# A Randomized, Double-Blind Trial of Repetitive Transcranial Magnetic Stimulation in Obsessive-Compulsive Disorder With Three-Month Follow-Up

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*Recent findings indicate that the motor and premotor cortices are hyperexcitable in obsessive-compulsive disorder (OCD). The authors have performed the first randomized, double-blind clinical trial of repetitive transcranial magnetic stimulation (rTMS) in OCD, with a 3-month follow-up. OCD patients (N=22) were assigned to either 2 weeks of active or sham rTMS to the supplementary motor area bilaterally. After 14 weeks, the response rate was 41% (7/12) with active and 10% (1/10) with sham treatment. At 14 weeks, patients receiving active rTMS showed, on average, a 35% reduction on the Y-BOCS, as compared with a 6.2% reduction in those receiving sham treatment.*

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Obsessive-compulsive disorder (OCD) is a chronic and disabling disorder marked by obsessions and/or compulsions; it causes significant distress to the patients and their families.[1] OCD is the fourth most common psychiatric disorder, affecting approximately 1%–3% of the world population, with a lifetime prevalence of 2%–3%, more than twice that of schizophrenia.[2]

Despite recent developments in drug and behavioral treatments of OCD, about 40%–60% of cases remain refractory to treatment.[3]

The neurobiology and etiology of OCD are incompletely understood.[4] The dominant model focuses on abnormalities in cortico-striatal circuitry, with emphasis on orbitofronto-striato-thalamic circuits.[5] Recent neurophysiologic and neuroimaging studies suggest that premotor and motor areas are hyperactive in OCD.[6–8] In particular, the supplementary motor area (SMA), which has extensive connections[9] and plays a central role in response control,[10,11] may be a useful transcranial magnetic stimulation (TMS) target for the treatment of medication-resistant OCD.

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Although not the first to try to modulate the SMA in patients with abnormal corticospinal excitability (see, for example, Boylan et al., 2001, in Parkinson's disease, and Q:1 Matsunaga et al., 2005), Mantovani et al.[12] were pioneers in attempting OCD treatment through modulation of this cortical site. Studies suggest that repetitive behavior can be related to a decrease in cortico-subcortical inhibition and a consequent increase in cortical excitability.[13] SMA connects with regions involved in both cognitive and motor functions.[14] Studies in primates have shown networks linking the SMA to cortical, thalamic, and basal ganglia neurons.[15]

In 2006, Mantovani et al.[12] carried out an open study with 10 patients with resistant OCD and Tourette's syndrome; 8 patients finished the study. OCD patients showed a decrease in the severity of the disorder, with a progressive reduction in Yale-Brown Obsessive-Compulsive Scale (Y-BOCS) between the first and the last evaluation. Sixty per cent of patients had sustained improvement until the third month. Despite the good results, the study had serious limitations, such as the small sample size and the absence of a control group.

Mantovani et al.[17] conducted the first randomized, sham-controlled study of SMA stimulation in the treatment of resistant OCD. Twenty-one medication-resistant OCD patients were assigned to 4 weeks of either active or sham low-frequency rTMS to the SMA. rTMS parameters were the following: 1,200 stimuli/day, at 1 Hz and 100% of Motor Threshold (MT). The Y-BOCS and Clinical Global Impression (CGI) scale were considered primary outcome measures. Nonresponders to sham and responders to active or sham rTMS were offered 4 additional weeks of open, active rTMS. After 4 weeks, the response rate in the completer sample was 67% (6/9) with active and 22% (2/9) with sham rTMS. At 4 weeks, patients receiving active rTMS showed on average a 25% reduction in the Y-BOCS, versus a 12% reduction for those receiving sham. On average, the group receiving active treatment for 8 weeks showed a 49% decrease in Y-BOCS (28.2 [SD: 5.8] to 14.5 [3.6]), as compared with 5% reduction in Y-BOCS (27.6 [5.2] to 26.3 [8.5]) for those who received 4 weeks of placebo and 4 weeks of active treatment.

The goal of our study was to assess the efficacy of low-frequency rTMS to the SMA in treatment-resistant OCD and further examine the duration of a significant clinical effect. To the best of our knowledge, this is the first study to assess the duration of beneficial clinical effects of supplementary motor area rTMS on OCD with a follow-up of 3 months after a treatment course, in a randomized, double-blind fashion.

## METHODS

### Subjects

Twenty-two right-handed outpatients (women: 13; men: 9), age 18 to 60 years, diagnosed according to DSM-IV-TR criteria and having OCD of at least moderate severity (Y-BOCS score ≥16) were enrolled in the study. All patients gave written informed consent for the study. Subjects with comorbid psychiatric disorders (except depression, by Hamilton Rating Scale) or history of drug abuse, significant head injury, or of any neurosurgical procedure, pregnant women, patients with metal implants, or illnesses that prevent attendance at sessions, patients with a history of seizure or wearing pacemakers, were excluded from the study. The study was approved by the local ethics committee.

### Study Design

Patients were randomly administered either real (N=12) or sham (N=10) rTMS, once per day, 5 days per week, for 2 weeks. Randomization was performed according to a computer-generated schedule. Subjects and scale-rater physician were blind to treatment status of individuals. Only the rTMS administrator was aware of group allocations. Treatment response was assessed by self- and clinician-rated scales before treatment, immediately after treatment, and 3 months thereafter, with the same examiner following a subject throughout the study. All patients included in the study had failed adequate pharmacological trials for at least two anti-OCD drugs. At the beginning of the study, pharmacological treatments included serotonin reuptake inhibitors (SSRIs; 16/22), atypical neuroleptics (4/22), clomipramine (2/22), and benzodiazepines (14/22); these drugs were continued without change in dosage regimens throughout the study.

### Stimulation Procedure

rTMS was administered by means of a NEURO-MS (NEUROSOFT, LTD.; Russia) with a focal 8-shaped, 70-mm coil. Stimulation parameters were 1-Hz, 20-minute trains (1,200 pulses/day) at 100% of resting MT, once per day, 5 days per week, for 2 weeks. To determine the resting motor threshold, we used the thumb-movement

visualization method, stimulating the left primary motor cortex.[18]

The coil was positioned over pre-SMA, targeted using the International 10–20 EEG System (Choi et al., 2006).[19] 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 toward the occiput to stimulate the pre-SMA bilaterally and simultaneously. The sham treatment was performed with the Neurosoft sham coil. A metal plate placed inside this coil prevents the magnetic field from stimulating the cortex. 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 patient blinding, we excluded all patients who, for any reason, had experienced active TMS in the past.

### Ratings

Subjects were rated by a researcher who did not participate in the rTMS sessions and who was blind to the subject's treatment group allocations at baseline, at the end of treatment and 3 months after treatment, using the following instruments: Y-BOCS and Y-BOCS–Self-Rating (Y-BOCS–SR), Hamilton Rating Scale for Depression, 24-item (Ham-D–24), Hamilton Rating Scale for Anxiety, 14-item (Ham-A–14), Beck Depression Inventory–II (BDI–II), Beck Anxiety Inventory (BAI), and CGI–Severity (CGI–S). The primary efficacy measure was the Y-BOCS. Patients with a 25% Y-BOCS reduction were classified as Responders.[20]

### Statistical Analysis

Statistical analysis was performed with SAS Version 9.2 (SAS Inc.; U.S.A.). Student's *t*-tests were applied to compare demographic and clinical data between the active and sham groups. $\chi^2$ test was used to evaluate the association between sex and group. Repeated-measures analysis of variance using a mixed-effects model with symmetric covariance structure was used to evaluate the effects of group, the time dependence, and interaction of these two effects of rTMS on psychometric scale mean scores. Pearson's correlation coefficients were estimated to examine the relationship between changes in depression scores, anxiety measures, and changes in OCD scores, and, similarly, changes in Clinical Global Impression and change in OCD scores. Baseline Ham-D–24 was used as covariate in the ANOVA (ANCOVA) to examine the effect of depression on OCD symptom changes. All tests were conducted with significance levels set at 0.05.

## RESULTS

### Recruitment and Retention

Of the 24 patients screened, only 22 were randomized and assigned to either active or sham rTMS. Two patients were excluded because of comorbid bipolar disorder.

### Demographics and Baseline Clinical Characteristics of the Study Population

Table 1 shows the socio-demographic and clinical characteristics of the sample. Mean age of the patients was 35.5 (SD: 7.5) years and 37.5 (SD: 5.7) years in active and sham groups, respectively. The male-to-female ratio was 4:8 in the rTMS and 5:5 in the sham rTMS group (NS). The mean duration of illness was 17 (SD: 5.3) years in the rTMS group and 19.5 (SD: 6.3) in the sham rTMS group (NS). The mean age at onset of illness was 18.6 (SD: 2.2) years in the rTMS group and 16.9 (SD: 2.9) years in the sham group (NS). There were no significant differences in age, sex, age at onset of illness, or total duration of illness between the two groups.

**TABLE 1. Demographic and Clinical Characteristics of the Completers**

| | Active rTMS | Sham rTMS |
|---|---|---|
| Sample size | 12 | 10 |
| Women/men | 8/4 | 5/5 |
| Age, years | 35.5 (7.5) | 37.5 (16) |
| Age at onset, years | 19.5 (3.0) | 16.0 (2.0) |
| Duration of illness, years | 17.0 (8.0) | 19.5 (12.0) |
| Duration of current episode, years | 2.0 (1.0) | 2.0 (1.0) |
| Patients on SSRIs, N | 7[a] | 6[b] |
| Patients with comorbid MDD | 9 | 8 |
| Baseline Y-BOCS | 36.4 (3.20) | 31.8 (3.50) |
| Baseline Ham-D–24 | 20.7 (9.80) | 18.7 (7.70) |
| Baseline BDI–II | 28.6 (3.70) | 24.9 (4.05) |
| Baseline Ham-A | 25.6 (8.20) | 27.2 (9.30) |
| Baseline CGI–S | 5.5 (0.43) | 5.0 (0.47) |

Values are mean (standard deviation), unless otherwise indicated. All p values are nonsignificant.

rTMS: repetitive transcranial magnetic stimulation; MDD: major depressive disorder; Y-BOCS: Yale–Brown Obsessive-Compulsive Scale; Ham-D–24: Hamilton Rating Scale for Depression, 24-item; BDI–II: Beck Depression Inventory–II; Ham-A–14: Hamilton Rating Scale for Anxiety, 14-item; CGI–S: Clinical Global Impression–Severity.

[a]four patients on 40 mg–60 mg/day fluoxetine; two patients on 30 mg–40 mg/day paroxetine; one patient on 150 mg/day sertraline.

[b]three patients on 30 mg–60 mg/day fluoxetine; two patients on 100 mg–150 mg/day sertraline; one patient on 40 mg/day citalopram.

### Results at 2 Weeks

Clinical measures at baseline, after 2 weeks, and after 14 weeks of both active and sham rTMS are presented in Table 2. The active and sham groups did not differ significantly in baseline clinical ratings. ANOVA of Y-BOCS total score showed a nonsignificant effect of Group ($F[1, 19.4]=3.16$ ; $p=0.091$), a highly significant effect of Time ($F[2, 18.4]=28.2$; $p<0.0001$), and a significant Time × Group interaction ($F[2, 18.4]=20.6$; $p<0.0001$). For Y-BOCS, a repeated-measures ANOVA revealed a significant main effect of Time × Treatment at 2 weeks ($F[1, 20]=8.8$; $p=0.0076$). On average, patients in the active group had a reduction of 15.3 (SD: 2.4) points on the Y-BOCS ($t[20] = -8.5$; $p<0.0001$), and the sham group 5.3 (SD: 2.6) points ($t[20] = -0.9$; NS) within 2 weeks. For anxiety (Ham-A–14 and BAI) repeated-measures ANOVA revealed a significant main effect of Time × Group interaction at 2 weeks ($t[20] = -5.1$; $p=0.026$ and $t[38.1] = -2.2$, $p=0.029$, respectively). On average, patients in the active group had a reduction of 19.6 (SD: 2.9) points in the Ham-A–14 ($t[38] = -6.6$; $p<0.0001$) and the sham group: 9.5 (SD: 3.2) points ($t[38] = -2.91$; $p=0.006$) within 2 weeks. For depression (Ham-D–24), there was no significant difference between groups in 2 weeks ($t[38.1] = -1.19$; NS). For CGI-S, repeated-measures ANOVA revealed a highly significant main effect of Time × Treatment at 2 weeks ($t[38.2] = -5.0$; $p<0.0001$). Analysis of 22 Completers after 2 weeks showed a response rate (Y-BOCS) of 42% with active and 12.% with sham rTMS ($p<0.001$).

### Results at 14 Weeks

An ANOVA analysis of Y-BOCS total scores over time (three observations: baseline, after rTMS treatment, and 14 weeks after the end of rTMS treatment), revealed a significant difference between active and sham stimulation until Week 14 after the end of rTMS ($t[18.5] = -5.5$; $p<0.0001$). On average, patients in the active group had a reduction of 12.7 (SD: 2.4) points on the Y-BOCS ($t[18.4] = -8.6$; 18.4; $p<0.0001$) and 2.0 (SD: 2.7) points in the sham group ($t[18.5] = -0.4$; NS) after 14 weeks. For anxiety (Ham-A–14) there was no significant difference between groups after 14 weeks ($t[38.3] = -1.1$; NS). For depression (Ham-D–24), there was no significant difference between groups at 14 weeks ($t[38.3] = -0.4$; NS). For CGI-S, repeated-measures ANOVA revealed a highly significant main effect of Time × Treatment at 14 weeks ($t[18.5] = -4.5$; $p<0.0001$). On average, patients in the active group had a reduction of 2.75 (SD: 0.37) points on the CGI-S ($t[38.5] = -7.39$; $p<0.0001$) and the sham group, 0.25 (SD: 0.41) points ($t[38.6] = -0.61$; NS) after 14 weeks. At 14 weeks, response rate (Y-BOCS) in the same 22 Completers was 35% with active and 6.02% with sham rTMS ($p<0.001$).

Time × Group interaction on the Y-BOCS and Y-BOCS–SR remained significant after controlling for baseline Ham-D–24 ($t[18.3] = -5.4$; $p<0.0001$).

Changes in depression were not correlated with Y-BOCS changes from baseline ($r=0.30$). Correlations were significant between OCD symptoms and anxiety ($r=0.50$; $p=0.024$) and between Y-BOCS and Clinical Global Improvement (CGI–S; $r=0.7$; $p=0.0001$)

### Side Effects

The TMS sessions were well tolerated. The main side effects were headache (N=3) and localized scalp pain (N=2). There were no seizures, neurological

**TABLE 2. Clinical Measures Across 4-Week Active or Sham Repetitive Transcranial Magnetic Stimulation (rTMS) to Supplementary Motor Area in 22 Patients With Obsessive-Compulsive Disorder**

| | Active rTMS (N=12) | | | Sham rTMS (N=10) | | | | |
|---|---|---|---|---|---|---|---|---|
| Variables | Baseline | Week 2 | Week 14 | Baseline | Week 2 | Week 14 | ANOVA[a] | ANOVA[b] |
| Y-BOCS | 36.4 (3.20) | 21.1 (3.1) | 23.7 (3.89) | 31.8 (3.50) | 26.5 (3.3) | 29.8 (4.2) | $F[2,18.4]=28.2$; $p<0.0001$ | $F[2,18.4]=20.6$; $p<0.0001$ |
| Ham-D–24 | 20.7 (9.80) | 12.6 (6.5) | 15.1 (5.60) | 18.7 (7.70) | 13.6 (7.3) | 16.2 (6.4) | NS | NS |
| BDI–IIc | 28.6 (3.70) | 20.1 (3.7) | 22.3 (3.70) | 24.9 (4.00) | 23.5 (4.1) | 21.7 (4.1) | $F[2,38.1]=9.6$; $p=0.0004$ | NS |
| Ham-A–14 | 25.6 (8.20) | 13.6 (8.5) | 17.6 (7.20) | 27.2 (9.30) | 21.1 (7.2) | 25.3 (5.2) | $F[2,38.2]=22.2$; $p<0.0001$ | NS |
| CGI–S | 5.5 (0.430) | 2.0 (0.4) | 2.83 (0.44) | 5.0 (0.47) | 4.1 (0 5) | 4.7 (0.5) | $F[2,38.4]=36.3$; $p<0.0001$ | $F[2,38.4]=15.4$; $p<0.0001$ |

Values are mean (standard deviation), unless otherwise indicated.

Y-BOCS: Yale–Brown Obsessive-Compulsive Scale; Ham-D–24: Hamilton Rating Scale for Depression–24-item; BDI–II, Beck Depression Inventory–II; Ham-A–14: Hamilton Rating Scale for Anxiety–14-item; CGI–S: Clinical Global Impression–Severity.

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

[b]Repeated-measures ANOVA, Time × Group (active versus sham) interaction.

complications, or subjective complaints about memory or concentration impairments.

## DISCUSSION

Studies on the pathophysiology of OCD have shown several changes in excitability of cortical and subcortical regions, as well as in cerebral blood flow. Greenberg et al.[6] were the first to show that OCD patients present significant less cortical inhibition. Saxena et al.[21] demonstrated, through functional neuroimaging, that OCD patients present hypermetabolism in the prefrontal cortex regions that is reversed after treatment. Greenberg et al.[7] showed an increase in cortical excitability in OCD patients. This fact, already demonstrated previously in Tourette's syndrome and focal dystonia, is relevant to the understanding of the pathophysiology of this disorder, as it is another source of information that brings it closer to other disorders involving subcortical structures.

Other studies have evaluated the effectiveness of rTMS in the treatment of OCD. Most studies were performed on the prefrontal cortex. Greenberg et al.[22] published the first study on rTMS for the treatment of OCD. In an open experimental study, the authors compared the effect of one session of high-frequency rTMS in left and right prefrontal cortices and occipital cortex in 12 OCD resistant patients. Compulsive symptoms improved significantly with right prefrontal stimulation during ($p<0.01$), 30 minutes ($p<0.01$), and 8 hours after treatment ($p<0.02$). There was some, but not significant, improvement, with stimulation of the left prefrontal cortex. Sachdev and collleagues[23] compared the therapeutic effect of rTMS in 12 resistant OCD patients, applying 30 sessions of high-frequency stimulation to the right and left prefrontal cortices. A significant sustained clinical response was observed in about one-quarter of the study patients, with a reduction of more than to 40% on the Y-BOCS scale.

Alonso et al.[24] carried out the first double-blind, placebo-controlled study. The goal was to evaluate the efficacy of low-frequency rTMS in the right prefrontal cortex in the treatment of resistant OCD. There were no significant differences between the active and sham groups. However, this study used a very different technique in comparison with the previous one, such as low-frequency rTMS and the use of a nonfocal, round coil, which could be related to the therapeutic failure. Prasko et al.[25] evaluated, in a randomized, double-blind, controlled study, the efficacy of low-frequency rTMS on the left prefrontal cortex in OCD patients during 10 sessions. The authors did not find statistically significant differences between the groups in 2 and 4 weeks of follow-up. Sarkel et al.[26] evaluated the efficacy of rTMS in a double-blind, placebo-controlled study, involving high-frequency rTMS applied to the right dorsolateral prefrontal cortex in the treatment of OCD, with the differences of a larger sample (N=42) and a longer follow-up (4 weeks). The study showed that both active and placebo stimulation significantly improved the obsessive and compulsive symptoms, but there were no differences between the groups. Because of the diversity of the parameters used and the conflicting results, one cannot reach a conclusion on the efficacy of rTMS in the treatment of OCD when applied to the prefrontal cortex.

In 2006, based on pathophysiology and neuroimaging findings, Mantovani et al.[12] hypothesized that inhibition of the supplementary motor area could be effective in treating OCD. Imaging studies suggest the participation of regions such as the orbitofrontal cortex, the cingulate, and basal ganglia in OCD symptoms.[27] Despite the fact that subcortical structures are not accessible to transcranial magnetic stimulation in a straightforward way, we can access them indirectly through interconnected cortical regions, such as the supplementary motor area. These regions become an attractive target for modulating subcortical regions and influencing OCD symptoms.

Moreover, the supplementary motor area is related to motor-planning and response-inhibition,[28,29] and is also connected with several regions widely implicated in cognitive and emotional processes.[30] The inhibitory stimuli in the supplementary motor area might cause suppression of the hyperexcitable right hemisphere and thereby improve dysfunctional symptoms in patients with OCD. Mantovani et al., in an open study,[12] and, later, in a controlled, double-blind study,[17] demonstrated that inhibition of the supplementary motor area has a specific effect in reducing OCD symptoms.

The present study is the first randomized, double-blind study with 14 weeks of follow-up to assess the efficacy and duration of clinical effects of supplementary motor area inhibition in controlling the symptoms of OCD. Our study showed better results than previous ones, mainly due to characteristics of the sample. Compared with the study of Mantovani et al., in 2010,[17] our sample was composed of patients with fewer

years of disease; that is, they were "less chronic," and with shorter duration of the current episode. These factors could influence the therapeutic response, explaining higher treatment effectiveness. Therefore, we have confirmed the hypothesis that inhibition of the supplementary motor area has a specific effect on OCD symptoms, which is not due to mere alleviation of depressive symptoms in these patients. It is unclear whether hyperactivity of the pre-motor areas is an integral part of OCD pathophysiology or is a compensatory mechanism. But, regardless of its nature, previous studies[12,17] have shown that cortical hyperexcitability-normalization may be directly related to clinical improvement in patients with OCD. However, confirmatory studies will be needed to prove such relationship. In terms of side effects and tolerability, inhibition of the supplementary motor area can be regarded as safe and well tolerated. The main reported side effect was headache (N=3), and no there were no changes in cognitive functioning.

In spite of its good results, this study had some limitations. According to Loo and Mitchell,[31] an ideal placebo system for rTMS must fulfill three conditions: 1) it must s not result in cortical stimulation; 2) it must produce acoustic and touch/sensory sensations identical to those of real stimulation; 3) it must be positioned the same way as the active coil. The sham coil used in this study had the same shape and was placed in the same location as the active one, but did not produce the same tactile sensation. Moreover, despite the fact that the sham coil is equipped with a metal plate that prevents the magnetic field from penetrating the cortex, it cannot be guaranteed that no cortical stimulation ever occurs, albeit minimal. This minimal stimulation could theoretically interfere with the results obtained in the placebo group. However, this sham coil represents the state of the art at this time; there is still no better way of performing sham rTMS stimulation.

Other limitations of this study are the small sample size; a minimum of 23 subjects in each treatment condition would be required to reach 85% power ($\alpha$=0.05), limiting the generalizability of results. Finally, the use of neuroimaging and neurophysiologic techniques, in addition to clinical assessment, would have been interesting to demonstrate neural patterns associated with clinical improvement, allowing for a better understanding of the specific neuronal actions of rTMS over the SMA. The use of an MRI-based neuronavigation system would have been especially interesting, since differences in subjects' head size and gyrification could influence the results.

One cannot exclude the possibility of a synergism between rTMS and the medications used by patients, since all patients were under pharmacological treatment. It is suggested that studies, with drug-free patients, be carried out in the future.

Although the treatment seems to be specific for OCD symptoms, it is suggested that further studies also exclude patients with depression, in order to allow for more definitive conclusions.

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# AUTHOR QUERIES

## AUTHOR PLEASE ANSWER ALL QUERIES

1—[AU: ] Please provide references for Boylan et al., 2001, and Matsunaga et al., 2005.

2—Reference 16 "Kang, Kim, Namkoong, et al, 2009" is not cited in the text. Please add an in-text citation or delete the reference.