It is not understood what kind of mechanism is involved (Guehl *et al.* 2009). Regardless of whether or not the task may trigger the dystonic cramp, the SMA is usually hypoactivated in focal dystonia patients (Ceballos-Baumann *et al.* 1995; Islam *et al.* 2009; Lerner *et al.* 2004; Oga *et al.* 2002). SMA hyperactivation was only noted after local botulotoxin injections to dystonic muscles (Ceballos-Baumann *et al.* 1997). As electrophysiological recordings in animal models of dystonia showed, the receptive fields of SMA proprioceptive neurons are abnormally enlarged (Cuny *et al.* 2008), meaning that the SMA in dystonia undergoes changes similar to those in the SI cortex.

Apart from voluntary movement preparation, the SMA is also involved in the suppression of movements. This may be essential for understating our results. The inhibitory effects of the SMA on primary sensorimotor cortex has been repeatedly demonstrated by imaging studies on healthy subjects with stop-inhibition task (Jaffard *et al.* 2008), imaginary movements (Kasess *et al.* 2008) or sensory modulation of passive and active movements (Dinomais *et al.* 2009). Our finding of rTMS-related strengthening of functional connection pointing from the SMA to SI, as suggested by model 8, is in accordance with this. Clinical improvement in our patients with writer's cramp then may have related to the SMA exerting its inhibitory effect on the sensorimotor cortex by suppressing overflow and genesis of unwanted aberrant movements.

In our study, rTMS-related activation was seen even in distant areas such as the anterior insular cortex, whose activation had previously been noted in patients with writer's cramp when compared to healthy subjects (Hu *et al.* 2006; Lerner *et al.* 2004; Peller *et al.* 2006). This may be related to involvement on the nociceptive mechanisms which also belong to the somatosensory system (Treede *et al.* 1999). It may also reflect a re-representation of awareness of body movement because the insular cortex probably holds a somatotopic representation of the subjective feelings of performed movements and is involved in feelings of body ownership (Craig 2009; Tsakiris *et al.* 2007). This may suggest that the SI rTMS-related hyperactivation in the anterior insular cortex as seen in our study was related to a change in subjective feeling or to improved discomfort in the hand during writing.

CONCLUSIONS

We found that 30-minute low-frequency rTMS applied for five consecutive days to the contralateral SI cortex of patients with writer's cramp had favorable therapeutic effects. Subjective improvement of dystonia was observed in ten out of eleven patients of the *advanced study*. All of them showed improvement in quality of writing lasting, like the subjective effect, several weeks. Conversely, no clinical improvement was noted after sham-rTMS. The *pilot study* highlighted the critical importance of accurate rTMS coil positioning over the selected portion of the SI cortex. A narrow strip along the postcentral sulcus was shown to be the optimal site for therapeutic stimulation. Apart from the clinical improvement, SI rTMS induced extensive functional reorganization of the cerebral cortex was reflected in BOLD signal increase in somatosensory areas of both hemispheres. All this suggests new options for treatment and, like in previous findings, supports the relevance of the sensory system in the pathogenesis of focal dystonia.

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