

# Patients with focal arm dystonia have increased sensitivity to slow-frequency repetitive TMS of the dorsal premotor cortex

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## Summary

We used PET to examine the pattern and time course of changes produced by repetitive transcranial magnetic stimulation (rTMS) over the dorsal premotor cortex (PMd) in healthy subjects and in patients with primary focal dystonia. Subjects received 1800 stimuli of sub-threshold 1 Hz rTMS or sham stimulation to the left PMd. Afterwards, we measured regional cerebral blood flow (rCBF) as a marker of synaptic activity at rest and during performance of freely selected random finger movement. In both groups of subjects, real rTMS caused widespread bilateral decreases in neuronal activity in prefrontal, premotor, primary motor cortex, and left putamen. Conversely, rCBF in the cerebellum increased. Effects were equivalent at rest and during movement, indicating that the pattern of movement-related activation did not change. rTMS-induced

changes in neuronal activity lasted for at least 1 h except in the medial aspect of the left globus pallidus. Conditioning effects on neuronal activity were larger in the patients than in the healthy subjects: there was a greater decrease of rCBF in lateral and medial premotor areas, putamen, and thalamus, including the stimulated premotor cortex, and a larger increase in cerebellar rCBF. Our findings indicate that, in healthy subjects and patients with dystonia, a single session of rTMS can produce powerful and widespread changes in regional synaptic activity as indexed by rCBF. Since the greater effects of premotor rTMS were not related to any differences in task performance, increased responsiveness of the motor system to rTMS reveals a physiological trait that characterizes patients with focal arm dystonia.

**Keywords:** dystonia; functional imaging; plasticity; premotor cortex; transcranial magnetic stimulation

**Abbreviations:** M = movement condition; M1<sub>HAND</sub> = primary motor hand area; PMd = dorsal premotor cortex; PMv = ventral premotor cortex; R = rest condition; rCBF = regional cerebral blood flow; rTMS = repetitive transcranial stimulation; SM1 = primary sensorimotor cortex; SMA = supplementary motor area; TMS = transcranial magnetic stimulation

## Introduction

Repetitive transcranial stimulation (rTMS) of the human brain can produce effects on function, both at the site of stimulation (Pascual-Leone *et al.*, 1994; Chen *et al.*, 1997a; Boroojerdi *et al.*, 2000) and in connected distant sites (Gerschlagel *et al.*, 2001; Münchau *et al.*, 2002; Schambra *et al.*, 2003), which last beyond the time of stimulation itself (e.g. review by Siebner and Rothwell, 2003). The possibility of inducing

changes in brain function has led several groups to use rTMS to treat a variety of neurological and psychiatric conditions from depression to Parkinson's disease, dystonia, and epilepsy (e.g. review by Wassermann and Lisanby, 2001). However, the clinical results have been variable and/or small.

Electrophysiological and pharmacological experiments on the motor cortex are beginning to provide some indication of

**Table 1** Clinical details of patients with focal hand dystonia

Case	Sex	Age at study (years)	Age at onset (years)	Diagnosis	Dystonic pattern	BOTX-free period (months)
1	M	44	25	Right arm focal dystonia	Elevation of the right shoulder, internal rotation and adduction of the whole upper limb, wrist flexion	4
2	M	61	54	Simple writer's cramp	Flexion of the thumb, index finger, and middle finger	3
3	F	54	35	Complex writer's cramp	Wrist flexion with ulnar deviation, flexion of the thumb and index finger	3
4	M	39	35	Simple writer's cramp	Wrist flexion with ulnar deviation, flexion of the thumb and index finger	8
5	M	39	25	Simple writer's cramp	Extension of the thumb and index finger	4
6	M	50	40	Simple writer's cramp	Flexion of the thumb, index finger, and middle finger	15
7	M	49	17	Dystonic hand tremor	Pronation and supination of the forearm. Subtle cervical dystonia	4

the groups of neurons that can be influenced by rTMS (Peinemann *et al.*, 2000; Di Lazzaro *et al.*, 2002), as well as evidence for the involvement of specific neurotransmitters in the long-term changes that it produces (Ziemann *et al.*, 1998b). However, information on the extent and magnitude of effects at sites distant from the point of stimulation are more limited. Electrophysiological studies with single-pulse or paired-pulse transcranial stimulation or EEG, have shown that after-effects at a distance occur (Wassermann *et al.*, 1998; Gerschlagel *et al.*, 2001; Münchau *et al.*, 2002; Strens *et al.*, 2002; Chen *et al.*, 2003; Schambra *et al.*, 2003), but their extent and magnitude, particularly in subcortical structures, is not known. In addition, most experiments to date have focused on healthy subjects, whereas recent data suggest that the response of a damaged CNS to rTMS may differ from that in healthy subjects. For example, rTMS to the primary motor cortex led to a reinforcement of intracortical inhibition in patients with writer's cramp or Parkinson's disease, but had no effect in healthy controls (Siebner *et al.*, 1999b; Siebner *et al.*, 2000a).

In order to address questions about the local and remote after-effects of rTMS we used  $H_2^{15}O$ -PET to image the extent and time course of changes in regional cerebral blood flow (rCBF) following a single session of 1 Hz rTMS to the left dorsal premotor cortex (PMd), both in healthy subjects and in a group of patients with focal arm dystonia. We chose 1 Hz rTMS to PMd since we have electrophysiological evidence of its action in healthy subjects (Gerschlagel *et al.*, 2001; Münchau *et al.*, 2002). Because rCBF is a well-established marker of regional synaptic activity (Fox and Mintun, 1989), repeated measurements of rCBF provided: (i) an estimate of the size of the effects with reference to changes in movement-related activity; (ii) an indication of the spatial pattern of changes in activity; (iii) information about whether the after-effects had a similar time course at all sites; (iv) data on

whether the after-effects influenced task related activity as well as resting activity; and (v) a comparison of the response of a normal and a dysfunctional motor system to an identical protocol of rTMS. This approach has been used successfully by others to study connectivity of motor cortex, frontal eye fields and frontal cortex in healthy subjects (Siebner *et al.*, 2000b; Paus *et al.*, 2001; Strafella *et al.*, 2001) and to image changes in the effects of repeated sessions of dorsolateral prefrontal rTMS in patients treated for depression (Speer *et al.*, 2000; Kimbrell *et al.*, 2002; Mottaghy *et al.*, 2002; Shajahan *et al.*, 2002).

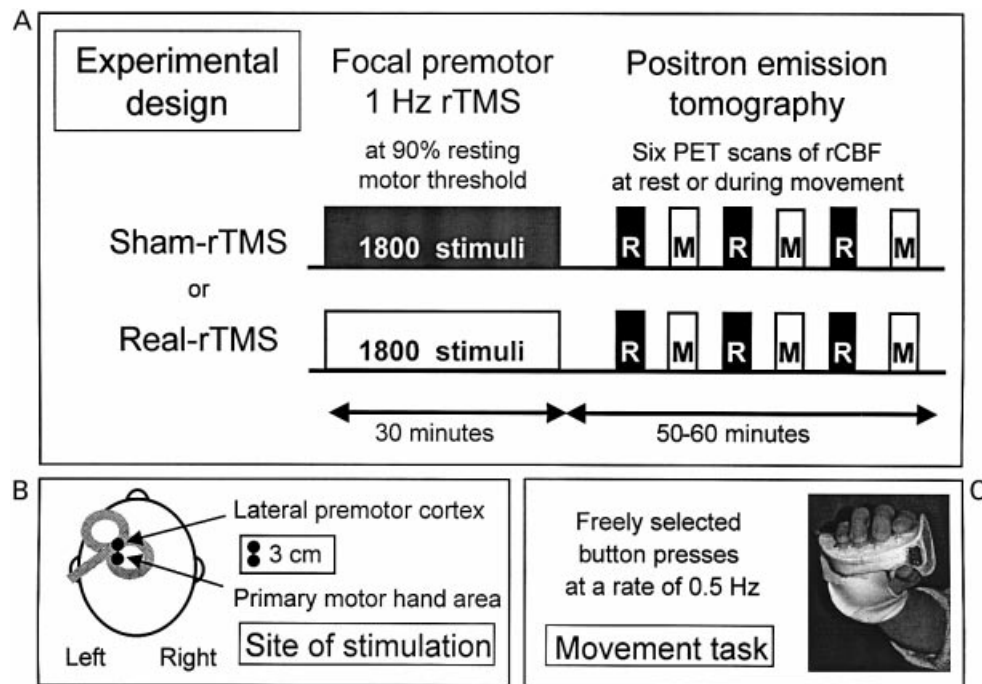
The present results reveal that there are surprisingly large and widespread changes in rCBF after a single session of rTMS to PMd, and that rTMS elicits greater effects on rCBF in patients with focal arm dystonia.

## Methods

### Participants

We studied seven patients (six males) with primary focal dystonia affecting the right upper limb. Patients were recruited from the Movement Disorders Out-patient Clinic at the National Hospital for Neurology and Neurosurgery, University College London Hospitals NHS Trust (Dr K. Bhatia, Dr C. Cordivari and Dr A. Lees). Inclusion criteria were: (i) no cause for dystonia disclosed by investigation, including CT or MRI and biochemical tests; (ii) a clinical course compatible with primary dystonia, with no features to suggest secondary dystonia; (iii) no history of neuroleptic medication; (iv) no history of other neurological or psychiatric disease.

One patient suffered from focal dystonia of the whole right arm. Four patients had simple writer's cramp and one patient had complex writer's cramp that also affected other manual skills. One patient had dystonic tremor plus modest cervical



**Fig. 1** (A) Experimental design. All participants received 1800 biphasic stimuli of real rTMS or sham rTMS given at a frequency of 1 Hz to the left rostral premotor cortex on two separate days. Changes in normalized regional cerebral blood flow (rCBF) induced by premotor 1 Hz rTMS were mapped at rest and during freely selected random finger movements using PET. Six sequential  $H_2^{15}O$ -PET scans were acquired at rest (referred to as condition 'R') or during the paced free selection of finger movements (referred to as condition 'M') in an alternating order during a 1-h period after the end of rTMS. The order of experimental conditions (R versus M) and interventions (real-rTMS versus sham-rTMS) were counterbalanced across subjects. (B) Site of stimulation. The centre of the coil was placed 3 cm rostral to the 'motor hot spot' which is a reliable functional marker for the localization of the primary motor hand area. The coil was positioned so that the handle formed a 45° angle with the midline with the handle pointing backwards. (C) Motor task. Subjects were required to freely select and execute brisk flexion movements with fingers II–V of their right hand. They were asked to make a fresh choice on each trial, regardless of previous moves. Movements were paced every 2 s to ensure a constant movement rate across scans.

dystonia. The patient details are given in Table 1. Their mean age was 48 years (range 39–61 years) and the mean duration of illness was 15 years (range 4–32 years). No patient was taking regular oral medication. All patients had been treated previously with botulinum toxin injections. However, the most recent injections were at least 10 weeks prior to the experiment, such that all patients were symptomatic at the time of participation in the study.

Seven normal volunteers (five males) were also studied. The mean age was 48 years (range 32–68 years). Healthy controls were recruited from a departmental register of volunteers and spouses of patients; they had no history of neurological or psychiatric disease. All participants were consistent right-handers according to the Edinburgh Handedness Inventory (Oldfield, 1971). Participants gave written informed consent prior to the experiment. The study was approved by the joint ethics committee of the National Hospital for Neurology and Neurosurgery and the Institute of Neurology.

### Study design

The study had a factorial design with three factors each with two levels: 'intervention' (real-rTMS versus sham-rTMS),

'group' (patients versus controls), and 'task' (movement versus rest). Figure 1A illustrates the study design. The real- and sham-rTMS were applied on two separate days, at least 1 week apart. Within each group, sham and real rTMS were counterbalanced across subjects. The after-effects of rTMS were assessed by consecutive PET measurements of regional cerebral blood flow (rCBF) during the first hour after rTMS. Within each scanning session, the rest and movement tasks were alternated. The order of tasks was kept constant within a subject between sessions, but counterbalanced across subjects and groups.

### rTMS

In each rTMS session, a total of 1800 biphasic stimuli were given over the left rostral PMd contralateral to the dystonic arm using a Magstim-rapid stimulator connected to four booster modules (Magstim Company, Whitland, UK; [www.magstim.com](http://www.magstim.com)). Premotor rTMS was applied in a room close to the PET scanner. Participants were comfortably seated in a wheelchair and pushed into the scanner room immediately after rTMS. All subjects received two 15-min

trains of 1 Hz rTMS separated by an inter-train interval of 1 min.

The coil was positioned tangentially to the curvature of the head and the handle of the coil formed a 45° angle with the subjects' body midline. The coil was manually held by one of the examiners. Stimulation intensity was set to 90% of the motor threshold of the relaxed first dorsal interosseus muscle. A standard eight-shaped coil (double 70 mm coil type P/N 9925; Magstim Company) was used for real-rTMS. The current flow of the initial rising phase of the biphasic pulse in the coil was such that the current flow in the underlying premotor cortex was posterior-to-anterior.

A specially designed sham coil which induced no magnetic field, but evoked a comparable acoustic artefact was used for sham-rTMS (Magstim Company). In contrast to real-rTMS, sham-rTMS elicited neither tactile sensation at the site of stimulation nor twitches of facial muscles in the vicinity of the transducing coil. Others have used a sham condition during which 'real rTMS' is administered by tilting the coil 45° off the scalp, with two wings of the coil touching the scalp to achieve a comparable amount of tactile sensation and muscle twitches during real and sham rTMS (Kimbrell *et al.*, 2002). This sham procedure, however, can produce substantial cortical stimulation (Lisanby *et al.*, 2001). Therefore, we decided to use a sham coil in our study to make sure that no effective stimulation of PMd occurred during sham rTMS.

We located the rostral PMd individually with respect to the position of the primary motor hand area (M1<sub>HAND</sub>). The location of the left M1<sub>HAND</sub> was functionally defined as the location on the scalp from which the largest muscle twitch in the right first dorsal interosseus muscle was elicited with the subject relaxed (referred to as 'motor hot spot'). Subsequently, the threshold for eliciting responses in the relaxed right first dorsal interosseus muscle was determined. The 'motor hot spot' was marked with a blue wax pen on the scalp. We defined this resting motor threshold as the lowest stimulation intensity that elicited at least five twitches in 10 consecutive stimuli given over the motor hot spot. The intensity of premotor rTMS was set to 90% of resting motor threshold.

In defining the site of stimulation of rostral PMd, we took note of the fact that the estimated area of stimulation in the mid-region of a figure-of-eight coil is up to 4 cm long (Barker, 1999). Thus, the site of stimulation is not very focal and a significant spread of excitation to more caudal motor areas (e.g. the caudal PMd and M1<sub>HAND</sub>) is likely to occur if the stimulation site is too close to the central sulcus. Using the centre of movement-related activation in M1<sub>HAND</sub> as an 'anchor point', a meta-analysis of various motor activation studies (Picard and Strick, 2001) revealed that peak activations in the rostral PMd related to higher-order processing were located on average 2.3 cm anterior to M1<sub>HAND</sub>, whereas peak activations in the caudal PMd were located on average 0.8 cm rostral to the centre of M1 activation. In our study, the premotor site for rTMS was located 3 cm rostrally to the motor hot spot (Fig. 1B). By

applying rTMS 3 cm rostrally to M1<sub>HAND</sub>, we sought to achieve an optimal balance between maximizing the effectiveness of rostral PMd stimulation and minimizing the risk of current spread to M1<sub>HAND</sub>.

### **Behavioural paradigm and motor assessment**

All subjects underwent six sequential H<sub>2</sub><sup>15</sup>O-PET scans in two sessions on two separate days (Fig. 1A). All scans were acquired during the first hour after premotor rTMS. The normalized rCBF was used as an index of regional synaptic activity in two experimental conditions: rest (referred to as condition 'R') and random selection of finger movements (referred to as condition 'M'). Three PET scans were acquired for each of the experimental condition in an alternating order (R–M–R–M–R–M or M–R–M–R–M–R). Subjects were required to keep their eyes open fixating a cross on the centre of a screen 0.7 m in front of their face. A pacing tone sounded every 2 s during both conditions. During the rest condition, subjects were instructed to listen, rest and not react to the tones. During the movement task, subjects were required to freely select and execute brisk flexion movements with one finger of the right hand to each tone (Fig. 1). A fresh choice was made on each trial regardless of previous moves, so as to produce a random sequence. Subjects were told to actively prepare the forthcoming movement and execute it as soon as they heard the pacing tone. To ensure a stable level of task performance, the random selection task started ~20 s prior to the onset of PET scanning and lasted for the entire 90 s period of PET data acquisition. During PET scanning freely selected random finger movement were videotaped and subsequently checked for the presence of task-related dystonia by two raters, both experienced in movement disorders (K.P.B. and C.C.).

Since our primary goal was to gain insight into the effects of rTMS in health and disease, we specifically selected a motor task that patients could perform in the same way as healthy controls, without risk of inducing dystonic movement. The random selection task required activation of motor areas involved in both preparation and execution of the movement. In this respect, the task was comparable to previous PET activation studies in generalized primary dystonia during freely selected joystick movements (Ceballos-Baumann *et al.*, 1995; Playford *et al.*, 1998). However, it put more emphasis on independent finger movements than grasping.

A previous study of rTMS of premotor cortex has revealed only minor behavioural effects on simple motor tasks in healthy subjects (Schlaghecken *et al.*, 2003). To confirm this finding in our group of subjects and patients we asked participants to perform two tapping tasks with the right hand after the first, third and fifth scans. In a 'fast tapping task', subjects tapped their right index finger as many times as possible in a 10 s interval. In a 'sequential tapping task', participants were asked to perform an ascending tapping sequence repetitively with their index, middle, ring and little

finger for 10 s. The interval between button presses, and the duration of each press, was recorded. Dystonic patients were also recorded by digital video to enable independent rating of dystonia severity during performance. To familiarize subjects with the task and to avoid learning effects during sequential PET scans, subjects performed each task twice in the PET scanner prior to rTMS.

Finally, we were interested to know whether rTMS over premotor cortex had any therapeutic effect on dystonic symptoms, since a small effect had been reported using similar parameters on the motor cortex by Siebner *et al.* (1999a, b). However, we were time limited in this since we could only evaluate hand movements fully after completion of the PET scans, about 1 h after the end of rTMS, whereas Siebner *et al.* (1999a, b) had examined patients at 20 min. A standardized protocol was videotaped and the severity of dystonia was scored by two blinded raters both experienced in movement disorders (K.B. and C.C.). The standardized examination included assessment of dystonic posturing at rest, stretching out both hands, pronation and supination of the hands, opening and closing the fist, a sequential thumb-to-finger tapping task, a finger-to-nose pointing task, speaking, opening and closing the eyes, leg tapping and walking. For each item of the motor examination, examiners scored the presence and severity of dystonia on a scale from 0 to 2 (0 = no dystonia; 1 = moderate dystonia, 2 = prominent dystonia). For hand and foot movements, dystonia was separately scored for each limb, resulting in a maximum possible score of 22.

To assess handwriting, patients were additionally required to repetitively write a standardized sentence ('The dog is barking') and to write their name. The writer's cramp rating scale published by Wissel *et al.* (1996) was used to score the severity of dystonia during continuous handwriting. The writer's cramp rating scale takes into account the motor pattern, the magnitude, and the time to onset of dystonic symptoms during writing. The total score of the rating scale ranges from 0 (no writer's cramp) to 30 (severe writer's cramp).

### **Behavioural data acquisition and analyses**

The subjects' responses were made on four buttons set under the fingertips on a moulded wrist splint. Behavioural data were not available for one of the normal subjects. All responses were recorded by computer (Apple Macintosh 7300) using COGENT Cognitive Interface Software (Wellcome Department of Imaging Neuroscience, London, UK). The data were analysed using MATLAB 6.0 (Mathworks, Sherborn, MA, USA) and SPSS 8.0 in WINDOWS 2000 (Microsoft Corporation, USA) on DELL Dimension computers (DELL, UK).

For each simple and sequential tapping task, the mean interval between responses, the mean duration of button presses, and the coefficient of variation of the inter-movement interval were calculated as an index of motor performance. These values were entered into a two-way repeated measures

analysis of variance, with 'intervention' (sham-rTMS versus real-rTMS) and 'group' (controls versus patients) as factors.

Since the free selection movement task was paced, only the duration of pressure, but not the interval between responses was considered a kinematic variable of interest. For this task, however, Simpson's equitability index was calculated for sequential response pairs and taken as a measure of the randomness of the sequence (Simpson, 1949). This index varies between 0 and 1. A value of 1 indicates that, over the course of a long series of responses, any given response was equally likely to be followed by any other response. The three repetitions of this task from each subject in each scanning session were analysed together to provide a single value of randomness after sham-rTMS and real-rTMS. This value was entered into a two-way repeated measures analysis of variance, with 'intervention' (sham-rTMS versus real-rTMS) and 'group' (controls versus patients) as factors.

The total scores of the global dystonia scale and the writer's cramp rating scale were compared using a repeated measures analysis of variance with 'intervention' (sham-rTMS versus real-rTMS) and 'time' (before rTMS versus after rTMS) as within-subject factors. The Greenhouse-Geisser method was used to correct for non-sphericity.

### **PET data acquisition and analyses**

PET was performed using a CTI ECAT HR+ scanner (CTI, Knoxville, TN, USA) in three-dimensional mode with inter-detector collimating septa removed. The axial field of view was 155 mm providing whole brain coverage. The subjects lay supine in the scanner. Head movement was reduced by a padded helmet with chinstrap, fixed to the head rest. The instructions and fixation point were presented on a TV monitor whose position was individually adjusted to give an unrestricted view of the instruction screen.

We measured rCBF after intravenous injection of  $\text{H}_2^{15}\text{O}$ . Background activity was counted over 30 s prior to each image. Six to ten millicuries (mean 8.9 mCi) were delivered over 20 s to the left arm. Image acquisition began 5 s before the rising phase of the count curve, ~25–35 s after injection, and continued for 90 s. Correction for tissue and helmet attenuation was made using a transmission scan from  $^{68}\text{Ga}/^{68}\text{Ge}$  sources at the start of each scanning session. The interscan interval was ~8 min. Corrected data were reconstructed by three-dimensional filtered back-projection (Hanning filter, cut off frequency 0.5 cycles/pixel) and scatter correction. Sixty-three transverse planes were obtained with a  $128 \times 128$  pixel image matrix, a resulting pixel size of  $2.4 \times 2.1 \times 2.1$  mm, and a resolution of 6 mm at full-width half-maximum.

In all subjects, the M1<sub>HAND</sub> site and the rostral PMd site (i.e. rTMS stimulation site) were marked on the skull using a capsule containing cod liver oil. Anatomical structural images were then acquired with the TMS surface markers in place using a VISION MR scanner at 2 T (Siemens, Erlangen, Germany) with a T<sub>1</sub> MPRAGE sequence [echo

time (TE) = 4 ms, repetition time (TR) = 9.5 s, inversion time (TI) = 600 ms, resolution  $1 \times 1 \times 1.5$  mm, 108 axial slices]. This structural image also excluded asymptomatic structural brain abnormalities.

All analyses of images were made using Statistical Parametric Mapping software, SPM99 (Wellcome Department of Imaging Neuroscience, ION, London, UK; <http://www.fil.ion.ucl.ac.uk/spm>) and MATLAB 6.0 (Mathworks). Images were realigned to the first image by rigid body correction for head movements between scans and change of position between sessions (Friston *et al.*, 1995a). All images were normalized to a standardized anatomic space (Talairach and Tournoux, 1988), by matching each realigned image to the standardized PET template of the Montreal Neurological Institute using linear and non-linear spatial transformations (Friston *et al.*, 1995a). Each image was smoothed with an isotropic Gaussian of 12 mm full-width at half-maximum in all directions to accommodate inter-subject differences in anatomy and enable the application of Gaussian fields to the derived statistical images (Friston *et al.*, 1990).

The first analysis employed a general linear model that included eight covariates that specified the task (movement versus rest) separately for each condition of treatment (real-rTMS versus sham-rTMS) and for each group (controls versus patients). The effect of global differences in cerebral blood flow between scans was removed by subject-specific ANCOVA scaling of global activity to a nominal mean global activity of 50 ml/100 g/min (Friston *et al.*, 1995b).

In a second analysis, we assessed the time course of rTMS-related changes in rCBF changes during each PET session which consisted of six consecutive PET scans. We were especially interested in the 'recovery' function of rTMS-

induced modulation of rCBF. Each scan was weighted linearly according to the time following real-TMS or following sham-TMS. The design matrix included eight separate covariates for scans of each task in each group for each session, and the corresponding covariate for the mean adjusted temporal weighting for each scan type. We were interested in specific real-TMS-related changes over time, rather than non-specific practice effects or fatigue that may have occurred. Therefore, we sought areas in which there was a difference in time-dependent changes between the real- and sham-TMS sessions. For contrasts based on the second analysis, an uncorrected threshold of  $P < 0.001$  was accepted for areas that had shown significant deactivation after rTMS in the first analysis (main effect of rTMS). Otherwise a corrected threshold of  $P < 0.05$  for whole brain was applied.

## Results

None of the participants reported adverse effects after rTMS over the PMd. Premotor rTMS did not evoke motor responses, which indicates that stimulation intensities were below motor threshold throughout the rTMS session.

### Behavioural and clinical data (see Table 2)

All participants found the motor tasks easy to perform and patients noticed no dystonic symptoms during the various motor tasks. Inspection of video recordings disclosed no manifestation of dystonia while patients performed freely selected random finger movements. A two-way ANOVA with group and type of rTMS as main factors revealed no

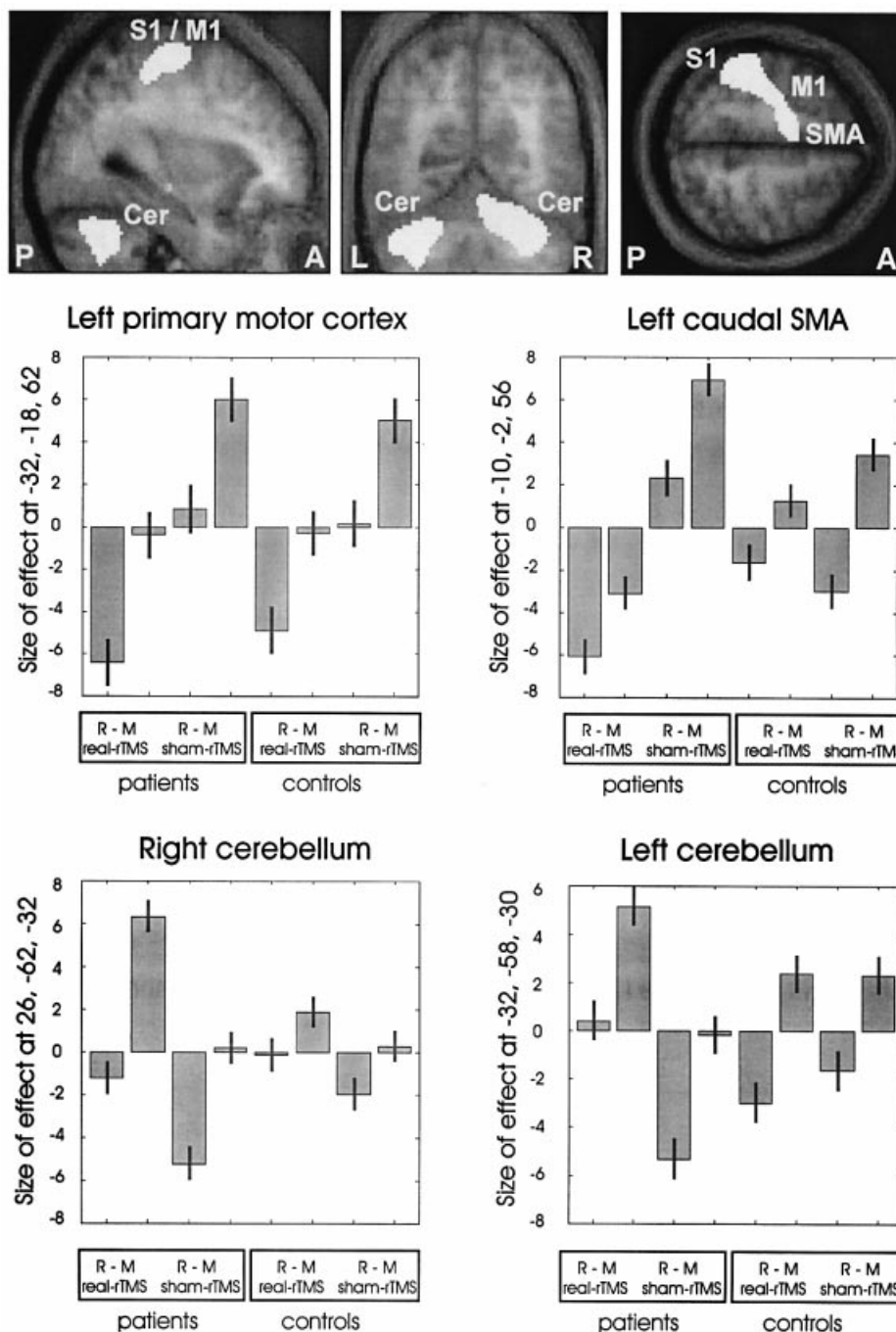
**Table 2** Mean group data ( $\pm$  SD) of the kinematic parameters and clinical scores after real rTMS and sham rTMS, respectively

	Patients		Control	
	After sham rTMS	After real rTMS	After sham rTMS	After real rTMS
Index finger tapping task				
Inter-movement interval				
Duration (ms)	215 $\pm$ 34	244 $\pm$ 39	208 $\pm$ 33	224 $\pm$ 42
Coefficient of variation	0.23 $\pm$ 0.10	0.34 $\pm$ 0.07	0.25 $\pm$ 0.10	0.25 $\pm$ 0.09
Duration of button presses (ms)	119 $\pm$ 21	144 $\pm$ 38	123 $\pm$ 23	133 $\pm$ 39
Sequential tapping task				
Inter-movement interval				
Duration (ms)	405 $\pm$ 98	423 $\pm$ 94	392 $\pm$ 120	382 $\pm$ 94
Coefficient of variation	0.30 $\pm$ 0.05	0.29 $\pm$ 0.07	0.27 $\pm$ 0.05	0.26 $\pm$ 0.04
Duration of button presses (ms)	222 $\pm$ 60	231 $\pm$ 68	203 $\pm$ 51	203 $\pm$ 30
Random sequence task				
Simpson's equitability index	0.70 $\pm$ 0.17	0.72 $\pm$ 0.17	0.80 $\pm$ 0.06	0.81 $\pm$ 0.09
Duration of button presses (ms)	240 $\pm$ 64	250 $\pm$ 93	282 $\pm$ 58	257 $\pm$ 57
Clinical assessment				
Global score for dystonia*	2.1 $\pm$ 2.4	2.1 $\pm$ 2.4	n.a.	n.a.
Specific score for handwriting*	5.7 $\pm$ 3.7	5.9 $\pm$ 4.6	n.a.	n.a.

\*For details of clinical scoring see Methods.

significant main or interaction effects, indicating that both groups performed the random movement task similarly and that motor performance during PET scanning was unaffected by rTMS.

In the finger tapping task tested between scans, real rTMS produced a subtle decrease in maximum speed of tapping movements in both groups of patients. There was a significant effect of real-rTMS on the interval between button presses [ $F$



**Fig. 2** Regional increases in synaptic activity during freely selected finger movements in dystonic patients and healthy controls. The sagittal, coronal and axial statistical parametric maps (upper panel) show brain regions which increased their normalized rCBF during freely selected random finger movements performed with the right dominant hand ( $P < 0.05$ , corrected). The white  $T$ -score maps are superimposed on the averaged  $T_1$ -weighted MRIs of all participants. The bar charts illustrate the region-specific profile of relative changes in rCBF for the voxels showing peak increases in rCBF during random finger movements. Each bar represents the mean percentage change in rCBF ( $\pm$  standard error) for each of the four conditions in dystonic patients and healthy controls. The rCBF values given on the ordinate are adjusted to the mean. M1 = primary motor hand area; S1 = primary sensory hand area; SMA = supplementary motor area; Cer = cerebellum. With the exception of the right cerebellum, there were no differences in movement-related activity between dystonic patients and healthy subjects.

**Table 3** Movement-related increases in rCBF: clusters showing significant increases in normalized rCBF in both groups and sessions for the contrast 'movement versus rest'

Brain regions		Side	Voxels per cluster	T-value of peak activity	Coordinates of peak activity		
					x	y	z
1.	Primary sensory cortex	Left	3223	8.83	-54	-28	38
	Inferior parietal lobule	Left		8.03	-44	-34	50
	SMA	Left		6.66	-10	-2	56
	Primary motor cortex	Left		6.11	-32	-18	62
2.	Cerebellum	Right	1825	10.48	22	-20	76
3.	Cerebellum	Left	1257	7.54	-32	-58	-30
				4.86	-18	-70	-24
				5.74	54	-34	44
4.	Inferior parietal lobule	Right	460	5.34	58	-24	26
	Parietal opercular cortex (secondary sensory cortex)	Right					
5.	Frontal opercular cortex	Right	115	5.70	54	10	2
6.	Insula	Left	93	5.22	-44	-2	2

= 9.7(1,11),  $P = 0.01$ ] and a near significant increase in the duration of each button press [ $F = 4.3(1,11)$ ,  $P = 0.06$ ]. However, there was no effect of real rTMS on the variability of inter-movement intervals ( $P > 0.1$ ), no difference in tapping between both groups and no interaction between 'group' and 'type of rTMS' for the three measures. The sequential finger movement task was performed equally well by both groups and was unaffected by rTMS.

As noted in Methods, clinical evaluation was carried out at least 1 h after the end of rTMS, after patients were removed from the scanner. At this time, there was no effect of rTMS on either the global dystonia rating or on the performance of the handwriting task.

## Imaging data

### Movement-related activity.

The performance of freely selected finger movements ('M' versus 'R', both groups, both sessions) was associated with an increase in synaptic activity (as indexed by an increase in rCBF) in a well-defined network of areas that are engaged in the generation of right-hand movements (Fig. 2; Table 3). The largest cluster showing a movement-related increase in rCBF was located in the left frontoparietal cortex, including the primary sensorimotor cortex (SM1), the left caudal supplementary motor area (SMA), and the inferior parietal lobule contralaterally to the moving hand. Additional activations were centred on the left anterior insula, the right inferior parietal cortex and the right frontal operculum. The cerebellum showed widespread activation, particularly on the right. With movement-related brain activation, we found no significant differences between patients and controls (Fig. 2). When a lower statistical threshold was applied ( $P < 0.001$ , uncorrected), a small focus in the paramedian region of the right cerebellar hemisphere demonstrated a relative increase in task-related rCBF in patients compared with healthy controls ( $T$ -score at peak increase in activity:

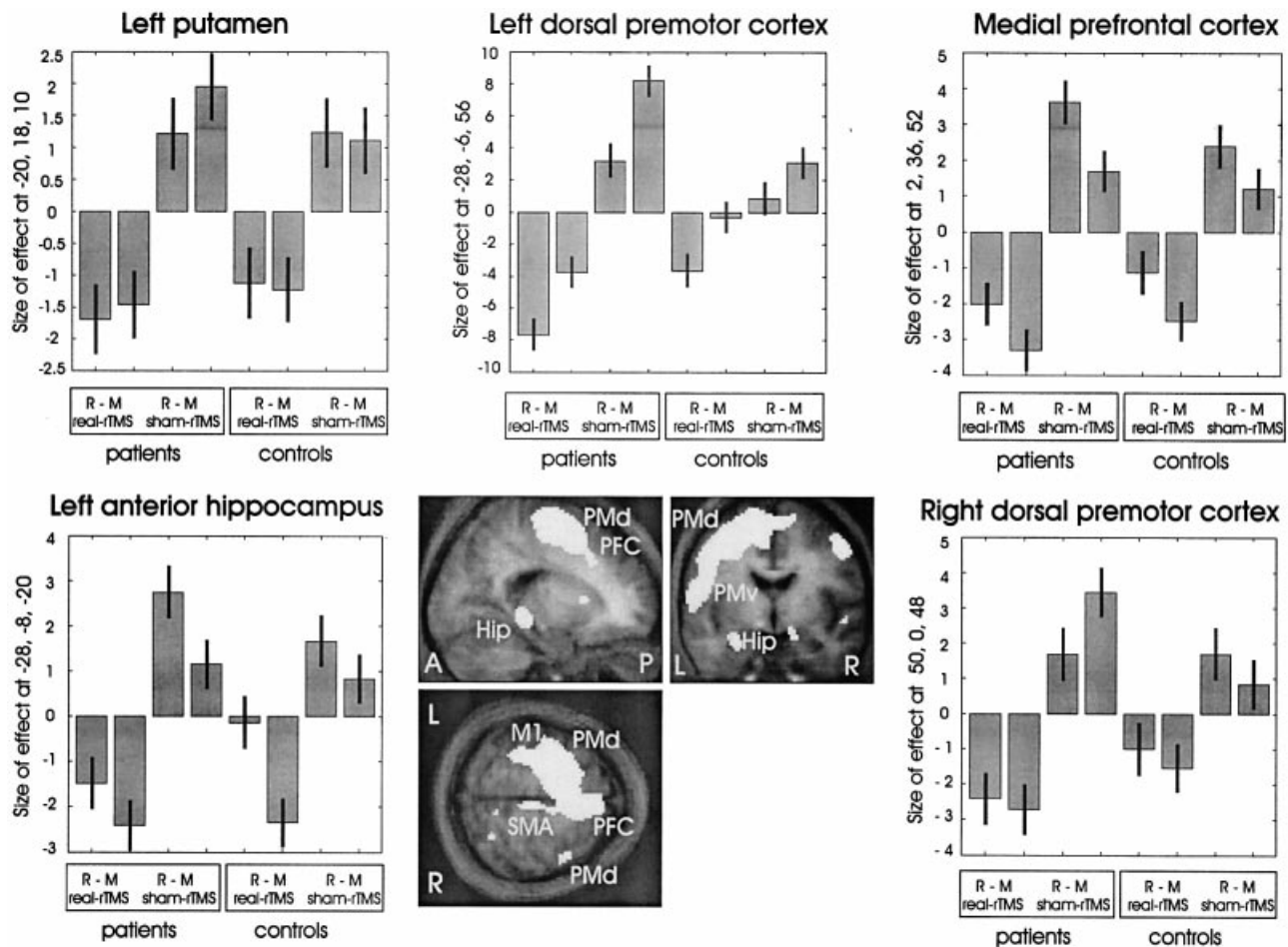
3.63; Talairach coordinates in millimetres:  $x = 26$ ,  $y = -62$ ,  $z = -32$ ).

### Changes in activity induced by rTMS.

Compared with sham-rTMS, real-rTMS gave rise to widespread bilateral reduction in synaptic activity (as indexed by a decrease in rCBF) in the frontal lobes with a left-hemispheric preponderance (averaged across groups and conditions; Fig. 3 and Table 4). The maximal reduction was found in the left premotor cortex, at the site of rTMS. On the lateral surface of the left hemisphere, the frontal cluster extended caudally into the ipsilateral SM1, laterally into the ventral premotor cortex (PMv) and rostrally into the lateral prefrontal cortex. The frontal cluster included the medial prefrontal cortex and the SMA, and extended to the right lateral premotor and prefrontal cortex. Separate right-hemispheric reductions in rCBF occurred in the PMv, PMd and SM1.

Real-rTMS over the left PMd also caused a reduction in rCBF outside the frontal cortex, including the temporal lobe, hippocampus, parietal areas and left putamen. The size of cortical decreases in synaptic activity did not diminish over the 1-h scanning session. No time-dependent increases in activity that might indicate 'recovery' from the reduced activation towards baseline were found. Subcortically, activity in the medial part of the left globus pallidus was initially suppressed by premotor rTMS and then increased back towards baseline (Fig. 4; maximum  $T$ -score = 3.90 at voxel  $x$ ,  $y$ ,  $z = -12$ ,  $12$ ,  $-6$ ).

In contrast to other brain areas engaged in the generation of random finger movements, the cerebellum showed widespread bilateral increases in synaptic activity after real-rTMS over the left PMd (averaged across groups and conditions). The lasting increase of rCBF in the cerebellum was most marked on the right ipsilaterally to the moving hand. Other brain regions showing a lasting increase in rCBF included the



**Fig. 3** Regional decreases in synaptic activity after real-rTMS to the left dorsal premotor cortex (both groups, both conditions). The statistical parametric maps in the centre of the figure illustrates which brain regions demonstrated a decrease in normalized rCBF after premotor 1 Hz rTMS ( $P < 0.05$ , corrected). The white  $T$ -score maps are superimposed on the averaged T<sub>1</sub>-weighted magnetic resonance images of all participants. The bar charts illustrate the region-specific profile of relative changes in rCBF for the voxels showing peak deactivation after premotor 1 Hz rTMS. Each bar represents the mean percentage change in rCBF ( $\pm$  standard error) for each of the four conditions in dystonic patients and healthy controls. The rCBF values given on the ordinate are adjusted to the mean. PMd = dorsal premotor cortex; PMv = ventral premotor cortex; SMA = supplementary motor area; PFC = prefrontal cortex; M1 = primary motor hand area; Hip = hippocampus.

right orbitofrontal cortex, the right putamen and the right insula.

Although real-rTMS resulted in widespread changes in rCBF, there was no change in the relative magnitude nor the spatial pattern of movement-related activity (defined by the interaction between intervention and the contrasts of freely selected finger movements versus rest) in patients or controls even at a reduced statistical threshold ( $P < 0.001$  uncorrected).

### *rTMS and task interactions with dystonia*

The magnitude of rTMS-induced changes in activity differed between patients and controls for both movement and rest conditions. Patients demonstrated significantly greater decreases in rCBF in the left rostral PMd (i.e. at the site of rTMS). A greater reduction in rCBF was also found in other

frontoparietal areas, including the precuneus, right rostral PMd, left PMv, left dorsolateral prefrontal cortex, SMA, anterior cingulate cortex and the left sensory cortex (Fig. 5 and Table 5). Subcortically, real-rTMS gave rise to a stronger decrease in rCBF in the left putamen and the left thalamus in patients with dystonia (Table 5). In contrast, healthy controls showed greater bilateral decreases in rCBF than patients in the lateral temporal lobe and the posterior insula as well as in the right angular gyrus. For rTMS-induced increases in rCBF, patients showed greater responses in the vermis and both cerebellar hemispheres.

### **Discussion**

We found that 1 Hz rTMS to the left PMd produced lasting changes in normalized rCBF in cortical and subcortical areas, indicating a widespread alteration in regional synaptic

**Table 4** Clusters of brain regions demonstrating a decrease in normalized rCBF in both groups and conditions after premotor 1 Hz rTMS

Brain regions		Side	Voxels per cluster	T-value of peak decreases	Coordinates of peak decreases		
					x	y	z
1.	PMd	Left	16299	−8.74	−28	−6	56
	PMd	Left		−8.70	−18	−4	62
	Medial frontal gyrus	Medial		−8.66	2	36	52
	Caudal SMA	Medial		−6.39	4	−20	72
	Primary sensorimotor cortex	Left		−6.40	−46	−10	40
	Primary sensorimotor cortex	Left		−6.41	−32	−32	54
2.	Ventral premotor cortex	Right	265	−6.43	58	4	16
3.	Primary sensorimotor cortex	Right	1286	−6.45	60	−18	40
	PMd	Right		−6.46	50	0	48
	Primary sensorimotor cortex	Right		−6.47	40	−22	48
4.	Medial temporal cortex	Left	202	−6.49	−16	−30	−4
5.	Inferior temporal gyrus	Right	329	−6.51	62	−48	4
6.	Inferior temporal gyrus	Left	994	−6.53	−56	−58	12
				−6.54	−52	−54	28
7.	Hippocampus	Left	281	−6.56	−28	−8	−20
8.	Medial temporal lobe	Right	88	−6.59	20	−12	−34
9.	Superior temporal gyrus	Right	35	−6.61	56	0	−4
10.	Cuneus	Right	49	−6.63	10	−78	32
11.	Precuneus	Right	46	−6.65	14	−64	56
12.	Intraparietal sulcus	Right	23	−6.67	28	−56	60
13.	Putamen	Left	50	−6.69	−20	18	10

activity. The conditioning effects of rTMS on the motor system were more prominent in patients than in healthy subjects, suggesting that disease can affect the modifiability of the brain to external conditioning.

In addition, the data show that: (i) the magnitude of the changes in rCBF was as large as the task-related changes seen in a standard finger movement task; (ii) the return towards pre-rTMS activity occurred faster in putamen than in other sites, compatible with the idea that the time course of the effects may differ in different brain regions; (iii) the changes occurred both in areas directly connected to the stimulated site (e.g. motor cortex, SMA) and in remote regions (e.g. cerebellum) two or more synapses distant; and (iv) the effects were present equally at rest and during the random finger task, meaning that the task-related activation was unchanged.

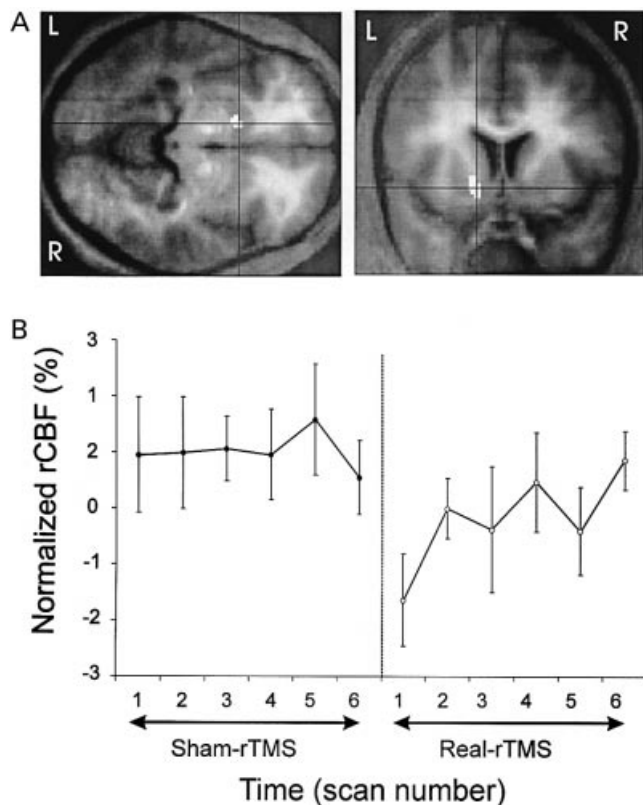
### ***Sustained changes in synaptic activity after premotor rTMS***

Previous PET studies have shown that high frequency rTMS over the SM1 (5 Hz) (Siebner *et al.*, 2000b) or midfrontal cortex (10 Hz) (Paus *et al.*, 2001) produce lasting *increases* of regional glucose metabolism or rCBF in the stimulated area of cortex. The present study extends these studies by showing that 30 min of lower frequency (1 Hz) rTMS over the rostral PMd can *decrease* normalized rCBF in the stimulated cortex for up to 1 h after the end of stimulation.

The changes in normalized rCBF after rTMS were widespread. The junction region of the coil we used is

~4 cm long so that some of this may have been due to local spread of stimulation to areas anterior and posterior to the PMd. This might account for the changes we saw in the frontal eye fields and perhaps motor cortex (but see below). However, other effects on rCBF occurred at distant sites in both cortical and subcortical structures. Much of this would be consistent with activation of anatomical connections from the stimulated areas. The PMd is known to have connections with the lateral prefrontal cortex, anterior cingulate, SMA, sensorimotor cortex, putamen and precuneus, all of which had decreased rCBF after rTMS. Effects in the right (contralateral) PMd and sensorimotor cortex may have been due to activation through transcallosal connections. Together, this pattern of distant changes in rCBF is in good agreement with previous PET studies (Siebner *et al.*, 2000b; Paus *et al.*, 2001) showing that PET imaging after a conditioning session of rTMS is useful for mapping the functional connectivity of the stimulated cortical area.

Premotor 1 Hz rTMS also changed neuronal activity in subcortical brain regions. In parallel with the reductions in rCBF observed in the left frontal cortex there was a *decrease* in rCBF in the left lateral putamen, indicating a suppression of synaptic activity within cortico-basal ganglia-thalamo-cortical re-entry loops. A remote after effect of frontal rTMS on basal ganglia was also demonstrated recently in a radioligand PET study on healthy subjects where high-frequency rTMS of the left dorsolateral prefrontal cortex reduced <sup>11</sup>C-raclopride binding in the left dorsal caudate nucleus (Strafella *et al.*, 2001).



**Fig. 4** 'Recovery' from rTMS-induced decrease in synaptic activity in the left globus pallidus. (A) Axial and transverse SPMs of voxels that showed an initial decrease in rCBF after premotor 1 Hz rTMS that recovered toward baseline levels during the 50-min period of PET scanning ( $P < 0.001$ , uncorrected). (B) Profile of time-dependent changes in normalized rCBF for the voxel with the stereotactic coordinates  $x = -12$ ,  $y = 12$ ,  $z = -6$  in millimetres.

In contrast to the decrease in rCBF found in the left lateral putamen, we noted a lasting *increase* in normalized rCBF in the cerebellum, particularly contralateral to the side of stimulation. Functional imaging studies in stroke patients have shown that impaired function in frontal cortex is associated with a decrease of synaptic activity in the contralateral cerebellum (Pantano *et al.*, 1986; Infeld *et al.*, 1995; Ishihara *et al.*, 1999). If the conditioning effect of rTMS on PMd in the present experiments had been equivalent to stroke then the same should have occurred here. The fact that the opposite happened indicates that premotor rTMS does not simply induce a cerebro-cerebellar disconnection.

Outside the primary motor system, we also found decreases in normalized rCBF in non-motor areas in the temporal, occipital and parietal lobes. We assign these remote deactivations to concurrent excitation of the frontal eye field and the lateral prefrontal cortex, which have connections to these remote areas. For instance, rTMS-induced excitation of prefrontal-temporal connections may have resulted in deactivation of mesial temporal areas which are strongly

interconnected with the prefrontal cortex in monkeys (Petrides and Pandya, 1999; Thierry *et al.*, 2000).

It is important to recall that these changes in rCBF at distant sites persisted after the end of rTMS. One explanation is that rTMS had a persisting effect on synaptic activity of premotor-cortical and premotor-subcortical pathways and that this secondarily led to changes in basal activity in connected areas of brain. An alternative explanation is that during rTMS premotor-cortical and premotor-subcortical pathways were stimulated repetitively and this pattern of activity provoked local changes in activity of target structures. At the present time, we cannot distinguish between these possibilities.

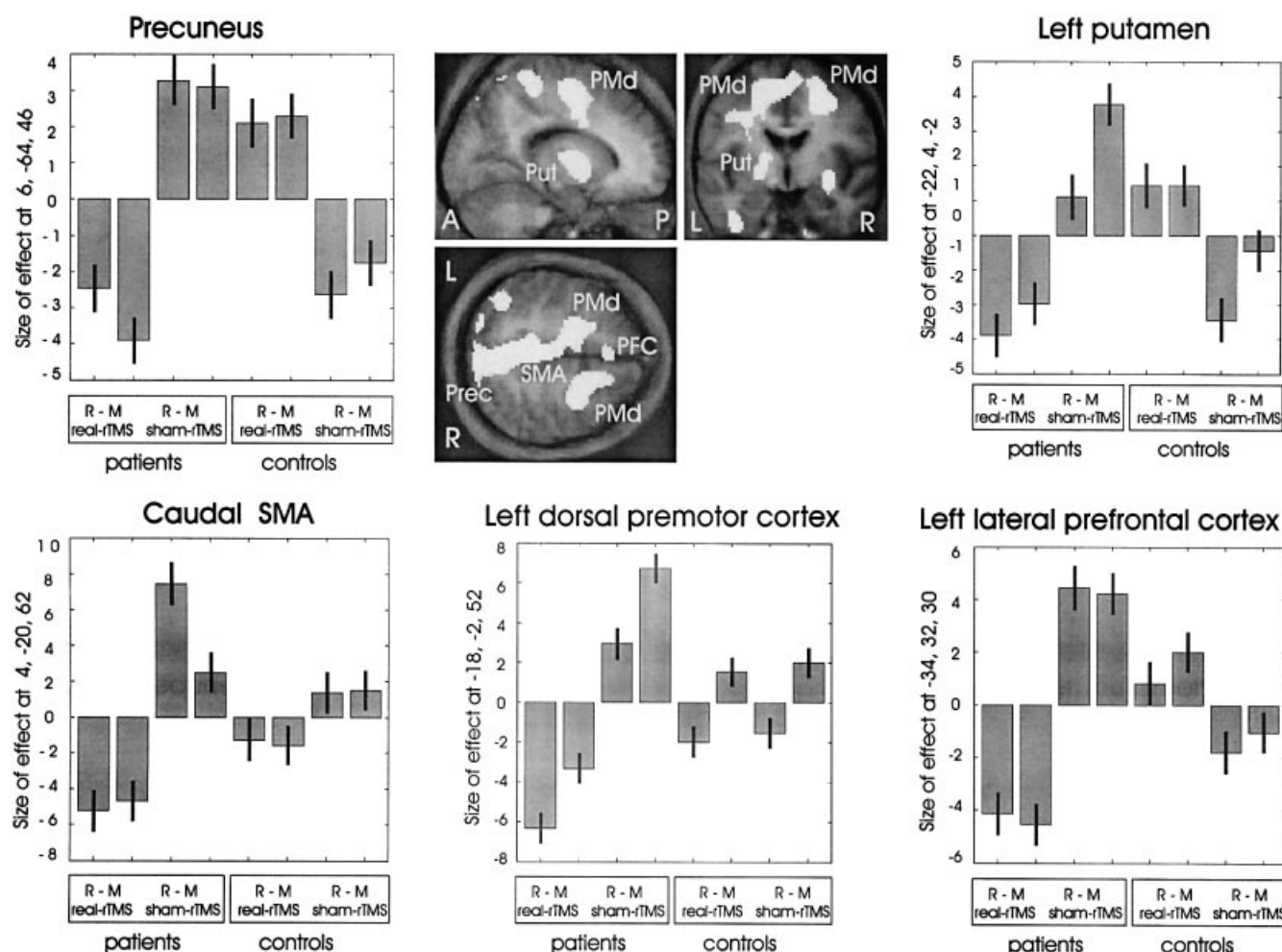
Both local and remote changes in cortical and cerebellar rCBF were stable over time across consecutive PET scans, indicating sustained suppression of cortical activity for at least 1 h after the end of premotor 1 Hz rTMS. By contrast, a focus of decreased synaptic activity in the medial aspect of the left globus pallidus was initially suppressed by premotor rTMS and then returned back towards baseline. This indicates that there are region-specific differences in the duration of conditioning effects in the human brain.

One of the most unexpected findings was the scale of the changes induced by rTMS. In many cortical areas, the magnitude of changes in rCBF after rTMS was as large as task-related activation seen with movement of the fingers. Such large changes in baseline activity indicate that there is substantial ongoing synaptic activity even at rest, and that this can be reduced by 1 Hz rTMS for up to 1 h after the end of stimulation.

### Increased modifiability of the motor system in dystonia

Patients showed a larger response to rTMS than the control group, both at the site of stimulation and in connected motor structures at a distance. This was not related to any differences in task performance since (i) the differences were present at rest and (ii) the task was performed equally well by patients and healthy subjects (Price and Friston, 1999). Therefore, increased responsiveness of the motor system to rTMS of the PMd reveals a physiological trait that characterizes patients with focal arm dystonia.

Patients with focal dystonia have two other physiological deficits that may be related to our findings. First, there is evidence of reduced excitability of inhibitory circuits in many areas of the motor system from cortico-cortical inhibition in motor cortex (Ridding *et al.*, 1995; Ikoma *et al.*, 1996; Chen *et al.*, 1997b; Filipovic *et al.*, 1997; Siebner *et al.*, 1999b; Abbruzzese *et al.*, 2001) to reciprocal inhibition in the spinal cord (Nakashima *et al.*, 1989; Panizza *et al.*, 1990). The former is associated with a reduced level of the inhibitory neurotransmitter GABA ( $\gamma$ -aminobutyric acid) in the sensorimotor cortex and the lentiform nuclei shown with MR spectroscopy (Levy and Hallett, 2002). The second deficit is



**Fig. 5** Areas of increased rTMS-induced reduction in synaptic activity in patients compared with healthy controls. The statistical parametric maps in the centre of the figure show regions in the brain where dystonic patients demonstrated a greater decrease in rCBF than healthy controls after premotor 1 Hz rTMS ( $P < 0.05$ , corrected). The  $T$ -score maps are superimposed on the averaged  $T_1$ -weighted magnetic resonance images of all participants. The bar charts illustrate the region-specific profile of relative changes in rCBF for the peak voxels showing a difference in deactivation between patients and controls. Each bar represents the mean percentage change in rCBF ( $\pm$  standard error) for each of the four conditions in dystonic patients and healthy controls. The rCBF values given on the ordinate are adjusted to the mean. For abbreviations see legend to Fig. 3.

an increased functional connectivity between cortical and subcortical motor areas that was described in earlier PET studies (Eidelberg *et al.*, 1995, 1998; Ibáñez *et al.*, 1999). Eidelberg *et al.* (1995) reported that the topographic covariance profile of resting brain glucose metabolism was abnormal in idiopathic dystonia. This profile was characterized by relative increases in metabolic activity in lateral premotor, lateral prefrontal areas and the rostral SMA, associated with covarying relative hypermetabolism in subcortical structures, including the lentiform nucleus, pons and midbrain. This abnormal topographic covariance pattern was also found in asymptomatic carriers of the DYT1 gene mutation, indicating that it may represent a primary functional abnormality (Eidelberg *et al.*, 1998). We speculate that in our patients the combination of reduced excitability of inhibitory systems and increased functional connectivity

contributes to the increased effectiveness of rTMS both at the site of stimulation and in distant connected sites.

### Movement-related activations in focal arm dystonia

Previous work has reported variable patterns of movement-related activity in patients with focal arm dystonia. Depending on the motor task, an increase in movement-related activity (Odergren *et al.*, 1998; Pujol *et al.*, 2000), a decrease in movement-related activity (Ceballos-Baumann *et al.*, 1997; Ibáñez *et al.*, 1999; Oga *et al.*, 2002) or normal levels of activity (Ibáñez *et al.*, 1999; Preibisch *et al.*, 2001) have been seen in executive motor areas such as the SM1 and the caudal SMA. In the right PMd, Ceballos-Baumann *et al.*

**Table 5** Clusters of brain areas that showed greater reductions in rCBF after real-rTMS in dystonic patients compared with healthy controls

Brain regions	Side	Voxels per cluster	T-value of peak differences	Coordinates of peak differences		
				x	y	z
1. Precuneus	Right	10739	9.50	6	-64	46
Precuneus	Medial		8.97	0	-46	46
PMd	Left		7.01	-18	-2	52
PMd	Right		5.40	32	-6	52
PMv	Left		6.87	-40	18	22
Anterior middle frontal gyrus	Left		8.18	-34	32	30
Posterior middle frontal gyrus	Left		7.85	-36	12	38
Superior frontal sulcus	Right		6.40	20	10	54
Caudal SMA	Medial		6.26	-4	-20	62
Medial prefrontal gyrus	Medial		6.01	2	28	42
Anterior cingulate cortex	Right		7.26	12	22	18
Anterior cingulate cortex	Medial		4.98	-2	4	42
Frontopolar cortex	Left		5.36	-30	52	8
Postcentral gyrus	Left		6.63	-22	-38	64
Superior parietal lobule	Left		4.91	-16	-62	66
2. Putamen	Left	90	7.23	-22	4	-2
3. Thalamus	Left	97	6.95	-6	-18	8
4. Medial frontal gyrus	Right	36	4.77	34	48	18
5. Superior temporal gyrus	Left	1151	7.50	-60	-46	18
Supramarginal gyrus	Left		7.32	-66	-42	30
Inferior temporal gyrus	Left		7.04	-68	-48	-2
6. Inferior temporal gyrus	Left	46	5.97	-38	-6	-40
7. Hippocampus	Right	24	5.13	24	-18	-22
	Right		5.12	32	-22	-16

(1997) found an enhanced increase in rCBF during handwriting, whereas Ibáñez *et al.* (1999) reported a bilateral decrease in activation. The reason for these differences may depend on whether the movements studied (and task performance) were affected by dystonia.

In our study, finger movements in dystonic patients produced the same amount and pattern of movement-related PET activation as in healthy subjects. This may have been because the motor task we used was relatively simple and did not provoke dystonia. Indeed, in a study of writer's cramp, Ibáñez *et al.* (1999) found normal activation of frontal motor cortex during finger tapping, but found reduced activation of the lateral premotor cortex during handwriting and the SM1 during sustained contraction. Alternatively, our patients may have had milder dystonia than those reported, for example, by Ceballos-Baumann *et al.* (1995).

One focus in the right cerebellar hemisphere showed a trend towards an increase in movement-related activity during freely selected movements in the patients. Obergren *et al.* (1998) and Preibisch *et al.* (2001) have also reported an increase in movement-related cerebellar activity in patients with focal hand dystonia. Conversely, Ceballos-Baumann *et al.* (1997) found that treatment with botulinum toxin injections reduced movement-related activity in the upper part of the right cerebellar hemisphere and the vermis. Increased responsiveness of the cerebellum to premotor rTMS and increased movement-related activity suggest a functional involvement of

the cerebellum in the pathophysiology of dystonia which warrants further study.

### **No change in movement-related activity following premotor rTMS**

Although rTMS had prominent after-effects, the pattern of movement-related changes in activity during freely selected finger movements was unchanged following premotor rTMS. Similarly, performance of the random finger task itself was unaffected by rTMS. This implies that changes in relative levels of activity are more likely to be related to task performance than absolute levels. Precisely what this basal level of activity represents is unclear. The fact that it has little effect on task performance suggests, at first sight, that it may not be critical. However, the random finger task was not very demanding since it was designed to be as easily performed by patients as healthy subjects. When we tested the motor system in a more demanding task between scans, the speed of rapid finger movements slightly decreased. Perhaps the basal level of activity is normally set to be in the optimal part of the 'dynamic range' of cortical performance. Moving it towards one end of that range with rTMS may then affect only the most demanding tasks.

Another possible explanation is related to the functional state of the left PMd during 1-Hz rTMS. It has been shown that the functional state of the stimulated cortex has a

considerable impact on the after-effects of rTMS (Ziemann *et al.*, 1998a). Since participants did not perform freely selected finger movements during rTMS, specific motor circuits concerned with task performance were 'idling' during rTMS. This, in turn, may have made them relatively resistant to the inhibitory effects of rTMS. A possible way to augment the after-effects of rTMS in a specific functional network would be to apply rTMS during task performance (Siebner *et al.*, 1999a).

### Possible therapeutic application of rTMS in dystonia

Although this study was not designed to evaluate the therapeutic potential of premotor 1 Hz rTMS in hand dystonia, the results are relevant for future therapeutic trials in dystonia. The good news is that a single session of 1 Hz rTMS to the left PMd is indeed capable of inducing sustained and wide-spread changes in neuronal activity throughout the motor system, especially in dystonic patients. The bad news, however, is that, at least when tested 1 h after the end of rTMS, there were no effects on handwriting or clinical scoring of hand movements. Of course, there may have been subtle effects at an earlier time, as suggested by previous studies (Siebner *et al.*, 1999a, b), but even if this had been the case, a reliable therapy would require longer-lasting effects. It is worth noting that deep brain stimulation produces therapeutic effects in dystonia only after prolonged stimulation (for weeks or months) (for review, see Volkmann and Benecke, 2002). Further studies are now needed to test whether more reliable and specific effects can be obtained with different stimulation protocols, or by giving repeated days of stimulation, or by giving rTMS when patients are performing tasks that activate specific neural circuits. However, a prerequisite for optimizing therapeutic efficacy of rTMS is a detailed knowledge of how rTMS interacts with the dysfunctional motor system in dystonia. The combination of rTMS with functional brain mapping provides a powerful approach to tackle these issues and will help to transfer rTMS from the merely scientific domain into a therapeutic application for neurological disorders.

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