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BRIEF REPORT

Repetitive transcranial magnetic stimulation (rTMS) in the treatment of obsessive–compulsive disorder (OCD) and Tourette's syndrome (TS)

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Abstract

There is evidence that motor and premotor cortex are hyperexcitable in obsessive–compulsive disorder (OCD) and Tourette's syndrome (TS). We tested whether low-frequency repetitive transcranial magnetic stimulation (rTMS) could normalize overactive motor cortical regions and thereby improve symptoms. Subjects with OCD or TS were treated with active rTMS to the supplementary motor area (SMA) for 10 daily sessions at 1 Hz, 100% of motor threshold, 1200 stimuli/day. Suggestions of clinical improvement were apparent as early as the first week of rTMS. At the second week of treatment, statistically significant reductions were seen in the YBOCS, YGTSS, CGI, HARS, HDRS, SAD, BDI, SCL-90, and SASS. Symptoms improvement was correlated with a significant increase of the right resting motor threshold and was stable at 3 months follow-up. Slow rTMS to SMA resulted in a significant clinical improvement and a normalization of the right hemisphere hyperexcitability, thereby restoring hemispheric symmetry in motor threshold.

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Key words: Obsessive–compulsive disorder, rTMS, supplementary motor area, Tourette's syndrome.

Introduction

Clinical phenomenology, mutual comorbidity, and patterns of heritability suggest that obsessive–compulsive disorder (OCD) is related to Tourette's syndrome (TS). Although the pathophysiology of neither illness is completely understood, there are overlaps in the implicated neurocircuitry and neurophysiological characteristics, which may guide the design of focal brain stimulation strategies to study and treat them. Studies suggest a network of regions including the orbitofrontal cortex (OFC) and supplementary motor area (SMA) as targets for focal brain stimulation to modulate activity in those circuits and improve symptoms in resistant patients (Sheppard et al., 1999). Repetitive transcranial magnetic stimulation (rTMS) is a non-invasive means of stimulating targeted regions, but its depth of penetration prohibits direct stimulation of the OFC. The SMA, however, is readily accessible to rTMS and has been stimulated in previous studies (Boylan et al., 2001; Matsunaga et al., 2005).

Neurophysiological data suggest that motor 'intrusive' and repetitive behaviours in OCD may be a consequence of reduced cortico-subcortical inhibitory phenomena and higher than normal level of cortical excitability (Rossi et al., 2005). Using paired-pulse TMS, Greenberg et al. (1998, 2000) found that OCD patients, and particularly those with 'tic-related' OCD such as those with TS (Ziemann et al., 1997) had decreased intra-cortical inhibition, and lower resting and active motor thresholds on the left hemisphere than normal volunteers. Given this evidence of deficient motor inhibition in OCD and TS, the use of

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low-frequency rTMS, reported to be inhibitory on motor cortex excitability, may be a fruitful avenue to explore as putative treatment.

Previous studies attempted to treat OCD and TS by modulating activity in prefrontal and motor circuits. Greenberg et al. (1997) found in a blinded trial of OCD patients that compulsions decreased significantly for 8 h after right lateral prefrontal high-frequency rTMS. Low-frequency stimulation to the right dorsolateral prefrontal cortex (DLPFC) by using a non-focal coil failed to show benefits in a double-blind study (Alonso et al., 2001). In contrast, an open study in refractory OCD patients who were randomly assigned to right or left DLPFC high-frequency rTMS found significant and sustained improvement in a third of patients, but there was no difference between right- and left-sided stimulation (Sachdev et al., 2001). No significant improvement of Tourette's symptoms was found after 1 Hz motor, premotor and sham rTMS using a cross-over design (Munchau et al., 2002). In another cross-over trial tics improved significantly over 1 wk and particularly with high-frequency stimulation on the left prefrontal cortex (Chae et al., 2004).

It remains to be tested whether the modest and contradictory results with rTMS in OCD and TS might be improved by selecting better brain targets and/or using different parameters of stimulation. The SMA may be a useful target for inhibitory stimulation in the treatment of OCD and TS because it has extensive connections with regions implicated in cognitive processes and motor control (Picard and Strick, 2001). Anatomical evidence from primates demonstrates that the SMA plays a role in the neural networks connecting cortical, thalamic and basal ganglia pathways, and substantiates how information is channelled from limbic to cognitive and motor circuits (Haber, 2003). Furthermore, selecting 1 Hz rTMS may provide a means of dampening the observed motor cortical hyperexcitability in these disorders.

We investigated whether rTMS applied over the SMA improves symptoms of OCD and TS, and whether it would normalize motor cortex excitability measures.

Methods

This was an open-label pilot study of active rTMS added onto ongoing pharmacotherapy. Ten right-handed outpatients (eight male; mean age = 33.5 yr, S.D. = 13.48 yr) who met DSM-IV-TR criteria for OCD, and/or TS were recruited from the psychiatric clinic at Siena University Polyclinic 'Le Scotte'. Although standardized measures of medication resistance were not obtained, the treating psychiatrist referred patients considered clinically resistant to different medication trials and, in case of OCD, to behaviour therapy as well. Five patients had OCD (four had contamination obsessions and cleaning compulsions, but without incompleteness symptomatology, one had aggressive and somatic obsessions and checking compulsions), three had TS, and two had OCD with comorbid TS (both had aggressive obsessions and checking compulsions). Eight patients met criteria for current major depressive episode, moderate. No patients met criteria for any other Axis I and/or Axis II disorders by using the Structured Clinical Interview (SCID-I and SCID-II) for the DSM. Individuals with a history of seizure or head trauma were excluded. All patients gave written informed consent, and the protocol was approved by the local Ethics Committee. All patients had been receiving pharmacological treatment for at least 12 wk at stable doses (paroxetine, fluvoxamine, citalopram, sertraline, venlafaxine, lorazepam, lithium, gabapentin, topiramate, haloperidol, risperidone, quetiapine, olanzapine). Medications were continued at stable doses throughout the rTMS and the follow-up period.

Patients were seated in a chair, wearing earplugs to protect their hearing. Immediately before and after each rTMS treatment, we determined the left and right hemisphere resting motor threshold (RMT), defined as the intensity required to elicit at least 5 motor-evoked potentials of 50 μV in 10 consecutive stimulations, when the magnet is placed over the optimal position to activate the abductor pollicis brevis. We used a 70-mm figure-of-eight coil, the Magstim Super Rapid stimulator (Magstim Company Ltd, Whitland, UK), and a conventional 4-channel EMG machine with bandpass filter 20 Hz–3 kHz. According to the international 10–20 EEG system, the vertex (Cz) was measured for each patient and the SMA defined at 15% of the distance between inion and nasion anterior to Cz 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 SMA. The rTMS parameters consisted of four daily trains, administered at an intensity of 100% of the RMT (using the lowest of the right and left hemisphere RMTs), a frequency of 1 Hz, for 5 min, and with an inter-train interval of 2 min (1200 stimuli/d).

Patients were treated from Monday to Friday, for a total of 10 d. Symptoms were rated by a psychiatrist, different from the treater, at baseline and after 1 and 2 wk of stimulation. Observer- and self-reported scales were used: Yale–Brown Obsessive–Compulsive Scale

(YBOCS), Yale Global Tic Severity Scale (YGTSS), Hamilton Depression Rating Scale (HDRS-24), Hamilton Anxiety Rating Scale (HARS-14), Clinical Global Impression (CGI), Symptoms Check-List (SCL-90), Beck Depression Inventory (BDI), Scale for Auto-evaluation of Depression (SAD), Social-Adaptation Self-evaluation Scale (SASS). The CGI was repeated at 1 and 3 months after completion of the treatment to evaluate the long-term stability of the clinical outcome.

Statistical analyses were performed using the SPSS library, 11.0 version (SPSS Inc., Chicago, IL, USA). Repeated-measures analysis of variance (ANOVA), with adjustments for non-sphericity, was applied to evaluate time-dependent effects of rTMS on OCD (YBOCS), TS (YGTSS), depression (HDRS, BDI, SAD), anxiety (HARS), general psychopathology (SCL-90) and social adjustment (SASS), followed by LSD post-hoc tests. We used the same statistical approach to test whether rTMS affected RMT. Student's t test was applied to compare RMT values of the two hemispheres before and after treatment. The same test was used to compare to baseline CGI scores obtained at 1 and 3 months follow-up. Pearson correlations were applied to examine the effect of changes in depression and anxiety on OCD and Tourette's symptoms. Baseline HDRS rating was used as a covariate in the ANOVA to examine the effect of depression on OCD and Tourette's symptoms changes.

Results

Table 1 shows the clinical characteristics of the study population. Eight patients completed the study. Two patients with comorbid OCD and TS dropped out after the first week. Although they showed an initial improvement, subjectively they did not feel any benefit from rTMS and decided to withdraw from the study. We used their last observation carried forward for all analyses. None of the patients reported side-effects. There were no seizures, neurological complications, or complaints about memory or concentration difficulties (no formal test of cognition was done).

Baseline, both 1- and 2-wk mean scores, and the mean effect of time on the clinical measures are presented in Table 2. The sample had a significant clinical general improvement (CGI) at the end of the first and second week of treatment, and maintained benefit at 1 month ($t=5.670$, d.f. $=9$, $p=0.000$) and 3 months follow-up ($t=5.582$, d.f. $=9$, $p=0.000$). The OCD group demonstrated a decrease in symptoms severity (from severe to moderate) with a significant reduction in YBOCS scores progressively from the beginning to the end of the treatment. The TS group showed a significant reduction in YGTSS scores, and a marked improvement during the first week that remained significant at the end of the second week.

Table 1. Clinical characteristics of the study population

	Obsessive–compulsive disorder	Tourette's syndrome
Age of onset	20.2 ± 1.9 yr	12.6 ± 3.8 yr
Duration of illness	15.6 ± 8.4 yr	18.6 ± 15 yr
Stability of severity	2.4 ± 1.1 yr	1.8 ± 0.9 yr
Family history of tics	0	2 subjects

Three out of five 'pure' OCD patients (without TS) had a clinically significant improvement, with a reduction in YBOCS scores $>40\%$, and two out of three 'pure' TS patients (without OCD) had a complete remission at 2 wk (total YGTSS scores of 0 from baseline scores of 90 and 70). Sixty per cent of the total sample had sustained clinical improvement with rTMS that persisted at 3 months follow-up.

The entire sample showed a significant reduction in depression and anxiety over time, as measured by the HDRS and HARS. Improvements were significant by the first week, and remained significant at the end of the treatment. HDRS and HARS changes from baseline were not correlated with YBOCS and YGTSS changes after treatment. HDRS scores at baseline did not affect YBOCS and YGTSS changes ($F=6.884$, d.f. $=2, 6$, $p=0.028$ and $F=5.868$, d.f. $=2, 6$, $p=0.039$).

Patients improved in the self-evaluated level of depression, as both BDI and SAD showed a progressive and significant reduction. The general psychopathology (SCL-90) and social adjustment (SASS) also improved significantly from the beginning to the end of the treatment. In particular, as we might have expected in a group so severely ill, the functional improvement was moderate and lagged behind that in OCD and TS symptoms.

Baseline, both 1- and 2-wk mean scores, and the mean effect of time on the physiological measures are presented in Table 3. The right hemisphere RMT increased significantly over time. Post-hoc tests revealed this variation was significant after both the first and second week of treatment. No significant change was found in the left hemisphere RMT. When analysed separately, the two diagnostic groups differed in the effects of rTMS on RMT. rTMS was associated with a significant increase of the right hemisphere RMT only in the OCD group. The significant hemispheric asymmetry in the RMT of OCD patients at baseline (R < L)

Table 2. Clinical measures across 2 wk of rTMS to SMA in patients with obsessive–compulsive disorder (OCD) and Tourette's syndrome (TS)

Dependent measures	Baseline (BL)	Week 1 (W1)	Week 2 (W2)	ANOVA	LSD Post-hoc BL vs. W1	LSD Post-hoc W1 vs. W2	LSD Post-hoc BL vs. W2
			OCD sample (5 OCD + 2 OCD/TS = 7)				
YBOCS	36.4 ± 7.5	28.8 ± 9.2*	26 ± 10.5*	$F = 14.687$, d.f. = 2, 12, $p = 0.001$	$p = 0.009$	$p = 0.033$	$p = 0.007$
			TS sample (3 TS + 2 TS/OCD = 5)				
YGTSS	71.2 ± 21.1	29 ± 24.6*	23.4 ± 28.6*	$F = 10.707$, d.f. = 2, 8, $p = 0.005$	$p = 0.037$	$p = 0.179$	$p = 0.024$
			Total sample (5 OCD + 3 TS + 2 OCD/TS = 10)				
CGI	5.9 ± 1.1	4.1 ± 1.7*	3 ± 1.6*	$F = 23.429$, d.f. = 2, 18, $p = 0.000$	$p = 0.005$	$p = 0.001$	$p = 0.000$
HARS	24.1 ± 10.7	17.6 ± 11.8*	12 ± 11*	$F = 21.528$, d.f. = 2, 18, $p = 0.000$	$p = 0.001$	$p = 0.016$	$p = 0.000$
HDRS	20.7 ± 11.4	14.9 ± 12.1*	10.8 ± 10.7*	$F = 16.386$, d.f. = 2, 18, $p = 0.000$	$p = 0.001$	$p = 0.061$	$p = 0.001$
BDI	10 ± 11	7.5 ± 8.4*	6.4 ± 7.8*	$F = 7.204$, d.f. = 2, 18, $p = 0.005$	$p = 0.028$	$p = 0.040$	$p = 0.022$
SAD	25.9 ± 15.9	21 ± 17*	16.5 ± 13.9*	$F = 15.956$, d.f. = 2, 18, $p = 0.000$	$p = 0.011$	$p = 0.031$	$p = 0.000$
SCL-90	89.2 ± 61.2	75.7 ± 65.9*	61.6 ± 59.8*	$F = 13.143$, d.f. = 2, 18, $p = 0.000$	$p = 0.050$	$p = 0.018$	$p = 0.001$
SASS	33.3 ± 9.24	35.4 ± 10.2	36.1 ± 9.8*	$F = 3.840$, d.f. = 2, 18, $p = 0.041$	$p = 0.130$	$p = 0.173$	$p = 0.048$

rTMS, Repetitive transcranial magnetic stimulation; SMA, supplementary motor area; ANOVA, repeated-measures analysis of variance, main effect of time. See Methods section for definition of scales.
* Denotes significant post-hoc comparison against baseline.

Table 3. Physiological measures across 2 wk of rTMS to SMA in patients with obsessive–compulsive disorder (OCD) and Tourette's syndrome (TS)

Dependent measures	Baseline (BL)	Week 1 (W1)	Week 2 (W2)	ANOVA	LSD Post-hoc BL vs. W1	LSD Post-hoc W1 vs. W2	LSD Post-hoc BL vs. W2
			OCD sample (5 OCD + 2 OCD/TS = 7)				
Right RMT	56 ± 12.1	61.8 ± 11.8*	64.8 ± 13.5*	$F = 5.833$, d.f. = 2, 12, $p = 0.017$	$p = 0.038$	$p = 0.208$	$p = 0.021$
Left RMT	65.8 ± 9.6	67 ± 10.1	64.8 ± 13.5	$F = 0.283$, d.f. = 2, 12, $p = 0.759$	n.a.	n.a.	n.a.
			TS sample (3 TS + 2 TS/OCD = 5)				
Right RMT	47 ± 4.3	56.6 ± 9.4	58 ± 7.2	$F = 3.846$, d.f. = 2, 8, $p = 0.068$	n.a.	n.a.	n.a.
Left RMT	47.7 ± 5.5	55.3 ± 8	56.7 ± 5.7	$F = 3.153$, d.f. = 2, 8, $p = 0.098$	n.a.	n.a.	n.a.
			Total sample (5 OCD + 3 TS + 2 OCD/TS = 10)				
Right RMT	52.1 ± 9.6	57.9 ± 10.5*	59.8 ± 11.6*	$F = 12.437$, d.f. = 2, 18, $p = 0.000$	$p = 0.008$	$p = 0.208$	$p = 0.001$
Left RMT	58.2 ± 11.1	61.1 ± 10.2	60.4 ± 10.7	$F = 1.214$, d.f. = 2, 18, $p = 0.320$	n.a.	n.a.	n.a.

rTMS, Repetitive transcranial magnetic stimulation; SMA, supplementary motor area; ANOVA, repeated-measures analysis of variance, main effect of time; RMT, resting motor threshold.
* Denotes significant post-hoc comparison against baseline.

($t = 4.144$, d.f. = 6, $p = 0.006$) disappeared at the end of the treatment ($t = 1.549$, d.f. = 6, $p = 0.172$). TS patients, who showed no RMT asymmetry before, indeed showed increases of both right and left hemisphere RMTs after treatment, but these were not statistically significant.

Discussion

To our knowledge this is the first study of SMA stimulation in the treatment of OCD and TS. We report a clinically significant improvement in OCD and TS symptoms with benefits lasting up to 3 months in

almost two thirds of the patients, similarly to that reported with conventional treatments (Carpenter et al., 1999; Pallanti et al., 2002).

Improvements in depression and anxiety were also seen. While it is possible that improvements in OCD and TS symptoms could be secondary to non-specific antidepressant or anxiolytic effects, the YBOCS and YGTSS changes were not correlated with changes in depression and anxiety. Although correlations are biased by the small sample size and no dissociation was observed between the onset of rTMS effects on OCD or TS and on mood or anxiety, the fact that both YBOCS and YGTSS changes were independent from the baseline level of depression strengthens the hypothesis of a specific effect of rTMS on OCD and TS. Moreover, most of rTMS studies showing antidepressant and/or anxiolytic effects targeted the DLPFC as the SMA is not a region typically implicated in depression circuitry (Mayberg, 2003). Although the SMA is not directly implicated in depression its stimulation indirectly could have affected other frontal regions. Given these reasons, it is more likely that both depression and anxiety improved secondarily to improvements in OCD and TS. This hypothesis could be directly tested in subsequent studies that exclude patients with comorbid depression.

We proposed the SMA as a useful target for inhibitory stimulation, and found an increase in OCD patients' right hemisphere RMT but no change in the left with restored symmetry between the two hemispheres which was absent at baseline. Other studies suggest that OCD treatment produces predominantly right-sided changes in cerebral activity (Kang et al., 2003, Saxena et al., 2002). In TS patients we observed no asymmetry between the right and left hemisphere RMTs at baseline, but after the treatment both RMTs increased. As opposed to OCD patients, in TS rTMS affected both hemispheres in the same way as drug treatment (Lampreave et al., 1998). The effect on motor cortex excitability may be explained by the fact that rTMS over the SMA and other pre-motor cortices not only affects neurons at the point of stimulation, but it also influences excitability in connected areas (Murase et al., 2005; Oliveri et al., 2003). Changes in RMT suggest that TMS administered to the SMA may have influenced the primary motor cortex. Direct stimulation of the primary motor cortex has been demonstrated to affect the striatum (Strafella et al., 2003). Therefore, it is possible that the clinical improvements in our sample may have been due to a combined action on cortical and subcortical structures (transsynaptically stimulated). The fact that clinical improvement in the OCD and TS groups was accompanied by differential effects in the right and left primary motor cortex (as indexed by RMT) may account for similar but not completely overlapping neurobiological loops (at least in terms of laterality).

Limitations are the open design and the small sample size. Without a sham condition we cannot rule out a placebo response. Making a placebo response less likely is that OCD and TS patients are recognized to have a low placebo response (de la Fuente-Fernandez et al., 2002; Huppert et al., 2004) in comparison to patients with other psychiatric disorders (e.g. depression), and that our patients had been ill for long periods of time and had tried many treatments previously without success. In addition, while placebo responses are usually transitory, the clinical improvement we found was gradually progressive, continuing into the second week of treatment, and persisting at 3 months follow-up. Finally, a clinical improvement seen in the context of significant changes in motor cortical excitability would be more difficult to explain as placebo effect, although the possibility that neurophysiological changes would be a biological substrate of a placebo effect cannot be excluded. Nevertheless, this suggestive result in an open trial does merit a follow-up sham-controlled trial to definitively test whether the clinical improvements observed here were the result of rTMS.

Another limitation is the allowance of concomitant medications. Concomitant medications were held at stable doses for 3 months prior to study entry and remained stable throughout rTMS up until the 3-month follow-up assessment, so it would be difficult to explain the improvements as resulting from medications alone. However, subsequent studies may reduce this confound by keeping patients with the simplest medication regimen (e.g. SSRI monotherapy).

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Statement of Interest

None.

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