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Randomized sham-controlled trial of repetitive transcranial magnetic stimulation in treatment-resistant obsessive–compulsive disorder

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Abstract

In open trials, 1-Hz repetitive transcranial magnetic stimulation (rTMS) to the supplementary motor area (SMA) improved symptoms and normalized cortical hyper-excitability of patients with obsessive–compulsive disorder (OCD). Here we present the results of a randomized sham-controlled double-blind study. Medication-resistant OCD patients ($n=21$) were assigned 4 wk either active or sham rTMS to the SMA bilaterally. rTMS parameters consisted of 1200 pulses/d, at 1 Hz and 100% of motor threshold (MT). Eighteen patients completed the study. Response to treatment was defined as a $\geqslant 25\%$ decrease on the Yale–Brown Obsessive Compulsive Scale (YBOCS). Non-responders to sham and responders to active or sham rTMS were offered four additional weeks of open active rTMS. After 4 wk, the response rate in the completer sample was 67% (6/9) with active and 22% (2/9) with sham rTMS. At 4 wk, patients receiving active rTMS showed on average a 25% reduction in the YBOCS compared to a 12% reduction in those receiving sham. In those who received 8-wk active rTMS, OCD symptoms improved from 28.2 ± 5.8 to 14.5 ± 3.6. In patients randomized to active rTMS, MT measures on the right hemisphere increased significantly over time. At the end of 4-wk rTMS the abnormal hemispheric laterality found in the group randomized to active rTMS normalized. The results of the first randomized sham-controlled trial of SMA stimulation in the treatment of resistant OCD support further investigation into the potential therapeutic applications of rTMS in this disabling condition.

Introduction

Up to 40–60% of obsessive–compulsive disorder (OCD) patients do not have a satisfactory outcome with currently available treatments (Pallanti *et al.* 2002; Simpson *et al.* 2006). The goal of the present study was to evaluate non-invasive focal repetitive transcranial magnetic stimulation (rTMS) for treatment-resistant OCD.

Some neurobiological models have associated OCD pathophysiology to deficits in inhibition of irrelevant information and response control (Chamberlain *et al.* 2005; van den Heuvel *et al.* 2005). Such models would explain the reduced ability of OCD patients to inhibit intrusive thoughts, impulses, or images and repetitive motor responses and have been associated with excessive activity in orbitofronto-striatal regions, but also in medial and lateral frontal areas [e.g. supplementary motor area (SMA), anterior cingulate, dorsolateral prefrontal cortex], and in parietal regions

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(Menzies *et al*. 2008). We found enhanced precentral somatosensory evoked potentials and hypofunctioning of centrifugal sensory gating in OCD that might reflect the inability to modulate sensory information due to a tonic high level of cortical excitability of motor and related areas (Rossi *et al*. 2005). Using TMS as a probe of cortical excitability, Greenberg *et al*. (1998, 2000) found that OCD patients had markedly decreased intracortical inhibition in primary motor cortex.

Consistent with these physiological findings, a recent neuroimaging study suggested that premotor areas, such as SMA and dorsal anterior cingulate (dAC), are hyperactive in OCD, and that this hyperactivity may relate to deficient inhibitory control (Yücel *et al*. 2007). The increased activation of SMA and dAC was interpreted to be compensatory, but it is possible that hyperactivation in these brain regions could represent a primary aspect of OCD. Whether hyperactivation in premotor regions is primary or compensatory is difficult to resolve by functional neuroimaging or neurophysiological studies alone. Focally altering cortical excitability via rTMS represents a means of testing the functional role of these findings.

A handful of studies examined the impact of rTMS on OCD with variable results. Greenberg *et al*. (1997) found that a single session of high-frequency rTMS to the right lateral prefrontal cortex significantly decreased compulsive urges. A double-blind study using right prefrontal low-frequency rTMS and a less focal coil failed to find significant effects (Alonso *et al*. 2001). In contrast, an open study in refractory OCD patients assigned to right or left dorsolateral prefrontal cortex (DLPFC) with high-frequency rTMS found clinically significant and sustained improvement in a third of patients (Sachdev *et al*. 2001). Recently Prasko *et al*. (2006) and Sachdev *et al*. (2007) found that either low- or high-frequency rTMS administered over the left DLPFC did not differ from sham (placebo).

Given the evidence for deficient inhibition in OCD, the use of low-frequency rTMS, which has been reported to be inhibitory on motor cortex excitability (Chen *et al*. 1997), may be a fruitful avenue to explore as a putative treatment. Furthermore, given the evidence of hyperactivation in SMA, a region that plays a central role in the higher cortical control of motor subroutines and the organization of motor actions in sequential order, low-frequency rTMS to SMA may be worth examining. If low-frequency rTMS to SMA improves symptoms and dampens hyperexcitability, that would be consistent with the model that functional hyperactivation seen in that region is primary rather than compensatory.

To test the potential value of low-frequency rTMS to SMA, we performed an open-label study on 10 patients with treatment-resistant OCD and Tourette's syndrome (TS) (Mantovani *et al*. 2006). OCD symptoms improved by an average of 29%, and improvements were significantly correlated with increases in right hemisphere motor threshold (MT) and normalization of baseline hemispheric asymmetry of cortical excitability. Sustained benefit was seen at 3-month follow-up. Subsequently we reported clinical benefit in ⩾2 cases of comorbid OCD and TS (Mantovani *et al*. 2007). While these open-label data are encouraging, it is important to determine whether improvements would be evident in a sham-controlled design.

Here we present a randomized sham-controlled trial of low-frequency rTMS to SMA in treatment-resistant OCD, and test the hypothesis that inhibiting this system, as evidenced by MT change, will be associated with clinical improvement.

Method

Design

This trial consisted of two phases: (1) 4-wk double-blind, and (2) 4-wk open-label. In phase 1 patients were randomly assigned in a 1:1 ratio to either active rTMS or sham, 5 times/wk, for 4 consecutive weeks. At the end of 4 wk, non-responders to sham and responders (as defined below) to either active or sham rTMS were offered the option of receiving open-label rTMS for an additional 4 wk in phase 2. Responders were invited back at 3 months following the last rTMS to assess persistence of benefits during naturalistic follow-up.

Subjects

All patients gave written informed consent, and the protocol was approved by the New York State Psychiatric Institute/Columbia University IRB. To be eligible patients had to be aged between 18 yr and 70 yr, have a primary diagnosis of OCD (confirmed by Structured Clinical Interview for DSM-IV; First *et al*. 1997), current episode duration of at least a year, have residual OCD symptoms [defined as a total Yale-Brown Obsessive Compulsive Scale (YBOCS) score of ⩾16] (Goodman *et al*. 1989*a,b*) despite treatment with an adequate trial of a serotonin re-uptake inhibitor (SRI) and cognitive behaviour therapy (CBT). An adequte SRI trial was defined as treatment for at least 12 wk on the SRI, that meets or exceeds recommended dosage level for OCD (Koran *et al*. 2007). Individuals who could not tolerate, due to side-effects, medications

of this class at the specified dose and duration were also included. An adequate trial of CBT was defined as at least once a week for 8 wk with clear evidence of exposure during sessions and homework given. Patients currently on medication and/or psychotherapy must have been in stable treatment for at least 12 wk before initiation and throughout the study. Patients were excluded if they were treatment-refractory [defined as non-response to clomipramine, at least two selective SRIs (SSRIs) at adequate dose and duration plus CBT in the last year], diagnosed with severe major depressive disorder (MDD) [defined as Clinical Global Impression (CGI) $\geqslant 4$], exhibited significant acute suicide risk, or had a history of bipolar disorder, of any psychotic disorder, or of substance abuse or dependence within the past year. Patients with neurological disorders, increased risk of seizure, use of proconvulsant medications (such as, bupropion, maprotiline, tricyclic antidepressants, classical antipsychotics), implanted devices, metal in the brain, unstable medical conditions, pregnancy, or breast-feeding were excluded. To avoid confounds on motor cortex excitability measures, medications with a known inhibitory effect on brain excitability (e.g. anticonvulsants, benzodiazepines, atypical antipsychotics) were not allowed. We excluded patients with prior TMS exposure to reduce risk of unblinding.

Twenty-one outpatients (eight female; mean age = 38.9 yr, S.D. = 11.9) who met study criteria were recruited between January 2005 and December 2007 from the Brain Behavior Clinic and the Anxiety Disorders Clinic of New York State Psychiatric Institute/ Columbia University. Of these, three did not complete the study for the reasons described below. Analyses were conducted on the entire sample and on the 18 completers (nine in the active and nine in the sham group).

Fourteen patients had as their primary symptoms aggressive and somatic obsessions and checking compulsions, two had contamination obsessions and cleaning compulsions, two had symmetry obsessions and counting, repeating, ordering compulsions. Five patients were on fluoxetine (average dose 76 mg/d), two on S-citalopram (average dose 30 mg/d), two on citalopram (average dose 60 mg/d), two on fluvox-amine (average dose 300 mg/d), and two on sertraline (average dose 225 mg/d). Five patients were on talk therapy during the trial. Ten patients met criteria for moderate non-psychotic MDD.

Outcome measures and response criteria

Patients were evaluated every 2 wk by raters blind to treatment assignment and also completed self-rating forms at the end of each week of treatment. Clinical measures included: YBOCS and YBOCS – Self-rating (YBOCS-SR), Hamilton Depression Rating Scale – 24-item (HAMD-24), Hamilton Anxiety Rating Scale – 14-item (HAMA-14), Beck Depression Inventory – II (BDI-II), Zung Self-Administered Scale (Zung-SAS), CGI – Severity (CGI-S), Patient Global Impression (PGI). The primary efficacy measure was the YBOCS. Patients with a 25% YBOCS reduction at the end of phase 1 were classified as responders (Simpson *et al.* 2008).

Side-effect ratings

Before and after each session patients were asked a series of questions in a structured form in order to rate TMS side-effects.

rTMS methods

rTMS was administered with the Magstim super-rapid stimulator (Magstim Company Ltd, UK) using a vac-uum cooled 70-mm figure-of-eight coil. Stimulation parameters were 1-Hz, 20-min train (1200 pulses/d) at 100% of resting MT (using the lowest value of right or left hemisphere), once a day, 5 d/wk, for 4 wk (in phase 1) to 8 wk (in phase 2). The coil was positioned over pre-SMA, targeted using the International 10–20 EEG System (Choi *et al.* 2006). Pre-SMA was defined at 15% of the distance between inion and nasion anterior to Cz (vertex) on the sagittal midline. The coil was placed with the handle along the sagittal midline, pointing towards the occiput to stimulate bilaterally and simultaneously the pre-SMA.

MT

Resting MT was defined as the minimum magnetic flux needed to elicit a threshold EMG response (50 μV in peak-to-peak amplitude) in a resting target muscle (abductor pollicis brevis) in 5/10 trials using single-pulse TMS administered to the contralateral primary motor.

Blinding

Sham rTMS was administered using the Magstim sham coil which contains a mu-metal shield that diverts the majority of the magnetic flux such that a minimal (<3%) magnetic field is delivered to the cortex (Rossi *et al.* 2007). This coil looks and sounds like an active coil; however, it does not feel like active rTMS, which generates a tapping sensation on the scalp. In order to maintain the blind, we kept the

raters blinded to treatment condition and created a separation between clinical team and rTMS treating physician. We also excluded patients who received TMS before.

Statistical analysis

Besides classifying patients according to categories of response, statistical analyses were performed using SPSS library, version 13.0 (SPSS Inc., USA). A worst-case scenario analysis was computed on the entire sample. χ^2 and Student's t tests were applied to compare demographic, clinical and neurophysiological data between the active and sham groups. χ^2 was used in the completer sample to compare response rate between the two groups; Fisher's exact test was used when expected counts in a cell were <5. Repeated-measures analysis of variance (ANOVA), with adjustments for non-sphericity, were applied to evaluate group and time-dependent effects of rTMS on psychometric scale mean scores. We used the same statistical approach to test whether rTMS affects measures of motor cortex excitability. Student's t test was applied to analyse differences in rating scales mean scores between baseline and 3-month follow-up. Pearson's correlations were applied to examine the relationship between changes in scores of depression and anxiety measures, and change in OCD scores and similarly change in clinical global impressions, and change in OCD scores. Baseline HAMD-24 was used as covariate in the ANOVA (ANCOVA) to examine the effect of depression on OCD symptom changes. Correlations were also performed to test whether baseline motor cortex excitability measures were related to response. All tests were conducted with two-sided significance levels ($\alpha = 0.05$) without corrections for multiple comparisons.

Results

Recruitment and retention

Of the 123 patients screened, 78 were eligible for the study, but only 21 were randomized and assigned to either active or sham rTMS. Most patients were excluded ($n = 45$) because of comorbid severe MDD ($n = 21$), comorbid bipolar disorder ($n = 4$), presence of psychosis ($n = 2$), comorbid TS ($n = 1$), history of seizures ($n = 4$), currently on non-allowed medications ($n = 11$), never tried conventional treatments for OCD ($n = 2$). Fifty-seven eligible patients declined participation before randomization. The main reasons for declining participation were unwillingness to participate

in research ($n = 17$), lack of time ($n = 12$), unable to commute long distances every day ($n = 28$).

Demographics and baseline clinical characteristics of the study population

As shown in Table 1, the active and sham groups did not differ significantly in demographics or baseline clinical ratings.

Randomized phase (phase 1)

Twenty-one patients entered and 18 completed phase 1. The three, who did not complete the study, were withdrawn before starting rTMS (two experienced a worsening of depression and the other fainted during MT determination). Applying a worst-case scenario analysis and assuming that of those three non-completers the two randomized to active were classified as non-responders and the one randomized to sham as a responder, at 2 wk the response rate of the entire sample was 36% (4/11) with active and 10% (1/10) with sham rTMS. At 4 wk, response rate in the entire sample was 54% (6/11) with active and 20% (2/10) with sham rTMS. Analysis of 18 completers showed at 2 wk a response rate of 44% (4/9) with active and 11% (1/9) with sham rTMS (Fisher's exact test, $p = 0.294$). At 4 wk, response rate in the same 18 completers was 67% (6/9) with active and 22% (2/9) with sham rTMS (Fisher's exact test, $p = 0.153$).

Clinical measures at baseline, after 2 wk, and 4 wk active or sham rTMS are presented in Table 2. Repeated-measures ANOVA revealed a significant main effect of time on OCD (YBOCS, YBOCS-SR), anxiety (HAMA-14, Zung-SAS), global assessment (CGI-S, PGI), and depression (BDI-II). The only measure that did not show a significant main effect of time was the HAMD-24.

Time × group interactions were examined to determine which of these improvements with time were related to active *vs*. sham group assignment. The only significant time × group interactions were seen with YBOCS-SR and CGI-S (Table 2). Time × group interaction on the YBOCS-SR remained significant after controlling for baseline HAMD-24 ($F = 2.6$, d.f. $= 4$, $p = 0.043$). On average, the active group showed a 25% reduction in YBOCS at 4 wk, while the sham group showed a 12% reduction. On the YBOCS-SR the active group showed a 30% reduction at 4 wk, while the sham group showed an 8% reduction.

Changes in depression and anxiety were not correlated with YBOCS and CGI-S changes from baseline. Correlations were significant between OCD symptoms and clinical global improvements in both self- and

Table 1. Demographic and clinical characteristics of the completers

	Active rTMS	Sham	p
Sample size	9	9	–
Right-handed	8	8	n.s.
Female/Male	4/5	3/6	n.s.
Age (mean $\pm$ s.d.)	39.7$\pm$8.6 yr	39.4$\pm$10.2 yr	n.s.
Employed/unemployed	7/2	6/3	n.s.
Age of onset	16.7$\pm$8.3 yr	16.8$\pm$10.1 yr	n.s.
Duration of illness	22.4$\pm$13.8 yr	22.1$\pm$7.3 yr	n.s.
Duration of current episode	3.5$\pm$3.7 yr	5.3$\pm$5.5 yr	n.s.
No. of SRI trials in the current episode	2.7$\pm$1.2	2.7$\pm$1.7	n.s.
No. of patients with co-morbid MDD	4	6	n.s.
No. of patients on SRI	6[a]	6[b]	n.s.
No. of patients on psychotherapy	3	2	n.s.
Baseline YBOCS	26$\pm$5.4	26.7$\pm$5.5	n.s.
Baseline YBOCS-SR	26.1$\pm$5.7	27.3$\pm$6.9	n.s.
Baseline HAMD-24	15.3$\pm$10.6	14.8$\pm$7.7	n.s.
Baseline BDI-II	21.2$\pm$15.4	15.4$\pm$10.2	n.s.
Baseline HAMA	17.4$\pm$10	14.2$\pm$7.1	n.s.
Baseline Zung-SAS	39.3$\pm$10	35.6$\pm$8.3	n.s.
Baseline CGI-S	5$\pm$0.7	5.2$\pm$0.9	n.s.
Baseline PGI	4.2$\pm$0.9	5.2$\pm$0.8	n.s.

rTMS, Repetitive transcranial magnetic stimulation; SRI, serotonin reuptake inhibitor; MDD, Major depressive disorder; YBOCS, Yale–Brown Obsessive Compulsive Scale; YBOCS-SR, YBOCS-Self-rating; HAMD-24, Hamilton Depression Rating Scale – 24-item; BDI-II, Beck Depression Inventory – II; HAMA-14, Hamilton Anxiety Rating Scale – 14-item; Zung-SAS, Zung Self- Administered Scale; CGI-S, Clinical Global Impression – Severity; PGI, Patient Global Impression.
[a] Three patients on 60–80 mg/d fluoxetine; one patient on 300 mg/d fluvoxamine; one patient on 200 mg/d sertraline; one patient on 60 mg/d citalopram.
[b] Two patients on 60–100 mg/d fluoxetine; two patients on 30 mg/d S-citalopram; one patient on 60 mg/d citalopram; one patient on 250 mg/d sertraline.

clinician-rated scales ($R=0.6$, $p=0.004$ and $R=0.7$, $p=0.001$, respectively).

***Open-label phase* (phase 2)**

Of 15 patients eligible to continue, 12 entered and completed the open-label phase (four initially randomized to active and eight to sham). The other three (two responders to active and one to sham) decided not to receive an additional 4-wk active rTMS. Demographics, symptoms ratings, and MT of those entering the open-label phase did not differ significantly from those who did not enter this phase.

The four patients initially randomized to active who received an additional 4-wk active rTMS showed further improvements from week 4 to week 8 on YBOCS (from 17.7$\pm$2.6 to 14.5$\pm$3.6) and YBOCS-SR (from 17.2$\pm$2.2 to 14.7$\pm$2.9; $F=10.7$, d.f.$=2$,

$p=0.010$). The eight initially randomized to sham had no significant change in their OCD symptoms after 4-wk active rTMS (YBOCS mean scores slightly increased, from 25.6$\pm$7 to 26.3$\pm$8.5, while YBOCS-SR mean scores decreased from 27$\pm$7.3 to 25.3$\pm$8.2). Since the open-label phase represents a mixture of patients who received active or sham in phase 1, we conducted separate analyses on those initially randomized to active (termed 'continued-active rTMS') and those initially randomized to sham (termed 'sham-to-active rTMS').

Repeated-measures ANOVA revealed that the continued-active group, which received 8-wk active rTMS, had a significant main effect of time on YBOCS ($F=13.2$, d.f.$=4$, $p=0.000$), YBOCS-SR ($F=7.3$, d.f.$=8$, $p=0.000$), BDI-II ($F=8.3$, d.f.$=4$, $p=0.002$), HAMA-14 ($F=3.7$, d.f.$=4$, $p=0.035$), Zung-SAS ($F=3.8$, d.f.$=4$, $p=0.030$), CGI-S ($F=10.7$, d.f.$=4$, $p=0.001$), and PGI

Table 2. Clinical measures across 4-wk active repetitive transcranial magnetic stimulation and sham to supplementary motor area in 18 patients with obsessive–compulsive disorder

Dependent measures	Active rTMS (n=9)				Sham (n=9)			
	Baseline	Week 2	Week 4	ANOVA[a]	Baseline	Week 2	Week 4	ANOVA[b]
YBOCS	26±5.4	21.8±6	19.4±5.6	$F=12.6$, d.f.=2, $p=0.000$	26.7±5.5	25±6.9	23.5±9	n.s.
YBOCS-SR[c]	26.1±5.7	20.4±7.1	18.4±8	$F=8.4$, d.f.=4, $p=0.000$	27.3±6.9	26.1±8.1	25.1±8.9	$F=2.8$, d.f.=4, $p=0.031$
HAMD-24	15.3±10.6	15.1±9.6	12.1±11.4	n.s.	14.8±7.7	13.7±8.1	14.1±8.8	n.s.
BDI-II[c]	21.2±15.4	15.8±14	14.5±16.6	$F=6.9$, d.f.=4, $p=0.000$	15.4±10.2	12.4±11.5	11.1±10.3	n.s.
HAMA-14	17.4±10	15.2±10.7	12.2±11.8	$F=3.6$, d.f.=2, $p=0.036$	14.2±7.1	10.7±5.8	11.3±6.4	n.s.
Zung-SAS[c]	39.3±10	34.4±7.9	32.4±6.5	$F=5.4$, d.f.=4, $p=0.001$	35.6±8.3	34.2±5.4	32.1±6.4	n.s.
CGI-S	5±0.7	4.4±0.8	4.1±0.9	$F=9.3$, d.f.=2, $p=0.001$	5.2±0.9	5.1±1.1	5±1.3	$F=3.4$, d.f.=2, $p=0.044$
PGI[c]	4.2±0.9	3.8±1.1	3.5±1.1	$F=5.8$, d.f.=4, $p=0.000$	5.2±0.8	5.1±1	4.7±1.3	n.s.

YBOCS, Yale–Brown Obsessive Compulsive Scale; YBOCS-SR, YBOCS – Self-rating; HAMD-24, Hamilton Depression Rating Scale – 24-item; BDI-II, Beck Depression Inventory – II; HAMA-14, Hamilton Anxiety Rating Scale – 14-item; Zung-SAS, Zung Self-Administered Scale; CGI-S, Clinical Global Impression – Severity; PGI, Patient Global Impression.

[a] Repeated-measures analysis of variance (ANOVA), main effect of time.
[b] Repeated-measures ANOVA, time × group (active *vs.* sham) interaction.
[c] Self-reported rating scales were administered every week; in the table we report the mean scores obtained every 2 wk.

($F=9.2$, d.f.=4, $p=0.001$) (Fig. 1). Changes in depression and anxiety were not correlated with YBOCS and CGI-S changes from baseline. Correlations were significant between OCD symptoms and clinical global improvement ($R=0.9$, $p=0.000$). The sham-to-active group after receiving 4-wk active rTMS showed a significant improvement in general anxiety (HAMA-14: $F=3$, d.f.=4, $p=0.033$; Zung-SAS: $F=3.8$, d.f.=4, $p=0.013$), but no significant change in OCD symptoms and depression. No change was reported in their clinical global impression.

On average, the group that received 8-wk active rTMS showed a 49% reduction on YBOCS (28.2±5.8 to 14.5±3.6), compared to a 5% reduction on YBOCS (27.6±5.2 to 26.3±8.5) for those who received 4-wk sham and 4-wk active rTMS. The group that received 8-wk active rTMS showed also a 45% reduction on YBOCS-SR (26.5±6 to 14.7±2.9), while the group that received sham and active had a 10% reduction on YBOCS-SR (28.1±6.9 to 25.3±8.2). CGI-S decreased from severe to mild in the first group and showed no change in the other.

3-month follow-up

The eight responders (two who received 4-wk active rTMS, four who received 8-wk active rTMS and two who received respectively just 4-wk sham and 4-wk sham+4-wk active rTMS) continued to meet response criteria at 3-month naturalistic follow-up without changes in their medications. The six responders to active rTMS showed a 51% decrease from baseline YBOCS ($t=2.7$, d.f.=8, $p=0.023$), a 64% YBOCS-SR score drop ($t=4.3$, d.f.=8, $p=0.002$), and a stable CGI-S improvement ($t=3.5$, d.f.=8, $p=0.008$) at 3 months. Significant reductions in depression and anxiety persisted ($t=2.8$, d.f.=8, $p=0.023$; $t=4.5$, d.f.=8, $p=0.002$). Of the two responders to sham, one went on to have 4-wk active rTMS, and they showed an average improvement of 62% on YBOCS, 48% on YBOCS-SR, and CGI-S score of 2 at 3 months.

MT

Resting MTs are presented in Table 3. Baseline MT in the right hemisphere was lower in patients randomized to active rTMS than sham ($t=-2.5$, d.f.=16, $p=0.020$). Both right and left hemisphere MTs at baseline were lower in responders than non-responders (right: $t=2.1$, d.f.=15, $p=0.049$; left: $t=2.1$, d.f.=15, $p=0.045$).

Repeated-measures ANOVA revealed a significant effect of time on the left hemisphere MT, but no time × group interaction. We found a significant time × group
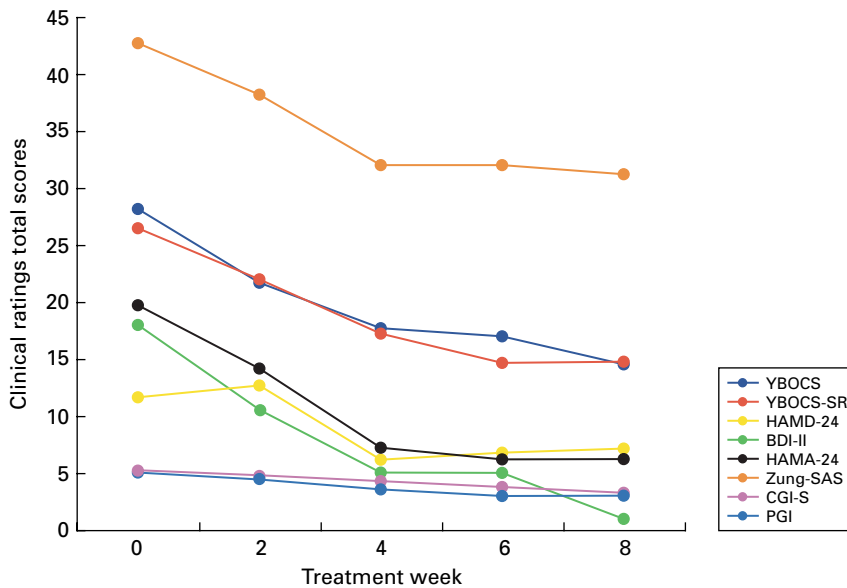
Fig. 1. Clinical measures across 8 wk of active repetitive transcranial magnetic stimulation to supplementary motor area.

interaction in right hemisphere MT. Repeated-measures ANOVA applied separately in each group showed that right hemisphere MT increased with time in the active group ($F=3$, d.f. $=4$, $p=0.032$), and did not change significantly in the sham group. In the active group changes in right hemisphere MT after the first 4-wk rTMS were correlated with clinical global improvement ($R=0.6$, $p=0.036$).

Left/right hemispheric laterality in MT was greater at baseline in those patients assigned to the active rather than sham group ($t=2.46$, d.f. $=16$, $p=0.031$), and this hemispheric difference was lost after 4-wk active rTMS. Baseline laterality and change in laterality from baseline to 4 wk correlated with change in CGI ($R=0.7$, $p=0.028$ and $R=0.6$, $p=0.041$, respectively). Change in laterality at 4 wk correlated with change in YBOCS-SR ($R=0.7$, $p=0.024$).

Safety

Besides one patient who fainted during MT determination, none of the others reported significant side-effects. The TMS sessions were well tolerated. There were no seizures, neurological complications, or subjective complaints about memory or concentration impairments. Ratings of common side-effects of TMS showed no difference between the active and sham groups (Table 4).

Discussion

This is the first randomized sham-controlled study of SMA stimulation in treatment-resistant OCD. We found that low-frequency rTMS delivered to SMA resulted in more clinical responders among those patients who completed 4-wk active treatment compared to those who received sham treatment. However, the difference in response rates was not statistically significant probably due to the small sample size, since a minimum of 23 subjects in each treatment condition would have been necessary to reach an 80% power ($\alpha=0.05$). On the other hand, on one of the continuous OCD measures (YBOCS-SR) and on one continuous global measure (CGI-S), there was a statistically significant difference between sham and active treatment at week 4.

Response to sham was low, and in line with findings that OCD patients have a low placebo response (Huppert *et al*. 2004). The response rate seen with rTMS in the present study compares favorably with reported response rates with medications (Soomro *et al*. 2008). These results support our hypothesis that modulation of SMA via rTMS could alter symptom expression, and encourage further work on the therapeutic potential of this intervention in treatment-resistant OCD.

A few other sham-controlled studies have tested rTMS effect in OCD (Alonso *et al*. 2001; Prasko *et al*. 2006; Sachdev *et al*. 2007). They targeted right or left DLPFC and found no difference between active and sham after 2 wk of either low- or high-frequency rTMS. When high-frequency rTMS was applied on the left DLPFC for up to 4 wk, there was a significant reduction in total YBOCS scores, but not after controlling for depression (Sachdev *et al*. 2007). It is possible that

Table 3. Physiological measures across 4-wk active repetitive transcranial magnetic stimulation (rTMS) and sham to supplementary motor area in 18 patients with obsessive–compulsive disorder

Dependent measures	Active rTMS ($n=9$)			Sham ($n=9$)			ANOVA[a]	ANOVA[b]
	Baseline	Week 2	Week 4	Baseline	Week 2	Week 4		
Right MT[c]	42.5 ± 6.4	43.7 ± 7.9	45 ± 8.7	52.6 ± 9.7	50.4 ± 11.6	48.7 ± 9.4	n.s.	$F=4.5$, d.f. $=4$, $p=0.018$
Left MT[c]	47 ± 10.7	45.3 ± 12.8	46.5 ± 13.6	48.7 ± 10.8	47.1 ± 10.3	45.5 ± 10.4	$F=3.4$, d.f. $=4$, $p=0.044$	n.s.

MT, Motor threshold.

[a] Repeated-measures analysis of variance (ANOVA), main effect of time.

[b] Repeated-measures ANOVA, time × group (active *vs.* sham) interaction.

[c] Right and Left MTs (resting motor thresholds) were measured every week; in the table we report the mean scores obtained every 2 wk.

our results were more favorable due to our selection of a different cortical target. Although rTMS to DLPFC has been shown to have an antidepressant and anxiolytic effect, it may be not optimal for OCD.

Our results are promising and consistent with those found in our previous open trials, where clinical improvements in OCD were sustained in the follow-up and were associated with normalization in motor cortex excitability (Mantovani *et al.* 2006, 2007). Additionally, we stimulated for up to 8 wk, while previous randomized trials stimulated for 2–4 wk. It has previously been reported that in depression longer rTMS treatments may be more effective (Gershon *et al.* 2003). Indeed, while the interpretation of the results obtained in phase 2 is confounded by being open-label, we found significant improvements when rTMS was continued for four additional weeks, to a total of 8 wk.

Improvements in depression and anxiety were also seen. While it is possible that improvements in OCD symptoms could be secondary to non-specific antidepressant or anxiolytic effects, changes in YBOCS were not correlated with changes in depression and anxiety, instead they were correlated with changes in CGI. Moreover, the fact that changes in YBOCS were independent from baseline level of depression strengthens the hypothesis of a specific rTMS effect on OCD with a secondary improvement in both depression and general anxiety.

As we hypothesized, and consistent with our prior reports, measures of cortical excitability correlated with response. At baseline responders showed a lower left and right hemisphere MT, which increased significantly following rTMS. Furthermore, abnormal laterality in MT at baseline (i.e. lower right MT

compared to left) predicted better response, and laterality normalized following rTMS. Recent neurophysiological and neuroimaging studies suggest that premotor and motor areas are hyperactive in OCD (Greenberg *et al.* 1998, 2000; Yücel *et al.* 2007). However, it is not known whether this hyperactivity represents part of OCD pathophysiology, or whether it may represent a compensatory mechanism. Our finding that baseline-increased motor-pathway excitability was associated with beneficial response to inhibitory low-frequency rTMS is consistent with prediction that rTMS may have been acting to normalize the functional hyperexcitability associated with OCD pathophysiology. However, confirmatory studies will be needed to prove such a connection. When patients initially randomized to sham received open-label active rTMS, they did not show significant improvement in OCD symptoms. The two groups did not differ in demographic or clinical features, but it is notable that they did differ in baseline brain excitability measures. At baseline, a lower MT was found in the right hemisphere of patients randomized to active rTMS. It is possible that this difference may have predisposed one group to be more responsive than the other to the selected rTMS parameters. Future studies should match groups for baseline MT to avoid this confound and to test definitively this hypothesis. Moreover, ongoing analyses of other neurophysiology measures collected during the trial (such as cortical silent period, intracortical inhibition and intracortical facilitation) might support our hypothesis that patients with asymmetry of excitability and particularly with relatively much more excitable right hemisphere might be the best candidates for inhibitory low-frequency rTMS. While the others with a different

Table 4. Frequency of transcranial magnetic stimulation (TMS) side-effects in phases 1 and 2

TMS side-effects	Phase 1				Phase 2	
	Active TMS ($n=9$)		Sham ($n=9$)		Active TMS ($n=12$)	
	Pre	Post	Pre	Post	Pre	Post
Headache	8.3	7.8	9.4	12.8	3.1	8.8
Neck pain	2.2	2.2	3.3	5	0.4	1.2
Scalp pain	0	0.6	0.6	2.2	0.4	1.2
Scalp burn	0	0	0	0	0	0
Seizure	0	0	0	0	0	0
Subjective hearing impairment	0.6	0	0.6	0.6	0	0
Subjective impaired cognition	0	0	2.2	1.7	0	0
Trouble concentrating	11.7	10	7.8	12.2	7.7	6.5
Memory impairment	10.6	9.4	1.1	1.1	7.7	5.4

Values are percentages.

neurophysiological asset might need a different rTMS treatment set up.

However, other factors such as the psychological effects of failing to improve after the first 4 wk of treatment cannot be ruled out and must be considered as a potential factor that made those patients initially randomized to sham fail to respond to the active treatment later.

A limitation of this study is the relatively small sample size. A larger sample and a longer controlled trial, given that the findings from the open-label phase suggested that continued rTMS treatment led to additional benefits, will be needed in the future to verify the hypothesis of SMA-rTMS effectiveness in OCD. Because the sham coil used looks and sounds like an active coil but does not feel like active rTMS, patients randomized to sham might have become unblinded during MT determination, when they felt the tapping sensations on the scalp, or when they received active rTMS in phase 2. Having clinical ratings performed by blinded clinicians, as we did in this study, would be expected to reduce but not entirely eliminate the impact of this. In future studies a sham system that feels like active rTMS, and a best-guess questionnaire for the patients should be used. Another limitation is the allowance of concomitant SSRI medications. Although we held them at stable doses for 3 months prior to study entry and throughout, it is possible that rTMS may have had a synergistic effect with medications, and they might confound cortical excitability measures. Finally, half of the sample had comorbid depression, and although we found a specific rTMS effect on OCD that did not correlate with change in depression, subsequent studies that exclude patients with comorbid depression would be more definitive. However, OCD and depression are frequently comorbid, making the evidence of rTMS on SMA effective in this comorbidity of special clinical relevance.

Although the study presents limitations, and the results of this first randomized sham-controlled trial of SMA stimulation in the treatment of resistant OCD should be considered tentative until replication, they are promising and support further investigation into the potential therapeutic applications of rTMS in this disabling condition.

Acknowledgements

Statement of Interest

a patent application for novel TMS technology developed in Dr Lisanby's laboratory, not related to the topic presented here. Dr Simpson has been on the Scientific Advisory Board of Jazz Pharmaceuticals and is receiving medication at no cost for a NIMH-funded grant from Janssen Pharmaceutica and research funds from Neuropharm Ltd to examine novel medications for OCD.

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