A Randomized Controlled Study of Sequentially Applied Repetitive Transcranial Magnetic Stimulation in Obsessive-Compulsive Disorder

Jee In Kang, MD; Chan-Hyung Kim, MD; Kee Namkoong, MD; Chang-il Lee, MD; and Se Joo Kim, MD

Objective: The present study investigated possible therapeutic effects and safety of sequentially combined low-frequency repetitive transcranial magnetic stimulation (rTMS) to the right dorsolateral prefrontal cortex and supplementary motor area in patients with treatment-resistant obsessive-compulsive disorder.

Method: Between February 2007 and January 2008, we carried out a study with a rater-blinded, sham-controlled design in which 20 patients with treatment-resistant obsessive-compulsive disorder, confirmed by a psychiatrist after use of the Structured Clinical Interview for *DSM-IV* Axis I Disorders-Clinician Version, were randomly assigned to either active rTMS (n = 10) or sham treatment (n = 10). Over 10 days, rTMS of 1 Hz was given at 110% of the motor threshold for 20 minutes over the right dorsolateral prefrontal cortex and sequentially at 1 Hz at 100% of the motor threshold for 20 minutes over the supplementary motor area. The primary outcome measure was the Yale-Brown Obsessive Compulsive Scale (YBOCS) score.

Results: For the between-group analyses, there were no significant differences over 4 weeks between the active and sham groups on the YBOCS ($F = 0.01$, $P = .92$) and the Montgomery-Asberg Depression Rating Scale (MADRS; $F = 0.39$, $P = .54$). In repeated-measures analyses on all subjects, there was a significant effect of time on the YBOCS ($F = 5.48$, $P = .009$) and the MADRS ($F = 6.55$, $P = .004$). There were no significant group-by-time interactions for the YBOCS ($F = 0.03$, $P = .94$) or the MADRS ($F = 0.09$, $P = .67$).

Conclusions: These findings suggest that 10 sessions of sequential rTMS of the right dorsolateral prefrontal cortex and the supplementary motor area at low frequency had no therapeutic effect on obsessive-compulsive symptoms. However, rTMS was a safe method of treatment, and there was no significant change in cognitive function after rTMS. Further controlled studies using a more sophisticated sham system in larger samples are required to confirm the effect of rTMS in obsessive-compulsive disorder.

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Corresponding author: *Se Joo Kim, MD, Department of Psychiatry and Institute of Behavioral Science in Medicine, Yonsei University College of Medicine, 134 Sinchon-dong, Seodaemun-gu, Seoul 120-752, Republic of Korea (kimsejoo@yuhs.ac).*

Obsessive-compulsive disorder (OCD) is a relatively common psychiatric disorder characterized by repetitive, intrusive thoughts and time-consuming behaviors or mental acts.[1] Many OCD patients who do not respond to conventional treatments experience severe distress and disruptions in their daily activities. Novel approaches including psychopharmacologic therapy and surgical techniques for treatment-resistant OCD have been proposed.[2,3] With recent advances in noninvasive techniques for stimulating the cerebral cortex, repetitive transcranial magnetic stimulation (rTMS) has been proposed as a potential therapeutic approach for various psychiatric illnesses, including OCD.[4,5]

Initially, a single session of rTMS on the right prefrontal cortex produced a significant reduction in compulsive urges in OCD patients.[6] In addition, Sachdev et al[7] reported that rTMS with high frequency on either the right or left prefrontal cortex showed significant reduction of both obsessions and compulsions in treatment-resistant OCD. However, other studies of rTMS treatment on the prefrontal cortex in OCD patients could not show satisfying effects.[8–10] Recently, the effect of 1-Hz rTMS on the supplementary motor area was reported in OCD and Tourette syndrome.[11] These investigators insisted that low-frequency rTMS applied to the supplementary motor area caused normalization of the hyperexcitable right hemisphere and thereby improved dysfunctional symptoms.[11]

Because of contradictory findings and a lack of controlled trials of rTMS in OCD,[12] rTMS cannot yet be recommended as routine therapy for OCD. However, rTMS may have a potential clinical effect as a putative add-on treatment for OCD and as an alternative therapy for treatment-resistant OCD.

For useful clinical application of rTMS, it is very important to develop methods to enhance the efficacy of rTMS. There are a number of putative ways to do this, and one of them is sequentially combining 2 forms of stimulation that are considered to have potential therapeutic effects. More

recently, the sequential application of 2 stimulation regimens (high-frequency left-side rTMS and low-frequency right-side rTMS to the prefrontal cortex) has been found to have a substantial therapeutic effect in patients with treatment-resistant major depression.[13] Therefore, the investigation of a sequentially combining effect of both right prefrontal cortex and supplementary motor area stimulation would be worthwhile in OCD patients.

We aimed to examine the efficacy of sequential rTMS, combining both right prefrontal cortex and supplementary motor area stimulation at low frequency under randomized, rater-blinded, sham-controlled conditions. We investigated whether sequentially applied rTMS influences symptoms of OCD and cognitive functions. We hypothesized that sequential active stimulation of the right prefrontal cortex and the supplementary motor area at a low frequency would produce a greater therapeutic effect than the sham stimulation with no significant cognitive side effects.

METHOD

Study Design

The patients were randomly assigned to either the active or the sham group. An urn randomization procedure was used to ensure equal representation in each group by age, sex, and symptom severity. The patients were blinded to the expected effects of each condition, and a rater (S.J.K.) was blinded to the treatment, but the operator administering the rTMS was aware of the treatment group. Considering the possibility of interaction between the subject and the unblinded operator, limited interaction was requested for both subjects and operators during rTMS sessions.

Participants

Participants were 21 outpatients of the OCD clinic at Severance Hospital, Seoul, South Korea. A psychiatrist (S.J.K.) confirmed the diagnosis of OCD by administering the Structured Clinical Interview for *DSM-IV* Axis I Disorders-Clinician Version (SCID-CV).[14] We included OCD patients who had failed adequate trials (a lack of at least a 25% reduction in the Yale-Brown Obsessive Compulsive Scale [YBOCS][15] score after at least 8 weeks of treatment) of at least 2 serotonin reuptake inhibitors (SRIs) and behavioral therapy. Subjects with major depressive disorder (without psychotic features) were included in the study only if the obsessive-compulsive symptoms were their most prominent symptoms and only if the onset of OCD antedated the onset of depression. Seven subjects (33% of the total sample [N = 21]) were diagnosed with major depressive disorder according to the *DSM-IV*. Subjects were excluded if they presented with a movement disorder other than a tic, any psychotic symptoms, other anxiety disorders, mental retardation, alcohol or other substance abuse within the last 6 months, or a history of psychosurgery, encephalitis, or significant head trauma. All participants had been taking medication (SRIs alone or SRIs + benzodiazepines) for at least 12 weeks at stable doses. Their pharmacologic regimen was not changed, but any other treatment strategies including cognitive-behavioral therapy were not performed during the rTMS therapy and follow-up period.

The study, conducted from February 2007 to January 2008, was approved by the Ethics Committee of Severance Hospital, and written informed consent was obtained from all participants. Because 1 of the active stimulation group members withdrew informed consent after 5 sessions of stimulation, a total of 20 patients (n = 10 for the active group and n = 10 for the sham group) were included in the final analyses.

Stimulation Parameter

A Magstim rapid magnetic stimulator with a 70-mm figure-eight coil (Magstim Company Ltd, Whitland, United Kingdom) was used for treatment. Patients received daily sessions during the first 2 weeks. Before the first session, the resting motor threshold (RMT) was determined in both groups over the right primary motor cortex by finding the minimal intensity required to elicit at least 5 motor-evoked potentials of 50 mV out of 10 stimulations of the left abductor pollicis brevis.

For the active group, rTMS was sequentially performed over the right prefrontal cortex and the supplementary motor area. The rTMS of the right dorsolateral prefrontal cortex was conducted at a point 5 cm anterior to the point at which the RMT was determined, and it was administered at an intensity of 110% of the RMT, with a frequency of 1 Hz and a duration of 10 minutes (1,200 stimuli/d).

The vertex (Cz) was measured for each patient, and the supplementary motor area was defined at 15% of the distance between the inion and nasion anterior to Cz on the sagittal midline according to the International 10–20 EEG System. The rTMS over the supplementary motor area was administered at an intensity of 100% of the RMT, with a frequency of 1 Hz and a duration of 10 minutes (1,200 stimuli/d).

For the sham-treatment group, the sham stimulation was applied with the coil angled at 45° from the scalp, with 1 wing touching the scalp, using the same parameters as the active stimulation group over the same area. Although this type of sham condition might have a limitation for potential cortical stimulation effects, it has been reported to produce a minimal level of intracortical activity.[16,17] In addition, this sham condition using a 45° coil-tilt method might have a potential risk of unblinding due to different scalp sensations and visual impact compared to the real stimulation. Therefore, we confirmed the preservation of blindedness by comparing the guess of the subject about the type of stimulation they thought they received by asking all patients to select active, sham, or uncertain at the end of the 10 rTMS sessions.

Table 1. Differences in Demographic and Clinical Data and Psychopathological Rating Scales at Baseline Between the Active and the Sham Groups (total N = 20)[a]

Variable	Active Group (n = 10)	Sham Group (n = 10)	t or χ^2	P
Sex, n			$\chi^2 = 0.39$	1.00
Male	8	9		
Female	2	1		
Age, y	28.60 ± 12.66	26.20 ± 10.52	$t = 0.46$	.65
Employment, n			$\chi^2 = 0.28$	1.00
No employment	2	3		
Student	7	6		
Full-time employment	1	1		
Handedness, n			$\chi^2 = 0.00$	1.00
Right	10	10		
Left	0	0		
Resting motor threshold, %	52.50 ± 9.08	49.90 ± 17.32	$t = 0.58$	.57
Age at onset, y	20.60 ± 14.36	16.90 ± 4.51	$t = 0.77$	.45
Duration of illness, y	8.17 ± 3.81	9.46 ± 9.41	$t = -0.40$	.69
Duration of current episode, y	2.51 ± 0.96	2.22 ± 1.01	$t = 0.66$	.52
No. of SRI trials in the current episode	2.40 ± 0.52	2.30 ± 0.48	$t = 0.45$	.66
Patients with comorbid MDD, n	4	3	$\chi^2 = 0.22$	1.00
Patients receiving SRIs, n	10	10	$\chi^2 = 0.00$	1.00
Concomitant medications				
Benzodiazepines				
No. of patients receiving	5	4	$\chi^2 = 0.20$	1.00
Lorazepam-equivalent dose, mg/d	2.30 ± 0.45	1.88 ± 1.55	$t = 0.59$	.57
Antipsychotics, no. of patients receiving[b]	2	2	$\chi^2 = 0.00$	1.00
YBOCS scores				
Obsession	13.10 ± 2.81	13.40 ± 1.43	$t = -0.30$	.77
Compulsion	13.40 ± 5.64	12.90 ± 3.07	$t = 0.37$	.72
Total	26.50 ± 5.64	26.30 ± 4.06	$t = 0.09$	.93
MADRS score	23.10 ± 9.12	20.50 ± 6.12	$t = 0.36$	.46
HARS score	17.10 ± 7.78	20.00 ± 8.21	$t = -0.81$	.43
STAI-S score	50.80 ± 4.21	48.20 ± 3.82	$t = 0.89$	.17
BDI score	18.10 ± 6.57	16.70 ± 10.02	$t = 0.37$	.72
Stroop task, hit rate, %	93.00 ± 6.27	96.50 ± 2.22	$t = -1.66$	.11
Stroop task, reaction time, ms	883.45 ± 479.16	746.73 ± 179.66	$t = 0.85$	.41

[a]Data are presented as mean ± SD except where noted otherwise.
[b]In the active group, the 2 patients were receiving quetiapine 37.5 mg/d and risperidone 2 mg/d, respectively; in the sham group, the 2 patients were receiving aripiprazole 5 mg/d and olanzapine 10 mg/d, respectively.
Abbreviations: BDI = Beck Depression Inventory, HARS = Hamilton Anxiety Rating Scale, MADRS = Montgomery-Asberg Depression Rating Scale, MDD = major depressive disorder, SRI = serotonin reuptake inhibitor, STAI-S = State-Trait Anxiety Inventory-State, YBOCS = Yale-Brown Obsessive Compulsive Scale.

Measures of Symptoms

Symptoms were rated by a psychiatrist (S.J.K.) at baseline, after 1 and 2 weeks of stimulation, and 2 weeks after the final session. The patients and the rater were blinded to treatment, but the clinician administering rTMS was aware of the treatment group. The patients were assessed with the YBOCS, the Montgomery-Asberg Depression Rating Scale (MADRS),[18] and the Hamilton Anxiety Rating Scale (HARS).[19] In addition, all participants completed the self-reports of the Beck Depression Inventory (BDI)[20] and the State-Trait Anxiety Inventory-State (STAI-S).[21]

The primary outcome measure for the study was the YBOCS score. Treatment response was defined as a 25% or greater reduction in YBOCS total score from baseline to 4 weeks.[22] The secondary outcome measures were scores on the MADRS, HARS, BDI, STAI-S, and cognitive functions. Treatment response for the MADRS and HARS was defined as a 50% or greater reduction in MADRS[23]and HARS[24] scores from baseline to 4 weeks.

Assessment of Cognitive Function

To examine the effects of rTMS on cognitive function, a computerized Stroop task was conducted. The Stroop task performed in the present study was a variant Stroop task that had previously reported significant interference effects[25] and that consisted of 3 color-words—RED, YELLOW, and BLUE—on a black background. Stimuli were presented for 1,500 ms with an interstimulus interval of 3,000 ms, and they were sequenced in a way to avoid potential repetition priming effects. Subjects were instructed to press the right color button as fast as possible while maintaining accuracy.

Statistical Analysis

We used the t test on continuous variables and χ^2 analyses or Fisher exact tests on categorical variables to evaluate differences in demographic data and baseline psychopathologic rating scale scores between groups.

To determine whether there was an effect of group or time for all outcome measures, a repeated-measures analysis of variance was performed. The psychiatric measures and cognitive function assessed by the Stroop task at baseline and at weeks 1, 2, and 4 were the 4 levels on the within-group factor. The 2 groups, active and sham stimulation, were the 2 levels on the between-group factor.

The proportions of patients meeting response criteria (YBOCS, MADRS, and HARS) were compared between the groups with Fisher exact tests. In addition, the proportion of patients guessing their treatment allocation was compared between the groups using Fisher exact test.

The data were analyzed using SPSS 15.0 for Windows (SPSS Inc, Chicago, Illinois). The significance was accepted at $P < .05$. All tests were 2-tailed.

RESULTS

There were no significant differences between the active and sham groups in terms of age, sex, and scores at baseline on the YBOCS (obsession, compulsion, and total), MADRS, HARS, BDI, and STAI-S psychopathology rating scales (Table 1).

Table 2. Mean Scores for Each Outcome Measure at Baseline and Weeks 1, 2, and 4 in the Active and Sham Groups (total N = 20)[a]

Outcome Measure/ Week	Active Group (n = 10)	Sham Group (n = 10)	Between-Group[b]		Within-Group[b]	
			F	*P*	*F*	*P*
YBOCS			0.01	.92	5.48	.009
Week 0	26.50 ± 5.64	26.30 ± 4.06				
Week 1	25.20 ± 6.13	24.80 ± 5.16				
Week 2	24.20 ± 6.71	24.50 ± 6.13				
Week 4	23.60 ± 7.38	22.90 ± 6.24				
MADRS			0.39	.54	6.55	.004
Week 0	23.10 ± 9.12	20.50 ± 6.11				
Week 1	22.30 ± 8.98	19.10 ± 6.35				
Week 2	19.70 ± 9.63	18.20 ± 7.47				
Week 4	19.00 ± 9.26	17.60 ± 6.64				
HARS			0.19	.67	11.82	< .001
Week 0	17.10 ± 7.78	20.00 ± 8.21				
Week 1	16.00 ± 7.36	17.00 ± 8.77				
Week 2	14.30 ± 6.83	16.00 ± 7.83				
Week 4	14.00 ± 7.04	14.20 ± 6.71				
BDI			0.04	.84	0.20	.89
Week 0	18.10 ± 6.57	16.70 ± 10.02				
Week 1	17.20 ± 7.60	17.10 ± 10.94				
Week 2	17.40 ± 9.50	16.60 ± 12.77				
Week 4	17.20 ± 10.89	15.80 ± 14.44				
STAI-S			3.50	.08	0.89	.47
Week 0	50.80 ± 4.21	48.20 ± 3.82				
Week 1	50.70 ± 6.08	46.80 ± 3.26				
Week 2	48.70 ± 6.22	47.30 ± 3.47				
Week 4	50.30 ± 5.01	47.20 ± 2.94				
Stroop task, hit rate, %			0.10	.76	2.89	.07
Week 0	93.00 ± 6.27	96.50 ± 2.22				
Week 1	95.90 ± 3.25	96.00 ± 2.54				
Week 2	96.70 ± 3.09	95.70 ± 2.41				
Week 4	97.50 ± 2.01	96.40 ± 2.17				
Stroop task, reaction time, ms			0.45	.51	2.80	.07
Week 0	883.45 ± 479.16	746.73 ± 179.66				
Week 1	842.61 ± 366.22	759.22 ± 245.81				
Week 2	809.46 ± 273.30	762.18 ± 208.43				
Week 4	767.19 ± 207.03	713.84 ± 184.95				

[a]Data are presented as mean ± SD.
[b]*F* score and *P* value are presented for repeated-measures analysis of variance.
Abbreviations: BDI = Beck Depression Inventory, HARS = Hamilton Anxiety Rating Scale, MADRS = Montgomery-Asberg Depression Rating Scale, STAI-S = State-Trait Anxiety Inventory-State, YBOCS = Yale-Brown Obsessive Compulsive Scale.

For the between-group analyses, there were no significant differences between active and sham stimulation on the overall YBOCS ($F = 0.01$, $P = .92$), MADRS ($F = 0.39$, $P = .54$), HARS ($F = 0.19$, $P = .67$), BDI ($F = 0.04$, $P = .84$), and STAI-S ($F = 3.50$, $P = .08$) scores. In addition, no significant between-group difference on the Stroop task was observed (accuracy: $F = 0.10$, $P = .76$; reaction time: $F = 0.45$, $P = .51$) (Table 2).

In the analyses of the primary outcome measure, a repeated-measures analysis on all subjects showed a significant effect of time on overall YBOCS score ($F = 5.48$, $P = .009$) (Table 2). However, there were no significant group-by-time interactions on the YBOCS ($F = 0.03$, $P = .94$) (Figure 1). When the data were examined individually over 4 weeks, the responders according to YBOCS criteria (≥ 25% reduction in score) were 2 patients in each group ($\chi^2 = 0.00$, $P = 1.00$).

In the analyses of the secondary outcome measures, a significant effect of time on overall MADRS ($F = 6.55$, $P = .004$) and HARS ($F = 11.82$, $P < .001$) scores was also observed in a repeated-measures analysis on all subjects (Table 2). There were no significant group-by-time interactions on MADRS ($F = 0.09$, $P = .67$) and HARS ($F = 3.09$, $P = .06$) scores (Figure 1). When the data were analyzed individually over 4 weeks, the only responder according to MADRS criteria (≥ 50% reduction in score) was 1 patient in the active rTMS group, with no responders in the sham group ($\chi^2 = 1.05$, $P = 1.00$). The responders according to HARS criteria (≥ 50% reduction in score) were 2 patients in the active rTMS group and none in the sham rTMS group ($\chi^2 = 2.22$, $P = .47$).

In addition, the BDI ($F = 0.20$, $P = .89$) and STAI-S ($F = 0.89$, $P = .47$) scores were not significantly reduced over 4 weeks. The overall performance on the Stroop task also showed no significant changes over time (accuracy: $F = 2.89$, $P = .07$; reaction time: $F = 2.80$, $P = .07$) (Table 2).

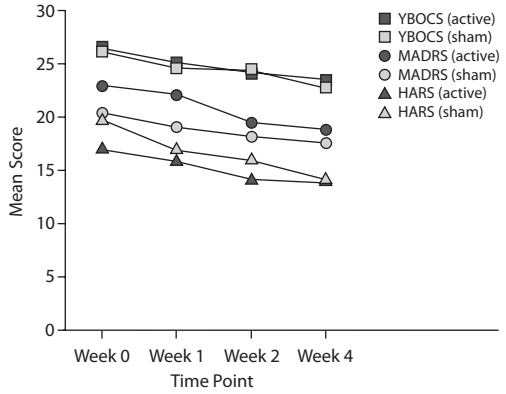
Regarding the aspects of tolerability and safety, there were no seizures in any of the patients. Only transient headache (n = 2) and localized scalp pain (n = 1) were present during the session among patients treated by active rTMS.

For the question of the preservation of blinding, the responses were active (n = 4), sham (n = 2), and uncertain (n = 4) in the active group and active (n = 6), sham (n = 2), and uncertain (n = 2) in the sham group. No significant difference in proportion was observed between the groups ($\chi^2 = 1.17$, $P = .84$). The majority of patients reported that the degree of symptom improvement rather than other factors such as scalp or acoustic sensations was the main reason for their guess.

DISCUSSION

The results of the present randomized, rater-blinded, sham-controlled study did not show any clinically meaningful efficacy of sequentially applied low-frequency rTMS over the right prefrontal cortex and the supplementary motor area in patients with OCD.

Figure 1. Change in Mean Values for Outcome Measures for Active and Sham Groups From Baseline to Weeks 1 and 2 (stimulation period) and Week 4 (2 weeks after final session)



Abbreviations: HARS = Hamilton Anxiety Rating Scale, MADRS = Montgomery-Asberg Depression Rating Scale, YBOCS = Yale-Brown Obsessive Compulsive Scale.

To date, there have been a few clinical trials of the effect of rTMS on OCD. Most of the previous rTMS studies have focused on the bilateral or unilateral prefrontal cortex as a useful target, and they have selected 10 to 20 sessions of rTMS as a treatment course using different stimulation parameters. For supportive evidence, Greenberg et al[6] showed that 1 session of rTMS on the right lateral prefrontal cortex produced a significant improvement in compulsive urges lasting for 8 hours in OCD patients (80% RMT, 20 Hz/2 seconds per minute for 20 minutes).[6] In addition, Sachdev et al[7] observed that about one-quarter of treatment-resistant OCD patients experienced a significant effect on both obsessions and compulsions from rTMS to either left or right prefrontal cortex (110% RMT, 10 Hz/5 seconds, 30 trains, 10 sessions).[7] However, a double-blind, placebo-controlled rTMS study[8] using low-frequency stimulation on the right prefrontal cortex failed to produce significant improvement of OCD (110% RMT, 1 Hz for 20 minutes, 18 sessions). A recent study[10] reported that rTMS on the left dorsolateral prefrontal cortex over 20 sessions produced improvements in total YBOCS scores, but there were no observations for changes in obsessive-compulsive symptoms after controlling for depression.[10] Although no clear conclusions can be drawn due to the lack of controlled studies and no standardization of the site of stimulation or treatment parameters, rTMS treatment to modify cortical excitability can be a potential therapeutic tool when considering neurophysiologic evidence of altered cortical excitability and reduced controlling of cortico-subcortical inhibition in the pathogenesis of OCD.[26,27] Careful consideration of target regions and potential methods to enhance the efficacy of rTMS seems to be critical for future rTMS study in OCD.

Although we could not find a significant therapeutic effect, this is the first study of sequential rTMS on the right dorsolateral prefrontal cortex and the supplementary motor area with low-frequency stimulation in treatment-resistant OCD. The present study was based on the hypothesis that the pathophysiology of OCD may be associated with abnormal hyperexcitability of specific regions and, therefore, that rTMS over the related regions may exert therapeutic effects by decreasing excitability of those regions in OCD patients. Previous imaging studies suggest that a network of regions including the orbitofrontal cortex, the cingulate, and the basal ganglia may be closely related to OCD.[28] In particular, OCD patients have been reported to have impaired prefrontal-subcortical functions.[29,30] Although the subcortical structures closely linked to OCD cannot be directly stimulated by rTMS, they can be indirectly influenced by stimulation of the connected areas. Therefore, certain anatomically and functionally interconnected regions can be considered as targets for focal brain stimulation to modulate cortical activity and to modify the dysfunctional symptoms of OCD. In addition, the supplementary motor area is suggested to have a specific role in motor planning, response inhibition, and word production[31–33] and is also extensively connected with various regions implicated in cognitive and emotional processes.[34] Inhibitory stimuli to the supplementary motor area might cause suppression of the hyperexcitable right hemisphere and thereby improve dysfunctional symptoms in patients with OCD.[11]

The lack of efficacy of sequential rTMS in OCD in our study might be caused by the following reasons: First, other OCD-related regional characteristics, such as left orbital frontal and bilateral prefrontal hypermetabolism,[35] may have contributed to the negative results in this study. Second, the absence of significant results in this study might reflect partial real stimulation effects in the sham-treatment group. Although no significant difference in efficacy was found between the active and sham groups, there was a significant effect of time on obsessive-compulsive symptoms as well as other symptoms such as depression and anxiety in both the active and the sham groups. Because sham treatment was applied to our subjects in the sham group with the coil angled at 45° from the scalp over the same area as for the active group, it is impossible to completely exclude the partial magnetic-field effects in the cortical area. Third, the total of 10 sessions might be insufficient to cause improvement, and OCD patients might need an extended treatment course lasting longer than 10 sessions. A longer stimulation period of up to 20 to 30 sessions would be necessary for any long-lasting effect or greater therapeutic benefit in chronically ill patients.[36,37]

In terms of side effects, our participants did not report any adverse effects except for transient mild headache (n = 2) and localized scalp pain (n = 1). Although a higher stimulation intensity (110% and 100%) and a larger number of 2,400 pulses per session were administered over the 10 days of this study in comparison to other studies, low-frequency rTMS over the right prefrontal cortex and the

supplementary motor area seemed to be safe and generally well tolerated. In addition, the rTMS did not cause any impairment of cognitive function as measured by the Stroop task.

The present study had some limitations in the sham system. We were unable to create ideal sham conditions of (1) no cortical stimulation effect, (2) acoustic and scalp sensations identical to real stimulation, and (3) visual impact and coil position identical to real stimulation.[16] As mentioned above, the 45° coil-tilt sham condition with 1 wing touching the scalp might have potential stimulation effects, even if it is a limited level of intracortical activity.[16,17] Furthermore, tilting the coil away from the scalp may feel different to patients than the flat position on the scalp used to measure the RMT. Although all our patients were naive to rTMS and there was no difference between the 2 groups when comparing the responses to what kind of treatment the subjects thought they received, our sham system could still raise the issue of whether different scalp sensations could potentially unblind the subjects. In addition, we could not blind the operator administering rTMS to the type of stimulations. Although the unblinded operator of rTMS did not seem to produce subjective biases or expectations of subjects because we limited the interaction between operators and patients, we cannot rule out the potential of the operator's bias completely.

To control for these pitfalls, several newly developed sham systems have been introduced. One of them is a real electromagnetic placebo device for sham rTMS that provides a low electric stimulation of the scalp by electrodes placed underneath the rTMS coil, which is kept flat on the scalp in both active and sham conditions.[38] In an even more sophisticated system, a computer randomly selects which coil is to be used (either active or sham) and whether to activate the magnetic or the electric stimulator, which makes no difference in terms of scalp sensations and keeps the operator blinded as well to the treatment condition.[39]

There were other limitations in this study. The sample size of each group in the present randomized study was small. In addition, all our subjects were receiving medication and were treatment-resistant OCD patients who had failed to respond to adequate pharmacotherapy with at least 2 SRIs. Further controlled studies of rTMS efficacy in OCD are needed, investigating rTMS not only as an add-on technique but also as a sole therapeutic intervention, and not only for refractory OCD patients but also for drug-naive patients in the early phase of the illness.

In summary, these findings suggest that 10 sessions of sequential rTMS of the right prefrontal cortex and the supplementary motor area at a low frequency had no therapeutic effect on the symptoms of treatment-resistant OCD patients. Although our results did not provide evidence supporting the efficacy of rTMS for OCD treatment or any difference from the sham rTMS results, our findings showed that sequentially applied rTMS is a safe and tolerable method, and cognitive function is not influenced after rTMS stimulation. To confirm the effect of rTMS in OCD, further controlled studies with more extended rTMS sessions in larger samples are required, using a more optimal system with no cortical activation effect and in which the treatment type is masked for all subjects, raters, and operators.

Drug names: aripiprazole (Abilify), lorazepam (Ativan and others), olanzapine (Zyprexa), quetiapine (Seroquel), risperidone (Risperdal and others).

Author affiliations: Department of Psychiatry, Ilsan Hospital, National Health Insurance Corporation, Gyeonggi-do (Dr Kang); Department of Psychiatry and Institute of Behavioral Science in Medicine, Yonsei University College of Medicine, Seoul (Drs Kang, C.-H. Kim, Namkoong, and S. J. Kim); and Yonsei Phil Psychiatric Clinic, Seoul (Dr Lee), South Korea.

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