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Update on Repetitive Transcranial Magnetic Stimulation in Obsessive-Compulsive Disorder: Different Targets

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Abstract Obsessive-compulsive disorder (OCD) is a chronic, disabling disorder. Ten percent of patients remain treatment refractory despite several treatments. For these severe, treatment-refractory patients, repetitive transcranial magnetic stimulation (rTMS) has been suggested as a treatment option. Since 1997, in published trials, a total of 110 OCD patients have been treated with rTMS. This review aims to provide an update on rTMS treatment in patients with OCD. First, the mechanism of action is discussed, followed by the efficacy and side effects of rTMS at various brain targets, and finally implications for the future. Due to the lack of studies with comparable stimulation or treatment parameters and with reliable designs, it is difficult to draw clear conclusions. In general, rTMS appears to be effective in open-label studies; however, this has not yet been replicated in randomized, sham-controlled trials.

Keywords Repetitive transcranial magnetic stimulation · rTMS · Treatment refractory · Obsessive-compulsive disorder · Targets

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Introduction

Obsessive-compulsive disorder (OCD) is a highly disablitating psychiatric disorder characterized by obsessions and compulsions. Obsessions are egodystonic, unwanted thoughts, images, or impulses that repeatedly enter one's mind. Compulsions are repetitive, time-consuming behaviors or mental acts often performed to neutralize the anxiety provoked by obsessions [1]. The prevalence of OCD in the general population is estimated at 1% to 3%, and the disorder is associated with impaired functioning and decreased quality of life [2, 3]. The general treatment of OCD is a serotonin reuptake inhibitor at an adequate dose, cognitive-behavioral therapy, or a combination of the two. However, up to 40% of patients fail to respond satisfactorily to these generally adequate treatment options, and 10% cannot be helped at all [1, 4].

With use of repetitive transcranial magnetic stimulation (rTMS), it has become possible to modulate local neural activity by inducing a depolarizing magnetic field pulse [5]. Because OCD may be related to increased neural activity in prefrontal subcortical circuits [6], the inhibitory effect of rTMS was hypothesized to be beneficial in OCD treatment.

In 1997, Greenberg et al. [7] introduced rTMS as a new treatment approach for OCD. Earlier, rTMS had been shown to have a positive effect on mood disorders with stimulation of the prefrontal cortex [8]. Greenberg et al. [7] hypothesized that inhibition of the prefrontal activity with rTMS might reduce obsessive-compulsive symptoms. They applied rTMS (80% motor threshold, 20 Hz for 2 s/min) for 20 min to 12 patients with OCD and found significantly decreased compulsive urges for 8 h after stimulation. Since then, rTMS has been investigated in OCD, targeting several brain areas within the corticostriatal network. In this article, the mechanism of action is discussed first, then the efficacy and side effects of rTMS at various brain targets, and finally implications for the future.

Mechanism of Action

In the early-1980s, the transcranial magnetic stimulation (TMS) device was developed by Barker and colleagues [5]. The device stimulates the human cortex directly using a contactless and noninvasive method. It uses a strong pulse of electrical current that is sent through a coil to induce a magnetic field pulse in the area under the coil. This pulse has the capacity to depolarize superficial local neurons [5]. To create a longer lasting effect of the depolarized neurons, application of rTMS is needed. The magnitude and direction of rTMS-induced neuronal modulation depend on extrinsic factors such as motor threshold, frequency, and total number of stimuli, and intrinsic factors such as the functional state of the cortex [9]. For example, it appears that low-frequency rTMS (0–5 Hz) results in decreased neural excitability and regional cerebral blood flow, as opposed to high-frequency rTMS (5–20 Hz), which increases both [10].

Because knowledge of involvement of specific brain circuits in OCD is advancing, rTMS has been applied to several brain targets (Table 1). The rationale for the first rTMS studies in OCD was based on functional neuroimaging studies of OCD that demonstrated abnormalities in the orbitofrontal subcortical circuits, especially in the orbital frontal gyri and medial caudate nuclei [11]. This circuitry may be manipulated with rTMS by 1) stimulation of the dorsolateral prefrontal cortex (DLPFC) [12], 2) inhibition of the orbitofrontal cortex (OFC) directly [13], or 3) inhibition of the supplementary motor area (SMA). The SMA was chosen as a useful target for rTMS because it has extensive connections with regions implicated in cognitive processes and motor control [14, 15].

Efficacy of Repetitive Transcranial Magnetic Stimulation in Obsessive-Compulsive Disorder

A total of 110 OCD patients in 10 studies have been treated with rTMS, targeting the DLPFC, the OFC, or the SMA. Four studies investigated the efficacy of rTMS in OCD in a double-blind, randomized, sham-controlled design [12, 16, 18•, 19]; three studies in a sham-controlled design, although not double-blind [13, 17•, 20]; and three case studies in an open fashion [7, 14, 21]. The characteristics of each study are summarized in Table 1.

Dorsolateral Prefrontal Cortex

The DLPFC has been the most investigated target for rTMS in OCD. In 1997, Greenberg et al. [7] treated 12 OCD patients with rTMS to the right DLPFC, the left DLPFC, and lastly the midoccipital cortex as a control condition [7]. Eight of 12 patients were stable on serotonin reuptake inhibitor treatment. rTMS was randomly applied to these targets in an open fashion on separate days, at 80% threshold, 20 Hz for 2 s/min for 20 min. Compulsions, as measured by the Yale-Brown Obsessive Compulsive Scale (Y-BOCS), decreased significantly with 34.8% immediately after right DLPFC stimulation ($P<0.01$) and remained significant 8 h afterward ($P<0.02$), whereas obsessions did not decrease significantly. Depressive symptoms decreased significantly as well, although the effect did not last longer than 8 h. Compulsions decreased instantly with 26.8% ($P<0.03$) following left DLPFC stimulation, but similar to depressive symptoms, they returned after 8 h. Midoccipital stimulation increased compulsions, as measured by the Y-BOCS (nonsignificantly) ($P=0.07$).

In 2001, Sachdev et al. [21] tried to replicate this study in 12 patients with treatment-resistant OCD. Right ($n=6$) and left ($n=6$) DLPFC stimulation was applied in an open fashion at 10 Hz, 100% motor threshold for 10 sessions of 2.5 min. At 4 weeks of follow-up, rTMS led to a mean decrease on the Y-BOCS of 57% for right DLPFC and 27% for left DLPFC. All 12 individuals were analyzed together, as there were no differences on any of the parameters measured, and showed a significant decrease of 42% on the Y-BOCS at 1-month follow-up ($P=0.003$). However, after corrections for depression scores on the Montgomery-Asberg Depression Rating Scale, the significance disappeared ($P=0.06$). In the same year, the first randomized, sham-controlled, double-blind rTMS OCD trial was completed. Alonso et al. [16] randomly assigned 18 patients with OCD to real rTMS ($n=10$) or sham rTMS ($n=8$) at the right DLPFC. The rTMS lasted 20 min at 1 Hz for both conditions, but the motor threshold was 110% for real rTMS and 20% for sham rTMS. This study failed to find significant improvement on the Y-BOCS or Hamilton Depression Rating Scale (HAM-D) after 18 sessions.

In 2006, this randomized, sham-controlled, double-blind design was repeated stimulating the left instead of the right DLPFC in 30 treatment-resistant OCD patients [19]. Patients were given 10 daily sessions of sham or real

Table 1 Summary of studies of repetitive transcranial magnetic stimulation in treatment of obsessive-compulsive disorder

	Study (year)	Target	*N*	Diagnosis	Medication continuation	Intervention	Time	Mean score (SD) on Y-BOCS pre-rTMS	Mean score (SD) on Y-BOCS post-rTMS	Mean score on mood scale pre-rTMS	Mean score on mood scale post-rTMS
Intervention	Greenberg et al. [7] (1997)	Right PFC or left DLPFC	12	OCD	Yes, *n*=8 (stable SRI treatment)	20 Hz/2 s/min (80% of motor threshold)	1 session of 20 min; measurement after 8 h	–	Compulsions decreased right PFC (P=0.02) (left PFC P=0.05)	–	No significant mood improvement
Control		Midoccipital	12[a]	OCD		20 Hz/2 s/min (80% of motor threshold)	1 session of 20 min; measurement after 8 h	–	Compulsions decreased (midoccipital P=0.07)	–	No significant mood improvement
Intervention	Sachdev et al. [21] (2001)	Right PFC	6	Treatment-resistant OCD	Yes, *n*=10 (stable SRI, benzodiazepine, neuroleptic treatment)	10 Hz (110% motor threshold)	10 sessions of 2.5 min in 2 week; measurement 4 week after last session	27.2 (9.0)	12.0 (3.9)	23.2 (12.5) on BDI	11.6 (14.6) on BDI
Control		Left PFC	6	Treatment-resistant OCD		10 Hz (110% motor threshold)	10 sessions of 2.5 min in 2 week; measurement 4 week after last session	22.5 (6.3)	16.5 (8.3)	19.7 (12.5) on BDI	10.8 (7.9) on BDI
Intervention	Alonso et al. [16] (2001)	Right DLPFC	10	OCD	Yes, *n*=7 (stable SRI, TCA treatment)	1 Hz (110% of motor threshold)	18 sessions of 20 min in 10 week; measurement after 10 week	24.0 (5.3)	20.6 (9.1)	11.1 (5.1) on HAM-D	10.8 (4.8) on HAM-D
Control		Right DLPFC	8	OCD	Yes, *n*=6 (stable SRI, TCA treatment)	Sham condition	18 sessions of 20 min in 10 week; measurement after 10 week	25.6 (6.1)	25.3 (8.3)	11.7 (2.7) on HAM-D	12.0 (3.0) on HAM-D
Intervention	Mantovani et al. [14] (2006)	SMA	10	OCD/TS	Yes, *n*=10 (stable SRI, benzodiazepine, neuroleptic treatment)	1 Hz (100% of motor threshold)	10 sessions of 20 min in 2 week; measurement 2 week after last stimulation	36.4 (7.5)	26.0 (10.5)	20.7 (11.4) on HAM-D	10.8 (10.7) on HAM-D
Control		–	–	–		–	–	–	–	–	–
Intervention	Prasko et al. [19] (2006)	Left DLPFC	15	SRI-resistant OCD	Yes, *n*=15 (stable SRI treatment)	1 Hz (110% of motor threshold)	10 sessions of 30 min in 2 week; measurement 2 week after last stimulation	29.8 (5.8)	21.4 (9.2)	–	–
Control		Left DLPFC	15	SRI-resistant OCD	Yes, *n*=15 (stable SRI treatment)	Sham condition	10 sessions of 30 min in 2 week; measurement 2 week after last stimulation	23.4 (5.0)	16.9 (5.9)	–	–
Intervention	Sachdev et al. [12] (2007)	Left DLPFC	10	OCD	Yes, *n*=9 (unknown treatment)	10 Hz (110% of motor threshold)	10 sessions of 2.5 min in 2 week; measurement directly after last stimulation	26.0	20.0	–	Symptoms improved over time but no difference between groups
Control		Left DLPFC	8	OCD	Yes, *n*=4 (unknown treatment)	Sham condition	10 sessions of 2.5 min in 2 week; measurement directly after last stimulation	24.0	19.0	–	Symptoms improved over time but no difference between groups
Intervention	Ruffini et al. [13] (2009)	Left OFC	16	Drug-resistant OCD	Yes, *n*=23 (stable SRI, neuroleptic, antiepileptic, benzodiazepine treatment)	1 Hz (80% of motor threshold)	15 sessions of 10 min in 3 week; measurement 12 week after last session	32.1 (6.0)	27.3 (9.4)	–	No mood improvement over time
Control		Left OFC	7	Drug-resistant OCD		Sham condition	15 sessions of 10 min in 3 week; measurement 12 week after last session	31.4 (6.9)	29.6 (6.7)	–	No mood improvement over time
Intervention	Kang et al. [17•] (2009)	Right DLPFC and SMA	10	Treatment-resistant OCD	Yes, *n*=10 (stable SRI, benzodiazepine treatment)	1 Hz (110% of motor threshold)	14 sessions of 10 min in 2 week; measurement 2 week after last session	26.5 (5.6)	23.6 (7.4)	18.1 (6.6) on BDI	17.2 (10.9) on BDI
Control		Right DLPFC and SMA	10	Treatment-resistant	Yes, *n*=10 (stable SRI, benzodiazepine	Sham condition	14 sessions of 10 min in 2 week; measurement	26.3 (4.1)	22.9 (6.2)	16.7 (10.0) on BDI	15.8 (14.4) on BDI

Table 1 (continued)

	Study (year)	Target	*N*	Diagnosis	Medication continuation	Intervention	Time	Mean score (SD) on Y-BOCS pre-rTMS	Mean score (SD) on Y-BOCS post-rTMS	Mean score on mood scale pre-rTMS	Mean score on mood scale post-rTMS
				OCD	treatment)		2 week after last session				
Intervention	Mantovani et al. [18•] (2010)	SMA	9	OCD	Yes, *n*=13 (stable SRI treatment)	1 Hz (100% of motor threshold)	20 sessions of 20 min in 4 week; measurement directly after last stimulation	26.0 (5.4)	19.4 (5.6)	15.3 (10.6) on HAM-D	12.1 (11.4) on HAM-D
Control		SMA	9	OCD		Sham condition	20 sessions of 20 min in 4 week; measurement directly after last stimulation	26.7 (5.5)	23.5 (9.0)	14.8 (6.9) on HAM-D	14.1 (8.8) on HAM-D
Intervention	Sarkhel et al. [20] (2010)	Right DLPFC	21	OCD	Yes, *n*=21 (TCA, SRI treatment)	10 Hz (110% of motor threshold)	10 sessions in 2 week; measurement 2 week after last session	25.7 (3.9)	Change in score, 5.0 (2.3)	12.5 (2.2) on HAM-D	Change in score, 3.8 (1.6) on HAM-D
Control		Right DLPFC	21	OCD	Yes, *n*=21 (TCA, SRI treatment)	Sham condition	10 sessions in 2 week; measurement 2 week after last session	23.6 (3.7)	Change in score, 4.2 (1.8)	12.1 (2.7) on HAM-D	Change in score, 3.2 (1.0) on HAM-D

[a] Same 12 individuals as investigated in the intervention group

BDI Beck depression inventory, *DLPFC* Dorsolateral prefrontal cortex, *HAM-D* Hamilton depression rating scale, *OCD* Obsessive-compulsive disorder, *OFC* Orbitofrontal cortex, *PFC* Prefrontal cortex, *rTMS* Repetitive transcranial magnetic stimulation, *SMA* Supplementary motor area, *SRI* Serotonin reuptake inhibitor, *TCA* Tricyclic antidepressant, *TS* Tourette's syndrome, *Y-BOCS* Yale-brown obsessive compulsive scale

rTMS (1 Hz, 110% motor threshold) in addition to ongoing serotonin reuptake inhibitor treatment. After 2 weeks of follow-up, obsessive-compulsive symptoms improved, with mean Y-BOCS reductions of 28%, but no differences between sham and real rTMS were observed. The authors concluded that rTMS did not result in an effect on OCD by stimulating the left DLPFC. Similarly, in a study by Sachdev et al. [12], high-frequency (10 Hz, 110% motor threshold) rTMS of the left DLPFC yielded significant Y-BOCS decreases (6.0 points, 23.1%) over 2 weeks in 10 OCD patients, but the effects were similar after sham rTMS in 8 patients (5.0 points, 20.4%).

Finally, in an Indian sham-controlled study, active rTMS at 10 Hz, 110% motor threshold (n=21) and sham rTMS (n=21) of the right DLPFC elicited similar improvement in obsessions and compulsions 2 weeks after the 10th session [20]. The Y-BOCS reduction for active rTMS was 5.0 points (19.5%), and 4.2 points (17.7%) for sham rTMS. Interestingly, depressive scores, as measured by the HAM-D, were reduced significantly over time in the real rTMS group compared with the sham rTMS group (P>0.04). A total of 76.2% of those receiving real rTMS were partial responders (25% reduction in HAM-D scores from baseline), compared with 66.7% in the sham group. The authors concluded that right DLPFC rTMS has no effect on OCD but is modestly effective in the treatment of comorbid depressive symptoms.

In conclusion, in open-label studies, high-frequency rTMS of the right and/or left DLPFC appears to be effective in reducing obsessive-compulsive symptoms. However, this could not be replicated in double-blind, sham-controlled studies. In those studies, neither low nor high rTMS and neither rTMS to the left nor to the right DLPFC appeared to be more effective than sham rTMS.

Orbitofrontal Cortex

In 2009, Ruffini and colleagues [13] examined the OFC as a new target for rTMS in drug-resistant OCD patients. The participants received 10 min of 1-Hz rTMS at 80% motor threshold for 15 sessions to the left OFC; however, the coil was placed parallel (active, n=16) or perpendicular (sham, n=7) to the scalp. They found significant reduction of Y-BOCS scores comparing active versus sham treatment for 10 weeks after the end of rTMS (P<0.02), with loss of significance after 12 weeks (P<0.06). Y-BOCS reduction was 19.7% immediately after rTMS and 14.7% after 12 weeks of follow-up, but only 6.7% and 5.7%, respectively, for the sham condition. There was also a benefit in terms of depressive and anxiety symptoms, but not at a significant level in the two groups. Similar to findings for DLPFC rTMS, this study suggests that low-frequency rTMS of the OFC may only acutely improve obsessive-compulsive symptoms.

Supplementary Motor Area

Two groups investigated the efficacy of low rTMS to the SMA in addition to ongoing pharmacotherapy. In 2006, Mantovani et al. [14] conducted an open-label study of 10 patients with OCD, Tourette's syndrome, or both. Individuals were treated with active rTMS to the SMA for 10 daily sessions at 1 Hz, 100% motor threshold. After 2 weeks of daily rTMS, the Y-BOCS reduction (28.6%) and HAM-D reduction (47.8%) were both significant, and they remained stable after 3 months' follow-up in the OCD as well as in the OCD/Tourette's syndrome group. In 2010, the same group examined rTMS (at 1 Hz and 100% motor threshold) to the SMA bilaterally in a randomized, sham-controlled, double-blind design [18]. After 4 weeks of stimulation, the Y-BOCS decreased significantly ($P<0.001$) in the active group (6 points, 25.4%) and the sham group (3.2 points, 12.0%) without significant differences between the two treatment conditions.

Finally, an open, sham-controlled study investigated the possible therapeutic effects and safety of sequentially combined low-frequency (1 Hz, 110% threshold) rTMS to the right DLPFC and the SMA in 10 patients with treatment-resistant OCD [17]. Similar improvements in obsessive-compulsive and depressive symptoms were observed for sham and real rTMS at 2 weeks after the last of 14 sessions. The Y-BOCS reductions were 2.9 points (10.9%) and 3.4 points (12.9%) for real and sham rTMS, respectively. rTMS was a safe method, and there was no significant change in cognitive functioning after stimulation. Similar to DLPFC and OFC stimulation, rTMS to the SMA was a safe method to immediately improve obsessive-compulsive symptoms; however, improvement did not linger on over time.

In conclusion, efficacy of low- and high-frequency rTMS to the left or right DLPFC, the OFC, or the SMA has been investigated in a total of 110 obsessive-compulsive patients over the past decade. Although open studies have initially demonstrated beneficial effects of rTMS on obsessive-compulsive and depressive symptoms during the first hours after stimulation, these effects disappeared during follow-up and, more importantly, rTMS did not show any advantages over sham stimulation in double-blind, sham-controlled studies.

Side Effects and Safety

rTMS is generally regarded as a safe and noninvasive therapeutic technique. Although extremely rare, the most severe acute adverse effect related to rTMS is the induction of epileptic seizures. The chance of getting a seizure during high-frequency rTMS is greater than during low-frequency rTMS. Other side effects that have been reported are induction of hypomania, local pain, headache, paresthesia, hearing changes, and thyroid-stimulating hormone and blood lactate level changes. The two latter have only been reported in high rTMS [22].

In the studies of rTMS in OCD patients, low-frequency rTMS study patients occasionally reported headache or localized scalp pain [14, 16, 17•], whereas in the high-frequency rTMS patients, side effects were more often noted. The most common complaint in those studies was headache, followed by localized scalp pain, facial nerve stimulation, fainting, and weepiness [12, 20, 21]. None of the side effects held on longer than 4 weeks after stimulation, and neither serious adverse events such as seizures and memory problems nor cognition problems were disclosed.

Conclusions and Future Directions

Since 1997, rTMS has been applied as an experimental treatment in cases of refractory OCD. Local induction of a depolarizing magnetic field pulse may decrease obsessive-compulsive symptoms by normalizing hypermetabolism in orbitofrontal-striatal circuits. The technique is noninvasive and yields no side effects or mild side effects, of which headache is the most common. Because of the lack of studies with comparable stimulation or treatment parameters and with reliable designs, it is difficult to draw clear conclusions; this corresponds with a Cochrane review from 2003 about TMS treatment in OCD [23]. Explorations of rTMS to the DLPFC, OFC, or SMA in a total of 10 studies have demonstrated only acute efficacy for obsessive-compulsive symptoms of rTMS and no differences with sham treatment.

To generalize the results of these studies, further research is necessary. Careful consideration of target regions and stimulation parameters, longer follow-up, and the use of a double-blind, sham-controlled design may allow us to draw founded conclusions in the future. Besides, as the efficacy of rTMS is often time limited, the necessity of a second rTMS after several weeks should be investigated. Moreover, functional MRI studies of rTMS in OCD are needed to clarify the specific stimulation region of rTMS. Nevertheless, rTMS may play an important role in research settings. For example, rTMS could be used to modulate obsessive-compulsive symptoms and brain activity in functional MRI and receptor-binding studies. Otherwise, as the improvement of symptoms is often noted in sham settings, it would be interesting to investigate the neural underpinnings of the placebo effect caused by sham rTMS. Finally, a novel stimulation paradigm was recently designed: theta-burst stimulation, a low-intensity burst of

rTMS at 50 Hz as a safer, more consistent, and longer lasting rTMS [24]. The results of the first case study with this paradigm in OCD and depression are promising and warrant further exploration [25•].

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