

Modulatory Effects of 5Hz rTMS Over the Primary Somatosensory Cortex in Focal Dystonia—An fMRI-TMS Study

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Abstract: Dystonia is associated with impaired somatosensory ability. The electrophysiological method of repetitive transcranial magnetic stimulation (rTMS) can be used for noninvasive stimulation of the human cortex and can alter cortical excitability and associated behavior. Among others, rTMS can alter/improve somatosensory discrimination abilities, as shown in healthy controls. We applied 5Hz-rTMS over the left primary somatosensory cortex (S1) in 5 patients with right-sided writer's dystonia and 5 controls. We studied rTMS effects on tactile discrimination accuracy and concomitant rTMS-induced changes in hemodynamic activity measured by functional magnetic resonance imaging (fMRI). Before rTMS, patients performed worse on the discrimination task than controls even though fMRI showed greater task-related activation bilaterally in the basal ganglia (BG). In controls, rTMS led to improved discrimination; fMRI

revealed this was associated with increased activity of the stimulated S1, bilateral premotor cortex and BG. In dystonia patients, rTMS had no effect on discrimination; fMRI showed similar cortical effects to controls except for no effects in BG. Improved discrimination after rTMS in controls is linked to enhanced activation of S1 and BG. Failure of rTMS to increase BG activation in dystonia may be associated with the lack of effect on sensory discrimination in this group and may reflect impaired processing in BG-S1 connections. Alternatively, the increased BG activation seen in the baseline state without rTMS may reflect a compensatory strategy that saturates a BG contribution to this task. © 2009 Movement Disorder Society

Key words: writer's cramp; primary dystonia; basal ganglia; sensory discrimination; sensorimotor cortex; premotor cortex; fMRI; TMS; repetitive TMS

INTRODUCTION

Writer's dystonia (writer's cramp) is a task-specific focal dystonia characterized by agonist and antagonist

muscle co-contraction causing abnormal posturing. Lesion studies suggest basal ganglia (BG) dysfunction.^{1–3} Hypotheses regarding underlying pathophysiological mechanisms include theories of disturbed surround inhibition suggesting an inability to constrain the pattern of evoked neuronal activity and to select appropriate neuronal responses resulting in involuntary movement.^{4–6} An alternative hypothesis suggests disturbed plasticity leading to motor system sensitization producing overactivity within the sensorimotor system.³ Recent electrophysiological and neuroimaging studies in genetic⁷ and non-genetic dystonia^{5,8} support these hypotheses.

In addition to abnormal motor behavior and disturbed motor learning,⁹ there is evidence of sensory involvement in writer's dystonia including impaired somatosensory discrimination.^{10,11} Structural S1 involvement¹² has

Additional Supporting Information may be found in the online version of this article.

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Potential conflict of interest: nothing to report.

Received 22 June 2009; Revised 4 September 2009; Accepted 6 September 2009

Published online in Wiley InterScience(www.interscience.wiley.com).

DOI: 10.1002/mds.22825

been demonstrated in focal dystonia. Functional imaging has shown abnormal activation of the primary sensorimotor cortex present during writing.¹³ Pathological BG function was demonstrated during a sensory discrimination task in which the orientation of gratings delivered to the index finger had to be discriminated.⁸ Furthermore, slow-frequent repetitive transcranial magnetic stimulation (rTMS) over the sensory cortex produces reduction of short afferent inhibition, a measure of sensorimotor integration, in writer's cramp, while healthy subjects showed no changes.¹⁴ The same rTMS stimulation protocol applied over the motor cortex, however, does not produce changes in patients.¹⁴ The importance of the sensorimotor involvement is furthermore supported by a finding that 8-week sensory training of Braille reading at Grade 1 for 30 to 60 min daily improves not only spatial acuity but also motor symptoms in arm dystonia patients.¹⁵

rTMS allows a noninvasive assessment of cortical excitability and can produce lasting effects on brain excitability of excitatory or inhibitory nature depending on distinct stimulation paradigms.¹⁶ Recently, rTMS has been explored regarding its potential to normalize distorted brain excitability with preliminary evidence emerging of electrophysiological and behavioral modification following rTMS.¹⁷ For example, 1 Hz-rTMS reduced motor and premotor cortex excitability; in focal hand dystonia this was accompanied by mild improvement in hand function.^{18,19} Others showed improvement of discrimination ability by high-frequent (facilitating) rTMS over the primary somatosensory cortex in healthy subjects.²⁰ In dystonia, potentially beneficial effects of high-frequent rTMS on impaired somatosensory abilities have not yet been explored.

Here, we aimed at improving tactile perception in focal arm dystonia through application of noninvasive high-frequent rTMS over the contralateral primary somatosensory cortex. To capture rTMS-induced neural activity changes, psychophysical studies^{21,22} were combined with event-related functional magnetic resonance imaging (fMRI). On the basis of previous results, we predicted modification of cortical and subcortical processing and improvement of tactile acuity in patients and controls.

SUBJECTS AND METHODS

Subjects

We studied 5 patients with writer's dystonia (2M; aged 59 ± 14.9 ; range: 43–80) affecting the dominant right hand. Average disease onset age was 49 ± 10.5 years, average disease duration was 9 years (range

5–21). Disease severity was mild to moderate based on the writer's cramp rating scale.²³ Patients scored between 4 and 8 points (range of scale: 0–28). Five healthy controls (3M; mean 34.3 ± 3 yrs; range: 31–46) without family history of movement or neuropsychiatry disorders were recruited from a departmental register of volunteers. Inclusion criteria for all subjects were a normal MRI brain scan, right-handedness, and absence of previous brain spinal or peripheral nerve surgery/trauma. Further inclusion criteria for patients were (1) clinically significant right-sided primary writer's dystonia, no other cause for dystonia ascertained by clinical assessment, blood tests to exclude secondary dystonia (full blood counts, copper studies, liver function tests, acanthocytes, white cell enzymes and metabolic screen) and neuroimaging; (2) absence of additional neurological or psychiatric disease; (3) no history of neuroleptic intake or current use of CNS-modulatory drugs; (4) absence of carpal tunnel syndrome or other causes of secondary reduced sensory impairment (e.g., diabetes mellitus); (5) no use of botulinum toxin in the previous 4 months.

The Joint Ethics Committee of the IoN/NHNN approved the study, which was performed according to the Declaration of Helsinki. Written informed consent was obtained. None of the participants reported any side effects from the experiment.

Data Acquisition

Frequency Discrimination Task

The task has been described elsewhere.¹⁷ Briefly, we applied different stimulation frequencies pair-wise (f1 and f2) to the right index finger for a duration of 1s each in a two-alternative force-choice design, using a Digitimer (Hertfordshire, UK) DS7A stimulator for electrical finger stimulation. Disposable surface-adhesive electrodes (SpesMedica, Battipaglia, Italy) were mounted on the radial side of the right index finger, with the anode to the distal phalanx and the cathode to the proximal phalanx. Stimulation intensity was set to 2–3-times the sensory threshold.

f1 and f2 were separated by variable interstimulus 2–4s intervals (randomly jittered in steps of 1s). Frequencies of f1 and f2 stimulation ranged between 20 and 36Hz, but were never identical within one stimulation pair. The absolute difference between the two frequencies for each event was 1–7Hz. A total of 10 events were presented for each frequency difference, resulting in 70 events. Following each pair of stimuli, subjects had to indicate whether the first or the second stimulation was of a higher frequency by

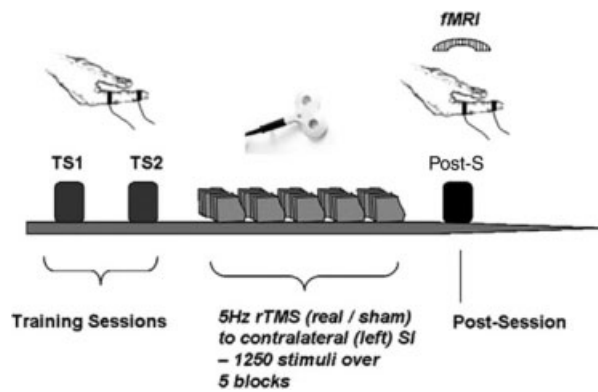


FIG. 1. Experimental design. Before the event-related fMRI sessions, participants practiced the sensory task with their right index finger during two training sessions (TS) outside the MRI scanner. After they reached a stable psychophysical performance, the rTMS coil was fixed over the S1 area. rTMS was applied, either using the real or the “sham” protocol. Within 7 min, participants were placed in the scanner. Event-related fMRI measurements were acquired during performance of the post-TMS sensory task.

pressing a button with the nonstimulated left index finger within 2s following f2. The mode of indicating the somatosensory judgment was counterbalanced across subjects. Two subjects had to indicate following the second stimulus whether the first or the second frequency was higher, the remainder whether the first or second frequency was lower. In either case, participants were instructed to press the button once to indicate the first stimulus or twice to indicate the second stimulus. During fMRI, stimulation trials were interleaved by so-called “null trials” which had the same duration as “real” trials but did not include tactile stimulation. “Null trials” occurred randomly throughout the experiment to assess baseline brain activity.

Figure 1 shows the study design. Subjects practiced for two training sessions to stabilize performance before rTMS application. Following rTMS the sensory task was performed during fMRI scanning. Each subject underwent the whole experiment twice, once with real, once with sham-rTMS (i.e. placebo condition) in a counterbalanced design. At least 48 hours separated both experiments to exclude carryover effects. Patients were instructed to be completely relaxed during the task and this was ascertained by observation during the training session. Pre-fMRI EMG recording was also performed to exclude involuntary muscle contraction.

TMS

We used a MAGSTIM Rapid Stimulator (Magstim, Whitland, Dyfed, UK) with a figure-of-eight-shaped

coil. Subjects sat in a comfortable chair. Using single-pulse TMS, we identified the right FDI representation on the left hemisphere M1 as the position with highest motor-evoked potentials (MEPs). The motor threshold (MT) was defined as the lowest intensity evoking 5 of 10 MEPs with an $>50 \mu\text{V}$ amplitude. The position of the right index finger representation in the left S1 was defined by moving the coil 2cm posteriorly in the parasagittal direction.²⁴

The rTMS intensity was set to 90% of the MT. For rTMS, a total of 25 trains of pulses were applied through the tangentially oriented coil positioned over S1, the handle pointing backwards. Each train consisted of 50 single 5Hz-pulses lasting 10s, with an 2s-intertrain interval. The 25 trains were grouped into blocks; each block consisting of five trains, thus a total of five blocks and 1250 TMS pulses. Each block was followed by a 1 min-stimulus-free interval before continuation. All participants tolerated rTMS well without side effects. In the sham (placebo) condition, the coil was oriented toward the same direction as during real-rTMS but tilted 90° off the surface of the head, thus, only the edge of the coil touched the scalp.²⁵ This causes tickling sensations on the skull without cortex stimulation. The TMS coil position was marked by vitamin E capsules. After rTMS application, with the capsule still fixed over the point of stimulation, subjects performed the post-rTMS sensory task (Post-S) while fMRI and structural MRI were performed. Both scans were coregistered. Using Statistical Parametric Mapping (SPM), we localized the capsule and assessed its MNI coordinates. The spatial relationship between the TMS coil position on the scalp and the rTMS-induced cortical changes was calculated as Euclidean distance between the capsule localization coordinates and both peak clusters.

Event-Related fMRI

fMRI measurements were performed with a 3T head scanner (Magnetom Allegra; Siemens, Erlangen, Germany). For acquisition of blood oxygenation level-dependent (BOLD) volumes, we used a gradient echo T2*-weighted echo-planar imaging (EPI) sequence (echo time, 30 ms; repetition time, 2.21s; flip angle, 90°). Each volume comprised 34 oblique (transversal–coronal, -10°) slices of 2 mm thickness and $3 \times 3 \text{ mm}^2$ in-plane resolution with a slice distance of 1 mm, which covered the whole brain except for the cerebellum. A total of 519 volumes per session were acquired continuously. A high-resolution T1-weighted anatomical image was acquired for coregistration with

the functional data. Whole-brain structural scans were acquired using a Modified Driven Equilibrium Fourier Transform (MDEFT) sequence²⁶ with optimized parameters as previously described²⁷ (176 sagittal slices with isotropic spatial resolution 1 mm; matrix 256×224 ; repetition time/echo time/inversion time = 7.92 ms/2.4 ms/910 ms, bandwidth per pixel BW = 195 Hz/Px, $\alpha = 15^\circ$).

Behavioral Data Analysis

We performed nonparametric statistical analysis using the Wilcoxon rank test for assessing within-group effects (real vs. sham; and pre vs. post-TMS). Effects between groups were analysed using the Mann-Whitney-U test (dystonia vs. healthy controls). Perceptual changes were expressed by differences in the percentage of correct responses across all frequencies ($f1-f2 = 1-7$ Hz).

Preprocessing and Analysis of Imaging Data

The data were preprocessed and analyzed using SPM software (SPM5; Wellcome Trust Centre for Neuroimaging, UCL, London, UK). We discarded the first six volumes during which BOLD signal reached steady state. The remaining 513 volumes entered preprocessing. Movement artifacts were removed using affine registration and the unwarp function as implemented in SPM5.²⁸ Volumes were spatially normalized to the standard template of the Montreal Neurological Institute (MNI; voxel size, 2 mm^3).²⁹ Finally, we smoothed the volumes using a 10 mm (full-width half-maximum) isotropic, three-dimensional Gaussian filter. Pooling data of both groups (i.e., dystonia and controls) in one model (i.e., full factorial design) enabled us to assess the effect of frequency discrimination in dystonia as compared to healthy controls. In a second model we included age as a nuisance variable to control for age differences between patients and controls. With this model, we assessed the main effect of rTMS (i.e., rTMS vs. sham TMS) in both groups and the interaction between group (patients vs. controls) and stimulation method (rTMS vs. sham TMS). All inferences were made at the between-subject level by entering the appropriate contrast into one-way ANOVA (threshold, $P = 0.0001$, uncorrected). All reported coordinates correspond to the anatomical MNI space as used in SPM5.

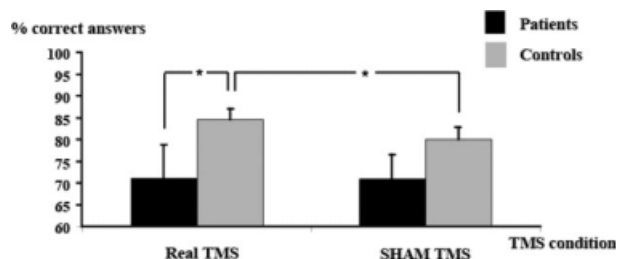


FIG. 2. Tactile discrimination in patients as compared to controls following real and sham TMS. Controls showed improved discrimination following real-rTMS as compared to sham stimulation. Dystonia patients performed worse than controls and failed to improve after rTMS.

RESULTS

Behavior

We found no sensory threshold differences between patients (1.7 ± 0.8 mA) and controls (1.6 ± 0.2 mA, $P = 0.8$). Stimulation intensity was adjusted to 4.0 ± 1.5 mA (patients) and 3.3 ± 1.1 mA (controls) ($P = 0.3$). MT was $60.3 \pm 8.4\%$ for patients and $59.4 \pm 5.5\%$ for controls. Correlating to 90% of MT the output intensity for rTMS was set to $54 \pm 8.1\%$ of the maximum output intensity for patients and $53.2 \pm 5.1\%$ in controls. Of 70 presented stimulus pairs in the baseline condition (following sham-TMS), controls identified $80 \pm 2.8\%$ correctly; patients answered $70.8 \pm 5.7\%$ correctly (Mann-Whitney-U test: $Z = -1.2$, $P = 0.2$) (Figure 2). After real-rTMS in patients frequency discrimination remained unchanged with $71 \pm 7.63\%$ correct discriminations compared to sham (Wilcoxon rank test: $Z = -0.1$, $P = 0.89$). Individual results are shown in Table S3 (Supporting Information). Controls, however, improved following real-rTMS (compared to sham-rTMS) now scoring $84.6 \pm 2.5\%$ correctly (Wilcoxon rank test: $Z = -2.0$, $P = 0.04$). Moreover, when comparing the influence of real-rTMS between groups, we found significantly improved frequency discrimination after real-rTMS in controls compared to patients (Mann-Whitney-U test: $Z = -2.0$, $P = 0.04$). For sham-rTMS we found no differences between groups ($Z = -1.2$, $P = 0.24$). There was no difference in discrimination accuracy between the seven stimulus frequency levels after real or sham stimulation in the patient group ($P > 0.05$).

fMRI

No signal abnormalities were detected in raw EPI-data after thorough image inspection. The vitamin E capsule indicating the stimulation area was over S1 in

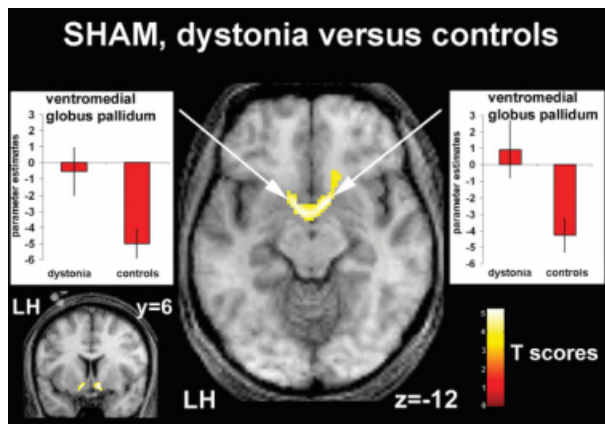


FIG. 3. Discrimination effects in patients vs controls during the sham condition. Dystonia patients show relative overactivity in the ventromedial pallidum bilaterally compared to healthy controls (left hemisphere (LH): $-6, 0, -12$ xyz in mm, $T = 5.19$, $P = 6.27E-06$; right hemisphere: $8, 6, -12$, $T = 5.24$, $P = 5.44E-06$).

all participants. The average Euclidean distance between vitamin E capsule location and S1 peak voxel was 9.22 mm in patients and 7.21 mm in controls. For fMRI data, cortical responses to TMS during tactile discrimination were estimated by comparing trials following real and sham-rTMS. Detailed results are shown in Table S3 (Supporting Information). Figures 3 and 4 and Table S1 show differences in hemodynamic activation.

Without rTMS application (i.e., comparing sham condition against baseline brain activity, see Methods for further details), patients showed greater activity at the level of the pallidum compared to controls (Fig. 3), whereas cortical activity did not differ in both groups. After real-rTMS, we observed a predicted increase in S1 hemodynamic responses both in healthy controls and dystonia patients. Additionally, we found elevated activity in premotor areas bilaterally. Changes in activation due to rTMS (i.e., rTMS vs. sham-TMS) are shown in Figure 4a (dystonics) and Figure 4b (controls). Only controls showed greater activity at the level of the BG output nuclei laterally after rTMS application, which was not present in dystonia patients.

For each group (i.e., patients and controls), we assessed effects of rTMS on hemodynamic responses by comparing real against sham-rTMS. This analysis showed that in both groups real-rTMS led to both an enlargement and enhancement of activation in the left rTMS-stimulated S1 (Fig. 4a,b). When testing for interaction between group (controls vs. patients) and stimulation method (rTMS vs. sham-rTMS) we found significantly more activity in the ventromedial pallidum bilaterally in controls (Fig. 4c).

DISCUSSION

In this study, we show differential effects of high-frequency rTMS applied over the primary somatosensory cortex on tactile discrimination and neural activity in five focal arm dystonia patients compared to 5 healthy controls. Our fMRI results reveal significantly greater pallidal activity in patients compared to healthy controls during tactile discrimination without rTMS (i.e., sham condition) (Fig. 3). This is in agreement with previous reports of increased BG activity during tactile discrimination in writer's dystonia.⁸ The conjecture here is that excessive neuronal processing reflects compensatory mechanisms and failure to efficiently process incoming sensory information.⁸ In line with previous findings of abnormal spatial,^{30,31} temporal,^{31,32} and kinaesthetic³³ tactile perception in dystonia, our patients showed a trend for an impaired tactile discrimination as compared to healthy subjects.^{11,34}

The prime rationale of this study, however, was to improve impaired perception in dystonics by rTMS, based on previous reports showing enhanced tactile discrimination induced by high-frequency rTMS and disrupted discrimination by low-frequency rTMS when applied over the contralateral S1 cortex in healthy subject.³⁵ While rTMS led to predicted gain in somatosensory discrimination in healthy subjects (in accord with Ref. 17) patients' performance did not improve after rTMS application. They performed similarly after real and sham-rTMS suggestive of resistance to plasticity effects of rTMS (Figure 2).

In our study, application of rTMS over the left S1 resulted in increased BOLD signal in the underlying left S1 and PMC, compared to sham, in both healthy subjects and patients (Figure 4). This is in accord with previous findings and can be interpreted as successful rTMS application in both groups.³⁶ However, only controls, but not patients, showed activation of BG output structures after real-rTMS, which may explain the discrepancy in behavioral gain between the groups (Figure 4c). Control subjects alone, who performed better after rTMS, showed rTMS-induced elevation of BG BOLD responses. In contrast, dystonia patients, who behaviorally lacked improvement of tactile abilities, showed no imaging correlate of increased BOLD signal after rTMS. This suggests improvement in tactile discrimination after rTMS is linked to simultaneous activation of S1 and the BG. Since rTMS only affects the cortex and not deeper structures,³⁷ increased hemodynamic responses in BG in healthy controls after real-rTMS is best explained by a propagation of inputs from the stimulated cortex to the BG via intact ana-

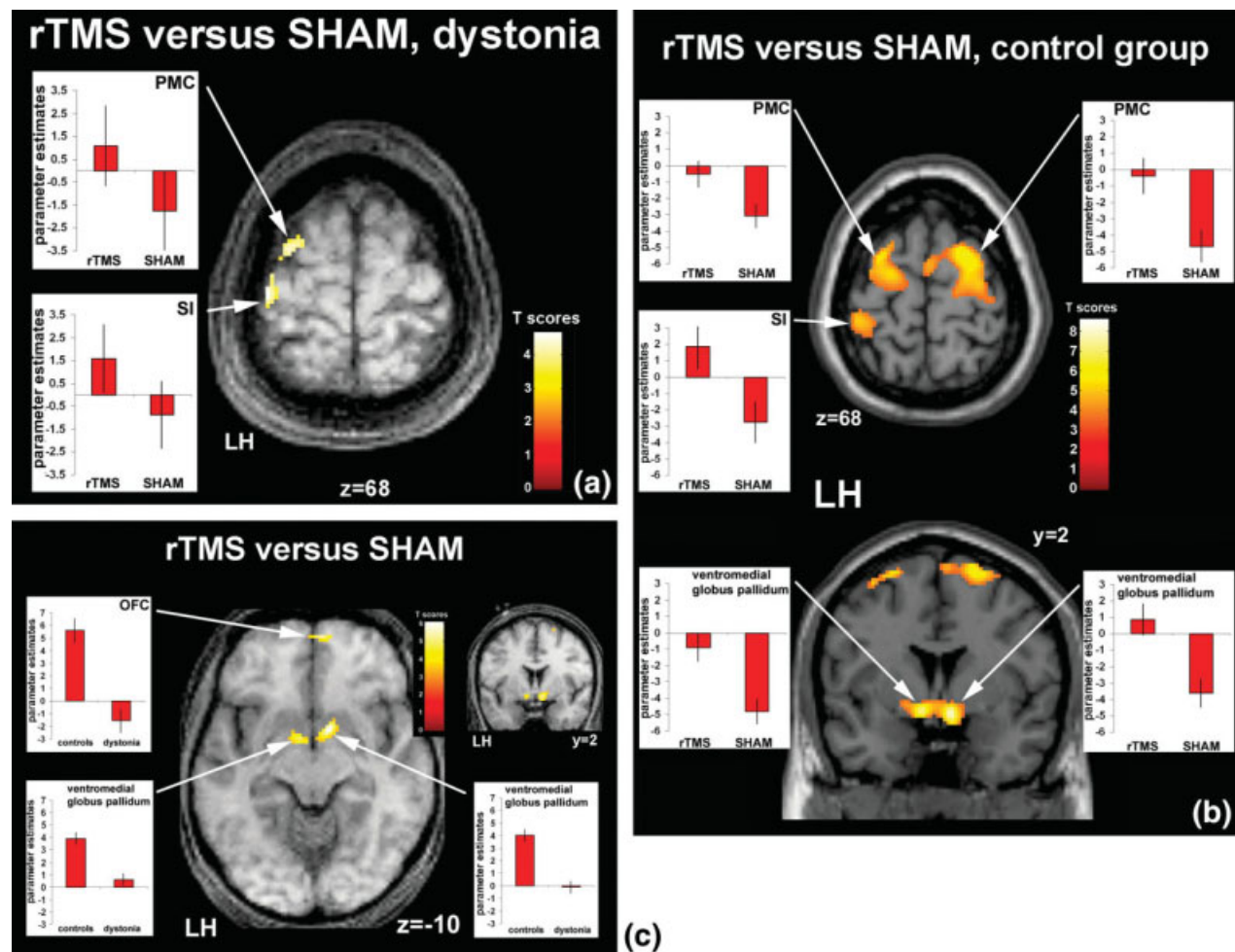


FIG. 4. Effects of rTMS (real versus sham condition) on hemodynamic activation during sensory discrimination task in dystonia patients (A) and controls (B). (C) Interaction (group \times condition) during rTMS, dystonia patients compared to controls. (A) Dystonia patients show relative overactivity in the left premotor cortex (PMC) and the left sensorimotor cortex (SI) (thus, ipsilaterally to the TMS-stimulated hemisphere) after real-rTMS compared to sham stimulation. (B) Healthy controls show relative overactivity in the left premotor cortex (PMC) and the left sensorimotor cortex (SI) following real-rTMS compared to sham stimulation, similar to dystonia patients. In addition, there is activation of the ventromedial pallidum bilaterally. (C) Compared to controls dystonia patients show reduced activity in the left orbitofrontal cortex (OFC) and the ventromedial pallidum bilaterally after real-rTMS compared to sham stimulation.

tomical connections.³⁸ However, in dystonia patients sensory circuits and sensorimotor integration are thought to be corrupted, which may explain the lacking rTMS effect.¹⁴

Vilela Filho³⁹ postulated that during pain perception excitatory glutaminergic cortico-striatal pathways project from the sensorimotor cortex to anterior putamen. The anterior putamen sends excitatory pathways to the

TABLE 1. Clinical data of study participants

Case No	Age/gender	Age of onset	Disease duration	WCRS score	Time since last Btx injection (Months)
1	43/f	38	5	8	4
2	64/f	57	7	5	4
3	80/m	59	21	4	4
4	60/m	55	5	7	4
5	46/f	38	8	4	4

WCRS, Writer's cramp rating scale (according to Wissel et al. 19²³ range of score 0–28); Btx, Botulinum toxin.

internal pallidum (striato-pallidal pathway), which modulates the thalamus and thalamo-cortical projections through the pallidothalamic GABAergic pathway. Similarly, in tactile perception this cortico-striato-thalamic loop may represent a crucial mechanism in fine-tuning of somatosensory inputs. The lack of activation in the BG output structures in dystonia patients after rTMS may rely on a disrupted corticostriatal pathway and may result in an impaired tactile perception before rTMS and a lack of behavioral gain after rTMS. This is in line with results from fiber tracking analysis in adult-onset focal dystonia patients, which point towards abnormal connectivity of sensorimotor projections at the level of putamen and pallidum (B.D., personal communication). An alternative explanation is that in dystonia an already elevated BG activation (Fig. 3) during discrimination (which may be a compensatory phenomenon) leads to a “ceiling effect” such that rTMS is unable to produce additional task-related BG activity and improvement of patients’ performance. Yet another explanation may be that primary defects are localized in S1, compatible with findings of structural S1 involvement.¹³

One of the shortcomings of our study is the relative small sample size. This is due to the endeavour to keep the patient group clinically as homogenous as possible. Another weakness is the relatively broad age range within the groups and between patients and controls. To control for age-related effects, we used a statistical model for our fMRI data which was age adjusted. This suggests that our findings are rather independent of degenerative or age-dependant effects.

In summary, this is the first study using rTMS over S1 cortex in dystonia patients. Our findings support the idea of a primary role of abnormal sensory processing in dystonia as suggested by Hallett.¹⁰ Further research using varied rTMS paradigms and application sites can shed further light on the likely pathogenic mechanisms of dystonia.

Acknowledgments: We thank all the participants in our study and the radiographers at the Functional Imaging Laboratory for their assistance acquiring the data. This research was supported by the Astor Studentship by the Brain Research Trust, UK (SAS) and a Wellcome Trust programme grant (RJD).

Financial Disclosures: SAS: Brain Research Trust, UK; Novartis Foundation, University Luebeck, Germany (Employment); BP: nothing to disclose; BD: funded through a Wellcome Trust grant (Ref: 075696/Z/ 418 04/Z); CC: Funding from Allergan for research on cervical dystonia (~£2000); JCR: Sources of support: 2005–2010 (£700k) Functional Connectivity of the motor system in healthy subjects and in patients with movement disorders or stroke *Medical Research*

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Author Roles: Research project: Conception, Organization, and Execution (S.A.S., B.P., B.D., C.C., K.P.B., R.J.D.); Statistical Analysis: Design and Execution, (B.P., B.D.), Review and Critique (C.C., J.R., K.P.B.); Writing of the first manuscript draft (S.A.S., B.P., B.D.), Review and Critique (C.C., J.R., K.P.B., R.J.D.).

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