Repetitive Transcranial Magnetic Stimulation to Supplementary Motor Area in Refractory Obsessive-Compulsive Disorder Treatment: a Sham-Controlled Trial

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BRIEF REPORT

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Abstract

Background: Repetitive transcranial magnetic stimulation has been explored in patients with obsessive-compulsive disorder, but with negative or conflicting results. This randomized double-blind study was designed to assess the efficacy of 1-Hz repetitive transcranial magnetic stimulation over the presupplementary area.
Methods: Forty medication-resistant patients were assigned to 4 weeks of either active or sham repetitive transcranial magnetic stimulation targeting the presupplementary area with the help of a neuronavigation system.
Results: According to the Yale-Brown obsessive-compulsive scale, the baseline-week 4 evolution showed no significant differences between groups. Responder rates at week 4 were not different between groups (repetitive transcranial magnetic stimulation 10.5% vs sham 20%; $P=.63$).
Conclusion: Low-frequency repetitive transcranial magnetic stimulation applied to the presupplementary area seems ineffective for the treatment of obsessive-compulsive disorder patients, at least in severe and drug-refractory cases such

as those included in this study. Further research is required to determine profiles of responder patients and appropriate repetitive transcranial magnetic stimulation parameters for obsessive-compulsive disorder.

Introduction

Obsessive-compulsive disorder (OCD) is one of the most common psychiatric disorders, with a mean prevalence of 2.3% in western countries, where it is a major cause of disability (Ruscio et al., 2010). Since 1980, treatment of OCD has dramatically improved with both the introduction of selective serotonin reuptake inhibitors (SSRIs) into clinical practice and the adoption of cognitive-behavioral therapy (CBT). Although SSRIs are effective in the treatment of OCD, a large number of patients remain refractory to drugs or are reluctant to take them because of side effects or discomfort with long-term pharmacological treatments (Pallanti and Quercioli, 2006). Similarly, CBT is neither always practicable nor always effective (Vogel et al., 2006). For these reasons, alternatives to classical therapies would be very helpful, and neuromodulation techniques offer very promising perspectives for OCD treatment, as they do for depression (Bais et al., 2014; Gaynes et al., 2014). Deep brain stimulation has shown very encouraging results in refractory patients, but this invasive method is not appropriate for larger scale use because of significant surgical risks. As a noninvasive technique, repetitive transcranial magnetic stimulation (rTMS) has been explored in several clinical trials with various targets and stimulation protocols (Saba et al., 2015). The majority of these studies focused on the dorsolateral prefrontal cortex (DLPFC), with low or high frequencies. According to several reviews of these controlled trials, there is no convincing evidence for the efficacy of rTMS to either the left or right DLPFC in the treatment of OCD (Jaafari et al., 2012; Bais et al., 2014; Saba et al., 2015). Two controlled studies have also explored the effects of low frequency rTMS on the orbitofrontal cortex with moderately positive effects but only in the short term (Ruffini et al., 2009; Nauczyciel et al., 2014).

Initially based on the observation of a defective inhibition and an excessive excitability of motor cortical regions in OCD patients, rTMS to the presupplementary motor area (SMA) has also been tried as a new target. After a first encouraging open-label study in patients with OCD or Tourette's syndrome (Mantovani et al., 2006), Mantovani et al. (2010a) conducted a controlled double-blind trial in 21 medication-resistant OCD patients assigned to 4 weeks of either active 1-Hz or sham rTMS to the pre-SMA bilaterally. Differences among groups were not significant by the end of treatment based on the Yale-Brown obsessive-compulsive scale (Y-BOCS), but a trend in favor of rTMS was observed: a decrease of 6.6 points (25.4%) vs 3.2 points (12.0%) in the sham group. Moreover, a significant improvement was shown by the self-rated Y-BOCS and the Clinician Global Impression (CGI-S) scale, and the abnormal hemispheric laterality found in the group randomized to active rTMS normalized. In a similar vein, Gomes et al. (2012) published the results of a sham-controlled study that did show significant benefits of 10-session pre-SMA rTMS (2 weeks) of low frequency (1-Hz) rTMS in 12 patients with OCD. A mean Y-BOCS reduction of 35% (7 responders in 12 patients) was obtained at 14 weeks follow-up, which was significantly larger compared to the sham TMS group's Y-BOCS mean reduction of 6% (1 responder in 10 patients). Another controlled study (Kang et al., 2009) investigated possible therapeutic effects of sequentially combined low-frequency rTMS to the right DLPFC and the pre-SMA, each

stimulation lasting 20 minutes for a total of 10 sessions. There were no significant differences at the end of treatment between the active and sham groups on the YBOCS.

Due to conflicting and uncertain results, and in the absence of other clearly effective rTMS targets to treat OCD patients, it seems important to obtain more conclusive information on the efficacy of the pre-SMA target. Thus, the goal of the present study was to explore the efficacy of low-frequency rTMS to the pre-SMA in a large sample of OCD drug-refractory patients, with a 2-month follow-up, in a randomized, sham-controlled trial.

Methods

Participants

Forty outpatients (23 women and 17 men), ages 19 to 63 years (mean 41.5, SD 10.7), with DSM-IV-TR OCD diagnosed using the Mini-International Neuropsychiatric Interview (Sheehan et al., 1998) were enrolled in the study in 3 hospital centers in France. To be eligible, these patients had to have a total Y-BOCS score of 15 or more, a total duration of the disease of at least 2 years, and received at least two 8-week adequate sequences of treatment with SSRIs without satisfying results. All patients gave written informed consent, and the protocol was approved by the Pitié-Salpêtrière ethics committee.

Ratings

Patients were assessed by a researcher who did not participate in the rTMS sessions and who was blind to the subjects' treatment group allocations. Clinical evaluation performed at inclusion, end of treatment (week 4), and follow-up (week 12) included Y-BOCS, CGI-S, CGI-Improvement, Maudsley Obsessive Compulsive Inventory, Obsessive Thoughts List, Montgomery-Asberg Depression Rating Scale, Beck Anxiety Rating scale (BAS), and Global Assessment of Functioning. The Mini-International Neuropsychiatric Interview 5.0.0 was used at inclusion to assess DSM-IV-TR OCD and main psychiatric comorbidity.

Protocol

Patients were randomly administered either active or sham rTMS once a day 5 days a week for 4 weeks. Randomization was performed according to a computer-generated schedule. Only the rTMS administrator was aware of group allocation, whereas patients and scale-rater clinicians were blind to treatment status of subjects.

All patients underwent a baseline evaluation of the motor cortex excitability in both hemispheres by measuring the resting motor threshold (RMT). RMT was defined as the minimum magnetic flux needed to elicit a threshold EMG response (50 mV 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 cortex.

The real rTMS was administered with the Magstim Rapid2 biphasic stimulator (Magstim Company Ltd, UK) using a 70-mm

figure-of-eight coil. Stimulation parameters were 1 Hz, 26-minute sessions (four 5-minute trains with an inter-train interval of 2 minutes, 1500 pulses/d), at 100% of RMT, using the lowest value of right or left hemisphere.

The 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 generate the same tapping sensation on the scalp like active rTMS. To maintain the blind conditions, we excluded patients who received TMS before. We also maintained the separation between the rating clinicians and the personnel performing the stimulations.

The coil was positioned to target the pre-SMA using neuronavigation (Brainsight, Rogue Resolution Ltd, Cardiff, UK; Eximia NBS, Nexstim Ltd, Helsinki, Finland) the T1-weighted magnetic resonance imaging of each participant. We considered the reference limit separating SMA proper from pre-SMA, the plane perpendicular on the bi-commissural line at the anterior commissure. The coil was placed with the handle along the sagittal midline, 2 cm anterior to the reference, to stimulate the pre-SMA bilaterally and simultaneously.

Statistical Analyses

Baseline characteristics of both groups were compared using the Mann-Whitney test for continuous variables and χ^2 or Fisher's-exact test for categorical variables. The main analysis was the comparison of changes in Y-BOCS total score between baseline and W4 in rTMS and sham groups. This analysis was performed using the modified intent-to-treat population (defined as all randomized subjects who received at least 1 stimulation). The primary criterion was missing for 2 patients (one in each group). According to the protocol, missing data was replaced with the mean variation of the group for the patient within the sham group, whereas the patient in the active group was considered a failure (no

improvement). Comparison of changes between baseline and W4 in Y-BOCS subscores and other symptomatic scales was performed using the Mann-Whitney test. Responder rates at W4 (25% Y-BOCS score reduction between inclusion and W4) were compared using the Fisher's-exact test. Evolution of Y-BOCS scores over 12 weeks were compared using a linear mixed model for repeated measures including terms for baseline scores, group, time, and time by group interaction. We used compound symmetry for the covariance structure. The alpha level was set at 0.05 (2-sided). Analyses were performed using SAS version 9.2 (SAS Inc.).

Results

Thirty-three patients completed the study, 36 were included in the main analyses (see flow chart Figure 1). At the beginning of the study, pharmacological treatments included SSRIs (n = 22), clomipramine (n = 12), other antidepressants (n = 8), antipsychotics (n = 12), and benzodiazepines (n = 22); these drugs were continued unchanged throughout the study. Among the patients of both groups, 18 (50%) had a current augmentation treatment, with a combination of an antidepressant and either another antidepressant or an antipsychotic.

No significant difference was observed between both groups at baseline for sex (males rTMS 35% vs sham 44%; $P = .6$), age (39.1 ± 10.4 vs 42.3 ± 10.6; $P = .32$), age at OCD onset (19.7 ± 9.5 vs 18.7 ± 10.6; $P = .7$), and duration of the disease (19.8 ± 12.8 vs 24 ± 10.9; $P = .1$). A DSM-IV-TR history of major depression was present in 75% of patients in both groups. Regarding history of drug treatments, 80% of the rTMS group patients and 75% of the sham group patients had received clomipramine in the past or were still receiving it. Score comparison at baseline (Table 1) showed no significant difference between groups for Y-BOCS total ($P = .27$), Y-BOCS obsessions ($P = .07$), Y-BOCS compulsions ($P = .24$), CGI-S ($P = .97$), Maudsley Obsessive Compulsive Inventory ($P = .81$), Obsessive Thoughts List ($P = .14$), Global Assessment of Functioning ($P = .86$), Montgomery-Asberg Depression Rating Scale ($P = .92$), and Beck Anxiety Rating scale ($P = .58$).
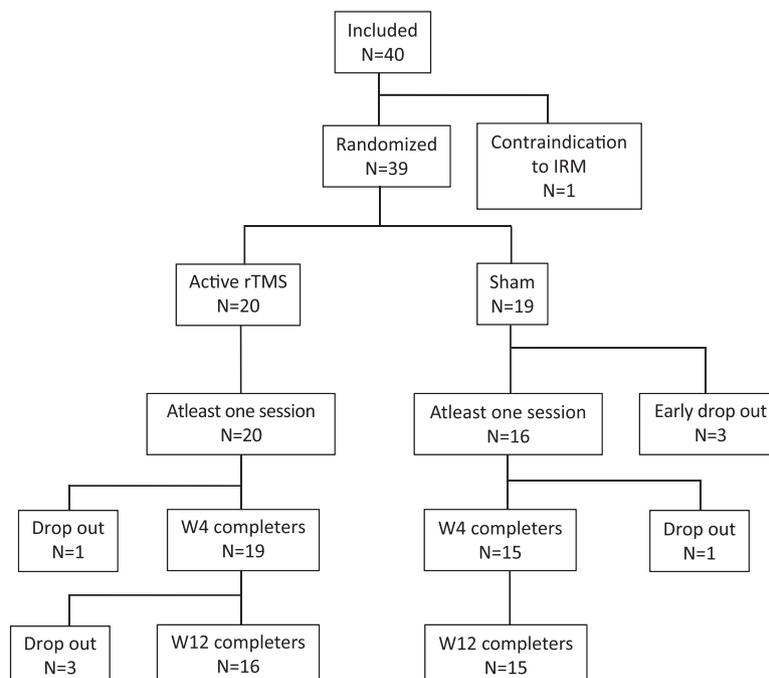

Figure 1. Flow-chart of the study.

Table 1. Scores in the Analyzed Population (n = 36), with Mann-Whiney Test Comparison of Change of rTMS and Sham Group Scores

	rTMS			Sham			
	Inclusion n = 20	W4 n = 20	Change n = 20	Inclusion n = 16	W4 n = 16	Change n = 16	Comparison
Y-BOCS total	30.2 (4.2)	27.8 (5.9)	-2.3 (5.0)	28.6 (4.6)	25.5 (7.6)	-3.5 (4.9)	P = .38
Y-BOCS obsessions	15.5 (2.4)	13.9 (3.2)	-1.5 (3.1)	12.9 (4.2)	11.7 (4.8)	-1.3 (2.7)	P = .73
Y-BOCS compulsions	14.7 (2.4)	13.8 (2.9)	-0.8 (2.2)	15.6 (2.4)	13.8 (3.5)	-2.2 (2.7)	P = .16
MOCI	18.6 (7.6)	22.5 (5.4)	4.1 (11.7)	19.1 (7)	20.6 (4.9)	1.2 (8.3)	P = .34
OTL	47.6 (16.4)	42.6 (12.5)	-6.7 (11.7)	38.7 (18.7)	37.7 (20.9)	-1.9 (13.7)	P = .17
CGI-S	6.0 (0.6)	5.7 (0.9)	-0.3 (0.6)	5.9 (0.6)	5.6 (0.9)	-0.3 (0.6)	P = 0.72
CGI-I	-	-	3.6 (0.9)	-	-	3.5 (1.1)	P = .54
GAF	51.8 (8.8)	53.3 (8.8)	1.6 (4.4)	51.9 (8.9)	54.3 (10.8)	1.9 (6.9)	P = .81
MADRS	10.6 (6.4)	11.7 (9.1)	0.7 (6.5)	10.4 (5.8)	10.1 (8.4)	0.1 (5.5)	P = .64
BAS	8.8 (6.3)	9.8 (7.3)	0.7 (3.9)	9.9 (6.1)	10.7 (7.6)	0.9 (4.5)	P = .84

Abbreviations: BAS, Beck Anxiety Rating scale; CGI-S and -I, Clinician Global Impression, Severity and Improvement; GAF, Global Assessment of Functioning; MADRS, Montgomery-Asberg Depression Rating Scale; MOCI, Maudsley Obsessive Compulsive Inventory; OTL, Obsessive Thoughts List; rtMS, repetitive transcranial magnetic stimulation; W4, week 4; Y-BOCS, Yale-Brown Obsessive Compulsive Scale.
Mean scores are shown, with standard deviation in parenthesis.

The baseline-W4 evolution of Y-BOCS scores showed no significant differences between groups, and the same was true for all other scales' comparison at W4 (Table 1). Responder rates at W4 were not different between groups (rTMS 10.5% vs sham 20%; P = .63). The secondary analysis performed on the W4 completer subjects (n = 34) showed no significant difference between both groups regarding total Y-BOCS score (median variation over 4 weeks of 0 in rTMS vs -1 in sham; P = .47). Comparison of the variation of total Y-BOCS score over 12 weeks showed no significant difference between groups. However, the study was not powered for this outcome. The total score decreased by 0.27 (standard error: 0.14) points per week in the rTMS group and by 0.3 (standard error: 0.11) points per week in the sham group.

We performed a linear regression to test if change in the Y-BOCS total score between randomization, and W4 was associated with age, disease duration, or total score of the Y-BOCS at baseline. We investigated if the treatment effect could depend on age by introducing in the model an interaction term (age x treatment). None of the factors studied was associated with response.

Concerning treatment safety, no serious adverse event was observed during the study. The most frequent adverse event was headache, without significant difference of incidence in rTMS (50%) vs sham (37.5%) groups (P = .5).

Discussion

This controlled study showed that low-frequency rTMS delivered to pre-SMA during 4 weeks had no better effects on drug-refractory OCD patients than sham stimulation. Whatever the measures taken into account (Y-BOCS total scores, subscores, questionnaires, clinician global inventory), and the type of analysis (dimensional changes or responder analyses performed), neither significant difference nor trends emerged between treatment groups. Contrary to Mantovani et al. (2010a) trial, a lack of statistical power cannot be a plausible explanation for these negative findings, because the samples sizes were superior to those of previous studies and becayse all trends are rather in favor of the sham group, for example, a higher responder rate in sham when compared with rTMS. The absence of efficacy of rTMS can neither be explained by methodological nor technical limitations. Indeed, the 4-week duration of treatment is the same or even longer than in previous studies, and we used a

parallel sham-controlled design. Furthermore, this study is the first to use a MRI-based neuronavigation system to target precisely the pre-SMA in OCD treatment. In comparison with previous studies, it is not sure that the stimulated targets were exactly the same, because other authors did not use a neuronavigation system but only cranial anatomical coordinates (Kang et al., 2009; Mantovani et al., 2010a; Gomes et al., 2012).

The total response rates (10–20%) and improvement levels (0–2.8 Y-BOCS points) were surprisingly low in both groups. However, we know that OCD patients have a global poor placebo response (Huppert et al., 2004). Moreover, a majority of the subjects included within the present study presented severe or very severe features. They had high baseline Y-BOCS median scores (31 and 28 in the rTMS and sham groups, respectively) compared with a Mantovani et al. (2010a) study, where mean Y-BOCS scores were 26 to 27. Nevertheless, this explanation is not totally satisfactory, because mean Y-BOCS scores (32–36) were also high in the Gomes et al. (2012) study.

Though, when our study is compared with Mantovani's (2010a) and Gomes's (2012) in terms of design and of subjects recruited, there are main differences that might shed some light onto the negative results we have found. First, after an initial double-blind sham-controlled phase, when 4 additional weeks of active rTMS were performed in Mantovani's study (2010a), a decrease of 49% at the Y-BOCS was found among those who received active rTMS during the initial phase. These results were statistically different from the results of those who received 4 weeks of sham rTMS and 4 additional weeks of active rTMS. Although applied in an open label phase, a longer duration of active rTMS might bring additional efficiency. Second, the use of baseline electrophysiological studies might help better predict responders that benefit from treatment. In fact, Mantovani et al. (2013) found a normalization of the RMT and an increased right hemisphere intracortical inhibition, whose change correlated with Y-BOCS scores. Third, as suggested by Gomes et al. (2012), their positive results compared with the other studies targeting the same area might be mainly due to the characteristics of the sample. Their sample was composed of patients with fewer years of disease whose current episode was of a shorter duration. These factors could influence the therapeutic response, explaining higher treatment effectiveness in their study.

Patients enrolled in the present study are highly refractory with other indicators of clinical severity and treatment

resistance, such as long duration of the disease (19–25 years) and high rate of depressive comorbidity (75%). The latter is higher than that found within other OCD clinical samples, and depressive comorbidity is known to affect treatment outcome negatively (Overbeek et al., 2002). As in previous studies, the patients included in our trial had to have failed adequate pharmacological trials for at least 2 anti-OCD drugs. But the fact that a majority of patients had received clomipramine is an indicator of higher severity and resistance, like the fact that 50% of included subjects had a current augmentation treatment (Pallanti and Quercioli, 2006). In Mantovani et al. (2010a) study, patients were excluded if they were treatment-refractory, defined as nonresponse to clomipramine, at least 2 selective SRIs at adequate dose and duration, plus CBT in the last year. We can thus hypothesize that the patients involved in the present study have severe and refractory OCD and that these features can partially explain the lack of efficacy of rTMS.

Further studies should also investigate the optimal way to enhance the effect of rTMS in the treatment of OCD. As an example, Mantovani et al. (2010b) obtained very significant improvements in 2 OCD cases treated with fMRI-guided rTMS to a functionally localized pre-SMA target. New targets and novel paradigms have been designed such as alpha-electroencephalogram-guided rTMS or theta-burst stimulation. Wu et al. (2010) showed that low intensity of theta-burst rTMS at 50 Hz had a consistent and long-lasting effect, while alpha-electroencephalogram-guided rTMS (adjusting the frequency to the α frequency, which was found to be abnormal in left and right frontal regions and temporal lobes) improved obsessions but not compulsions (Ma et al., 2014). The combination of rTMS with CBT could be also a new strategy for refractory OCD, as suggested by a recent case report (Grassi et al., 2015). Another region of interest in the treatment of OCD is the orbito-frontal cortex, with 2 positive controlled studies needing larger confirmations (Ruffini et al., 2009; Nauczyciel et al., 2014). Lastly, a recently published open study showed an interesting effect of 1-Hz rTMS over the medial prefrontal cortex in 10 patients with OCD (Modirrousta et al., 2015).

To summarize, low-frequency rTMS applied to the pre-SMA remains a promising area of study in the treatment of OCD-related symptoms, but the optimum protocol for OCD has yet to be determined, identifying a more clinically relevant design and finding appropriate inclusion criteria.

Acknowledgments

Statement of Interest

None.

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