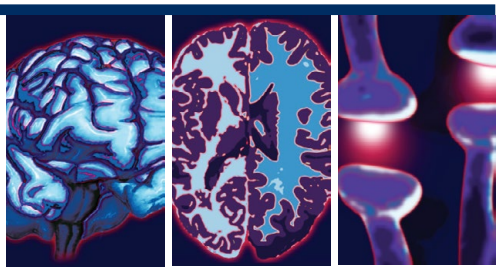
Short communication



# An Update of the Application of Repetitive Transcranial Magnetic Stimulation (rTMS) in Patients with Obsessive Compulsive Disorder

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## Abstract

Obsessive Compulsive Disorder (OCD) is a disabling illness that is currently managed primarily by pharmacotherapy and CBT. Though results are good, there is significant number of patients resistant to existing modalities of treatment. TMS is a relatively newer technique of treatment, which has shown effectiveness in treatment of OCD patients, both new and those resistant to other treatments. This update aims to look into the application of rTMS in patients with obsessive-compulsive disorder.

## Introduction

Obsessive Compulsive Disorder (OCD) is an illness characterized by repetitive intrusive thoughts and associated acts, in which patient is compelled to carry out compulsive activities to avoid anxiety. This causes significant distress and dysfunction in the patients suffering from OCD. Widespread research into OCD led to the development of several treatment options. These treatment options have been shown to limit effectiveness in the management of OCD. The limitation of effective options leads to some difficulty in deciding the initial management plan. Several guidelines suggest Selective Serotonin Re-Uptake Inhibitors (SSRIs) as the first line of treatment. Cognitive Behavior Therapy (CBT) has also been suggested as an effective first line strategy, and the choice between SSRIs and CBT is to be made keeping in mind the patient profile and tolerability of the treatments offered to the patients [1]. Even with recent advancements in treatment option available to psychiatrists today, OCD remains a difficult disorder to treat. Nearly 40-60% of the patients do not respond to the first line of treatment offered to them [2].This poses a significant challenge to the treating physician. Several alternative strategies have been tried in patients suffering from OCD, in an attempt to find a better success rate. Unfortunately, these additional treatment options have proven to be inadequate as, and thus, the quest to look for more treatments that are effective continues.

Transcranial Magnetic Stimulation (TMS) is one such newer method under investigation. TMS is a non-invasive brain stimulation technique, which can modulate cortical activity and excitability and has been investigated as a possible therapeutic modality in the OCD [3]. Barker et al introduced it in 1985 as a diagnostic and investigational tool [4]. Its use has expanded since then and is now seen as a possible therapeutic intervention in several neuropsychiatric disorders. Greenberg et al. were the first to investigate the possible role of rTMS in OCD in 1997 [2]. Since then, research into this direction has gained momentum. The quality of studies has improved, with studies incorporating a control in the form of sham stimulation, leading to more results that are robust. So far, the results of these studies are promising.

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## Possible Mechanism of Action

As with most psychiatric disorders, the basic pathophysiology of OCD continues to elude us. Different approaches, focusing primarily on biological investigations, have been used to try to understand the underlying pathophysiology of OCD. Neuroimaging studies have been a major cornerstone of such research. Though the underlying mechanism behind OCD is far from clear, several neurobiological hypotheses have been put forth. One result of these neurobiological hypotheses is the identifications of possible target areas for intervention by the way of brain stimulation.

There is considerable evidence from different studies implicating Cortico-Striato-Thalamo-Cortical (CSTC) circuit. The key areas identified in this circuit are the orbitofrontal cortex, anterior cingulate cortex and the basal ganglia [3-6]. When studying patient of OCD compared to healthy controls, studies have found several changes in these key areas in patients suffering from OCD. The most consistent finding of these studies has been hyper perfusion and hyper activation in these areas [7]. As a proof of concept, studies have also shown reversal of these changes with adequate treatment, leading to reinforcement of the hypothesis that the underlying pathology in OCD may indeed stem from the above-mentioned areas [8].

Recently, the focus has been on the effect of TMS in patients with OCD. TMS studies have shown that OCD patients have less cortical inhibition compared to healthy controls [9]. Among different applications of rTMS, low frequency rTMS has shown to decrease cortical excitability and cerebral blood flow of areas under stimulation [10]. Hence it has been postulated that low frequency rTMS can have therapeutic benefits in patient with OCD by inhibiting the hyper-excitable CSTC circuit.

## Clinical Studies

A review of literature reveals that there is not much work done on TMS and OCD. Whatever research is available is varied in methodology. Thus, in our update we decided to focus mainly on randomized, sham controlled trials. Although a number of such studies are available, they have been heterogeneous in terms of site of stimulation and various stimulus parameters **(Table 1)**.

## Site of Stimulation

Most of the initial studies chose either right or left dorsolateral prefrontal cortex as the site of stimulation [2, 8, 11-18]. Only one of the randomized sham controlled studies was able to find any significant benefit of real rTMS over sham rTMS [18]. One of the possible reasons for this non-response could be the number of rTMS sessions given. The previous studies administered relatively less number of sessions as compared to more recent work. In most of the studies 10 sessions of rTMS was given over a period of 2 weeks, whereas recent studies have shown good results with higher number of treatment sessions [19]. The stimulation parameters were also not consistent with some studies using high frequency rTMS [10, 12, 15, 19] whereas others using low frequency [13, 20] limiting the robustness of the combined evidence made available by these studies. Low frequency rTMS is describes as that delivering magnetic pulses at 1 Hz or less, while high frequency rTMS usually delivers pulses at a usual rate of 1-10 Hz. Since both these modalities produce opposite effects, with low frequency rTMS causing cortical inhibition, while high frequency rTMS causes cortical stimulation, it is difficult to compare findings of studies when the stimulation parameters are different.

The supplementary Motor Area (SMA) has been used as another target for intervention. This is because it has extensive connections with different cortical and subcortical regions implicated in OCD [21]. Mantovani et al. (2010) for the first time targeted the SMA in an open label study. He found significant reduction in symptom severity of the patients suffering from OCD after 10 daily sessions of low frequency rTMS, although the sample size was too less to make any definitive inferences. The same authors carried out the first randomized sham controlled trial targeting the same area with a larger sample size [22]. Twenty-One treatment resistant OCD patients were randomized to either sham or real rTMS, and the number of treatment sessions was increased to 20 over a period of 4 weeks. The authors observed that almost two-thirds patients in the real group responded to the interventions and the difference was significant from the sham group. Another recent study by Gomes et al (2012) [23] targeted the SMA in twenty-two treatment resistant OCD patients using similar stimulation parameters and found that almost 40% of the patients responded to rTMS.

Orbito-frontal cortex (OFC) seems to be one of another important area implicated in

**Table 1:** Randomized, sham controlled trials.

| Author | Year | N (active / sham) | Region | Frequency / Intensity | Sessions | Results |
|---|---|---|---|---|---|---|
| Pedapati et al | 2015 | 10 / 8 | Right DLPFC | 1 Hz / 110% RMT | 1 | Active group did not have neural activity changes after rTMS [16] |
| Haghighi et al | 2015 | 21 crossover | B/L DLPFC | 20 Hz / 100% RMT | 20 | rTMS a successful intervention for treatment-resistant OCD |
| Nauczyciel et al | 2014 | 19 crossover | Right OFC | 1 Hz / 120% RMT | 10 | Stimulation related to a bilateral decrease in OFC metabolism [20] |
| Ma et al | 2014 | 25 / 21 | B/L DLPFC | Variable / 80% RMT | 10 | αEEG-guided TMS may be an effective treatment for OCD and related anxiety [18] |
| Mantovani et al | 2013 | 9 / 9 | Pre-SMA | 1 Hz / 100% RMT | 20 | Abnormal hemispheric laterality found in the group randomized to active rTMS normalized [22] |
| Gomes et al | 2012 | 12 / 10 | Pre-SMA | 1 Hz / 100% RMT | 10 | At 14 weeks follow-up, 41% patients who received active rTMS showed improvement, as compared to 10% in sham group [23] |
| Mansur et al | 2011 | 13 / 14 | Right DLPFC | 10 Hz / 110% RMT | 30 | Active rTMS not superior to sham in treatment resistant OCD |
| Sarkhel et al | 2010 | 21 / 21 | Right DLPFC | 10 Hz / 110% RMT | 10 | No significant effect of rTMS [15] |
| Ruffini et al | 2009 | 16 / 7 | Left OFC | 1 Hz / 80% RMT | 15 | Significant but time-limited improvement in OCD [24] |
| Kang et al | 2009 | 10 / 10 | Right DLPFC | 1 Hz / 110% RMT | 10 | No therapeutic effect on obsessive-compulsive symptoms |
| Sachdev et al | 2007 | 10 / 8 | Left DLPFC | 10 Hz / 110% RMT | 10 | Two weeks of rTMS over the left DLPFC is ineffective for treatment-resistant OCD [8] |
| Alonso et al | 2001 | 10 / 8 | Right DLPFC | 1 Hz / 110% RMT | 18 | Low-frequency rTMS of the right prefrontal cortex failed to produce significant improvement of OCD and was not significantly different from sham treatment [13] |

pathogenesis of OCD. Compared to the SMA, it is a more difficult area to stimulate directly as it is located deeper in the brain. Ruffini et al. [24] targeted the OFC (which corresponded to Fp1 area of International 10-20 EEG system) in a randomized sham controlled study. Twenty-three patients were given 15 sessions of low frequency rTMS. The authors found significant difference in response between the sham and real group. In a sham controlled trial, Nauczyciel et al (2014) [20] employed a double cone coil to apply low-frequency rTMS to the Right OFC in patients with OCD, and found a greater reduction in YBOCS score in patient's receiving real stimulation, though the findings were not statistically significant ($p = 0.07$). Till date these are the only published study targeting OFC and there is a need for other studies targeting this area with larger sample size.

From the currently available studies, it appears that SMA and OFC are two potential areas, which can be targeted while managing OCD using rTMS.

## Localization Technique

The DLPFC region in most studies was clinically identified following the 5 cm rule, that is, localizing a point measuring 5 cm anterior and in a parasagittal line from the point of maximum stimulation of contralateral APB muscle [25]. This method has been criticized on several accounts, like neglecting individual variations in skull morphology, and high inter-rater variability [2]. This could be one more possible reason for the poor results obtained in studies involving DLPFC, as the studies which targeted OFC or SMA used 10-20 EEG system to localize individual areas. The 10-20 EEG systems take into account the individual morphological variations, and thus have an advantage over the 5 cm rule.

With the advancements in functional neuroimaging, neuronavigation directed rTMS has been used in several trials of rTMS in depression. These studies have shown superiority of this method over the traditional methods mentioned above [26]. Future studies can make use of this technique to improve the localization of the site of stimulation in patients with OCD as well.

## Patient Selection

It is seen that majority of the studies [8, 11, 27] have been conducted in treatment resistant population. Also, different criteria have been used to define treatment resistance in different studies. Such factors limit the generalizability

of the results of these studies. Although the available data is limited, at-least some robust studies have shown effectiveness of rTMS in treatment resistant population. Pallanti et al and the International Treatment Refractory OCD Consortium proposed ten levels of non-response with increasing levels suggestive of failure to greater number of interventions [1]. Future studies can use some definitions that could help in clearly establishing at what rTMS should be considered in the patients with OCD. Most of the studies have excluded patients with co morbid depression and other Axis I condition. This poses a big question mark on applicability of rTMS in a large subset of OCD population in which depression is usually co-morbid.

## Stimulation Parameters

### ■ Intensity

The exact relation between clinical efficacy and stimulation intensity is unknown. Padberg et al. [28] suggested positive correlation between the two. On the other hand, a few other studies have suggested that even very high stimulus intensity can be suboptimal. Stimulation intensity is calculated based on resting motor threshold (MT) of an individual. Studies which failed to show beneficial effect of rTMS used higher stimulus intensity of 110% of MT compared to the studies with positive result [8] (between 80-100% MT). This appears to support the hypothesis that there appears to be certain optimal range of stimulus intensity and apparently, higher stimulus intensity does not offer any benefit and can increase the risk of seizures.

### ■ Frequency

All the randomized sham controlled trial-using high frequency rTMS [15] failed to find any beneficial affect whereas the studies which used low frequency rTMS [11, 13, 14, 24, 27] have obtained positive result. This support the widely believed hypothesis that the beneficial effect of rTMS in OCD appears to be mediated by decreasing the hyper-excitability of CSTC circuit using low frequency rTMS.

### ■ Duration of treatment

Just like other treatment parameters, the total number of treatment sessions administered varied a great deal between different studies. Currently available data suggests that studies, which gave greater number of rTMS sessions, obtained better results compared to studies with lesser number of sessions. Mantovani et al. and Ruffini et al. gave 20 and 15 sessions respectively in their trials, and got a positive result that was more promising when compared to studies, which gave 10 sessions. Though this was the norm, there were a few exceptions, where a higher number of sessions did not produce better results [22-24].

### ■ Duration of effect

Only two studies have tried to look into the duration of the beneficial effect obtained in patients with OCD. Ruffini et al. found that the rTMS of the left OFC produced significant but time-limited improvement in OCD patients compared to sham treatment, as the significance between the two groups was lost at 12 weeks. Contrary to this, Gomes et al found that the beneficial effect of rTMS persisted even at end of 12 weeks.

### ■ Safety

One of the major concerns raised with rTMS trials is its possible role in precipitating seizures. None of the studies conducted in patients with OCD has any reported incidence of seizures and in general, rTMS was well tolerated with insignificant number of patients dropping out due to intolerable side effect. Most commonly reported adverse effect has been headache, localized scalp pain and dizziness.

## Conclusion

Obsessive compulsive disorders is a disabling condition, which, despite the varied treatment options available, warrants further improvement in management strategies. TMS is a newer modality, which has shown promising results in patients suffering from this disorder. Earlier studies did not reveal much benefit of this modality, though that may have been due to methodological issues. Newer studies with more successful methodologies have demonstrated that TMS is indeed a safe and effective modality to manage OCD. Despite the promising results, there is a lot of scope for further research in the area, especially regarding the comparison of TMS with pharmacotherapy, and the long-term benefits of this therapy. With adequate development, TMS may prove to be a useful toll in the psychiatrist's arsenal to tackle OCD.

## References


1. Pallanti S, Hollander E, Bienstock C, Koran L, Leckman J, et al. (2002) Treatment non-response in OCD: methodological issues and operational definitions. Int J Neuropsychopharmacol 5: 181-191.
2. Greenberg BD, George MS, Martin JD, Benjamin J, Schlaepfer TE, et al. (1997) Effect of prefrontal repetitive transcranial magnetic stimulation in obsessive-compulsive disorder: a preliminary study. Am J Psychiatry 154: 867-869.
3. Del Casale A, Kotzalidis GD, Rapinesi C, Serata D, Ambrosi E, et al. (2011) Functional neuroimaging in obsessive-compulsive disorder. Neuropsychobiology 64: 61-85.
4. Fineberg NA, Chamberlain SR, Hollander E, Boulougouris V, Robbins TW (2011) Translational approaches to obsessive-compulsive disorder: from animal models to clinical treatment. Br J Pharmacol 164: 1044-1061.
5. Milad MR, Rauch SL (2012) Obsessive-compulsive disorder: beyond segregated cortico-striatal pathways. Trends Cogn Sci 16: 43-51.
6. Aouizerate B, Guehl D, Cuny E, Rougier A, Bioulac B, et al. (2004) Pathophysiology of obsessive-compulsive disorder: A necessary link between phenomenology, neuropsychology, imagery and physiology. Progress in Neurobiology 72: 195-221.
7. Rauch SL, Jenike MA, Alpert NM, Baer L, Breiter HC, et al. (1994) Regional cerebral blood flow measured during symptom provocation in obsessive-compulsive disorder using oxygen 15-labeled carbon dioxide and positron emission tomography. Arch Gen Psychiatry 51: 62-70.
8. Sachdev PS, Loo CK, Mitchell PB, McFarquhar TF, Malhi GS (2007) Repetitive transcranial magnetic stimulation for the treatment of obsessive compulsive disorder: a double-blind controlled investigation. Psychol Med 37: 1645-164-169.
9. Ziemann U, Paulus W, Rothenberger A (1997) Decreased Motor Inhibition in Tourette's Disorder?: Evidence From Transcranial Magnetic Stimulation. J Psychiatry 1277-1284
10. Rosa MA, Lisanby SH (2012) Somatic treatments for mood disorders. Neuropsychopharmacology 37: 102-116.
11. Prasko J, Pasková B, Záleský R, Novák T, Kopecek M, et al. (2006) The effect of repetitive transcranial magnetic stimulation (rTMS) on symptoms in obsessive compulsive disorder. A randomized, double blind, sham controlled study. Neuro Endocrinol Lett 27: 327-332.
12. Sachdev PS, McBride R, Loo CK, Mitchell PB, Malhi GS, et al. (2001) Right versus left prefrontal transcranial magnetic stimulation for obsessive-compulsive disorder: a preliminary investigation. J Clin Psychiatry 62: 981-984.
13. Alonso P, Pujol J, Cardoner N, Benlloch L, Deus J, et al. (2001) Right prefrontal repetitive transcranial magnetic stimulation in obsessive-compulsive disorder: a double-blind, placebo-controlled study. J. Psychiatry 158: 1143-1145.
14. Mantovani A, Lisanby SH, Pieraccini F, Ulivelli M, Castrogiovanni P, et al. (2006) Repetitive transcranial magnetic stimulation (rTMS) in the treatment of obsessive-compulsive disorder (OCD) and Tourette's syndrome (TS). Int J Neuropsychopharmacol 9: 95-100.
15. Sarkhel S, Sinha VK, Praharaj SK (2010) Adjunctive high-frequency right prefrontal repetitive transcranial magnetic stimulation (rTMS) was not effective in obsessive-compulsive disorder but improved secondary depression. J Anxiety Disord 24: 535-539.
16. Pedapati E, DiFrancesco M, Wu S, Giovanetti C, Nash T, et al. (2015) Neural correlates associated with symptom provocation in pediatric obsessive compulsive disorder after a single session of sham-controlled repetitive transcranial magnetic stimulation. Psychiatry Res 233: 466-473.
17. de Wit SJ, van der Werf YD, Mataix-Cols D, Trujillo JP, van Oppen P, et al (2015) Emotion regulation before and after transcranial magnetic stimulation in obsessive compulsive disorder. Psychol Med 45: 3059-3073.
18. Ma X, Huang Y, Liao L, Jin YA (2014) randomized double-blinded sham-controlled trial of alpha electroencephalogram-guided transcranial magnetic stimulation for obsessive-compulsive disorder. Chin. Med. J. (Engl). 127: 601-606.
19. Gershon AA, Dannon PN, Grunhaus L (2003) Transcranial magnetic stimulation in the treatment of depression. Am J Psychiatry 160: 835-845.
20. Nauczyciel C, Le Jeune F, Naudet F, Douabin S, Esquevin A, et al. (2014) Repetitive transcranial magnetic stimulation over the orbitofrontal cortex for obsessive-compulsive disorder: a double-blind, crossover study. Transl Psychiatry Psychiatry 4: e436
21. Yücel M, Harrison BJ, Wood SJ, Fornito A, Wellard RM, et al. (2007) Functional and biochemical alterations of the medial frontal cortex in obsessive-compulsive disorder. Arch Gen Psychiatry 64: 946-955.
22. Mantovani A, Simpson HB, Fallon BA, Rossi S, Lisanby SH (2010) Randomized sham-controlled trial of repetitive transcranial magnetic stimulation in treatment-resistant obsessive-compulsive disorder. Int J Neuropsychopharmacol 13: 217-227.
23. Gomes PVO, Brasil-Neto JP, Allam N, Rodrigues de Souza EA (2012) Randomized, double-blind trial of repetitive transcranial magnetic stimulation in obsessive-compulsive disorder with three-month follow-up. J Neuropsychiatry Clin Neurosci 24: 437-443.
24. Ruffini C, Locatelli M, Lucca A, Benedetti F, Insacco C, et al. (2009) Augmentation effect of repetitive transcranial magnetic stimulation over the orbitofrontal cortex in drug-resistant obsessive-compulsive disorder patients: a controlled investigation. Prim Care Companion J Clin Psychiatry 11: 226-230.
25. Rollnik JD, Düsterhöft A, Däuper J, Kossev A, Weissenborn K, et al. (2002) Decrease of middle cerebral artery blood flow velocity after low-frequency repetitive transcranial magnetic stimulation of the dorsolateral prefrontal cortex. Clin Neurophysiol 113: 951–955.
26. Schönfeldt-Lecuona C, Lefaucheur JP, Cardenas-Morales L, Wolf RC, Kammer T, et al. (2010) The value of neuronavigated rTMS for the treatment of depression. Neurophysiol Clin 40: 37-43.
27. Kumar N, Chadda RK (2011) Augmentation effect of repetitive transcranial magnetic stimulation over the supplementary motor cortex in treatment refractory patients with obsessive compulsive disorder. Indian J Psychiatry 53: 340-342
28. Padberg F, Zwanzger P, Keck ME, Kathmann N, Mikhaiel P, et al. (2002) Repetitive transcranial magnetic stimulation (rTMS) in major depression: relation between efficacy and stimulation intensity. Neuropsychopharmacology 27: 638–645.