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# The effect of low-frequency repetitive transcranial magnetic stimulation on left dorsolateral prefrontal cortex in patients with the obsessive-compulsive disorder: a double-blinded, sham-controlled clinical trial

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## Abstract

**Background:** Obsessive-compulsive disorder (OCD) is a complicated neuropsychiatric disorder, which its prevalence ranges from 2 to 4%. In 30–60% of patients due to intolerance of side effects or partial response to treat symptoms of the disease remain or relapse. Repetitive transcranial magnetic stimulation (rTMS) is a non-invasive therapeutic option to treat this condition. Transcranial magnetic stimulation can be applied for treating with no anesthesia. The current study intended to evaluate the effectiveness of low-frequency rTMS on the left dorsolateral prefrontal cortex as an adjunct treatment in combination with standard medication in patients with OCD.

**Results:** In both groups of intervention and sham, the Y-BOCS scale was decreased. There was no significant difference between the two groups ($P$=0.82). Also after 15 sessions, the symptoms of OCD patients were improved. Although the treatment process was the same in the control group, none of the patients showed any serious complications, such as seizures, severe headache, neurological complication, or cognitive impairment during treatment.

**Conclusions:** It seems that treatment with 1 Hz rTMS on the left dorsolateral prefrontal cortex does not play an effective role in the recovery of OCD patients.

**Trial registration:** Name of the registry: Therapeutic effect comparison of the Repetitive Transcranial MagneticMagnetic Stimulation (RTMS) combination therapy with drug versus medication monotherapy in obsessive-compulsive disorder (OCD). Trial registration number: IRCT ID: IRCT20200728048240N1. Date of registration: 2020/8/8.

**Keywords:** Obsessive-compulsive disorder, Therapy, Neuropsychiatry, Repetitive transcranial magnetic stimulation

## Background

Obsessive-compulsive disorder (OCD) is a chronic psychiatric problem with varying degrees, ranging from very severe and debilitating to mild symptoms [1]. The prevalence of this disease has been reported at 1–3% in the general population [2]. In Iran, the prevalence of OCD is reported as 5.1, based on a recent national survey [3]. The distribution of the disease is almost the same between both genders, although it affects most men during childhood and early adolescence [4]. The exact etiology of OCD is not known, but there is ample evidence of an Orbitofrontal striatalpalidothalamic neurological disorder. Similar neural flow disorders have been reported in the dorsolateral prefrontal cortex (DLPFC), orbitofrontal cortex (OFC), medial prefrontal (MPF), anterior cingulate (ACC), supplementary motor area (SMA), and basal

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ganglia (BG) [5–7]. Different research on brain-imaging functions, for instance, positron emission tomography (PET), is associated with an enhanced function of the frontal lobes, the basal ganglia (particularly the caudate), and the cingulum of those who suffer from OCD. Studies on pathological aspects of OCD have shown that affecting these areas is more due to corticostriatal pathways than amygdale mechanisms [8, 9].

Selective serotonin reuptake inhibitors (SSRI) are the first-line treatment for OCD. SSRI often declines the intensity of OCD presentations by 20–30%, which is low [10]. These patients benefit from cognitive-behavioral therapy (CBT) [11, 12]. In refractory cases, selective serotonin-norepinephrine reuptake inhibitor (SNRI) is the next therapeutic option [13, 14]. Unfortunately, many patients (40–60%) do not respond satisfactorily to pharmacotherapy, and even after switching to other treatments, the final goal is still not obtained [15], which has been seen in severe cases resistant to OCD treatment.

Brain stimulation (BS) methods have been proposed as adjuvant therapy in OCD. BS is based on applying electrical flows or magnetic fields to change neuronal firing. Currently, several tools can be used to elicit such as neuromodulation. Each tool contains a various range of actions. Such tools are based on using an electrical or magnetic field or embedding the electrodes within the body to create electrical flows to a cranial electrical stimulation (CES), electroconvulsive therapy (ECT), transcranial direct current stimulation (tDCS), transcranial magnetic stimulation (TMS), and magnetic seizure therapy (MST). The surgical methods contain cortical brain stimulation (CBT), deep brain stimulation (DBS), and vagus nerve stimulation (VNS) [16, 17]. TMS and other types of magnetic stimulation may have a promising effect on the symptoms of OCD because of its focality and non-invasiveness. TMS contains using quickly altering magnetic field to the upper layer of the cerebral cortex, which causes regional stimulation of electric flows. Also referred to as eddy TMS is an example of a noninvasive induction method of focal areas of the brain and it can also be applied for studying or treating with no anesthesia.

DLPFC is one of the most effective rTMS regions for the treatment of OCD patients. Research on the pathophysiological aspect of OCD has shown that this area is associated with cortical and subcortical lobe hyperactivity [18]. This area plays an important role in executive processes and cognitive control. This includes the ability to focus thoughts and change flexibility [19]. Research suggests that stimulation of rTMS in the DLPFC region may be effective in orbitofrontal cortex hyperactivity. This effect may be achieved by activating the indirect inhibitory pathway or by direct connection between the DLPFC and the orbitofrontal cortex [20]. In healthy individuals, high-frequency (HF) rTMS may modulate dopamine release in the orbitofrontal cortex and caudate nucleus by inducing a stimulatory effect of rTMS on DLPFC [21, 22]. Whereas low-frequency (LF) rTMS with inhibitory effect leads to reduction of regional blood in the orbitofrontal cortex [23]. Studies in this field have heterogeneous designs in terms of excitation location (right vs. left), parameters and excitation frequency (LF vs. HF), session duration, sham conditions, and coil shape, this has led to conflicting results in this area [15, 24], so there is a need for further studies with different strategies in this field. The current study intended to evaluate the effectiveness of low-frequency rTMS on the left dorsolateral prefrontal cortex as an adjunct treatment in combination with standard medication in patients with obsessive-compulsive disorder.

## Methods

Based on the effect size ($f = 0.9$) obtained from previous studies, for a critical $P$ value of 0.05 and a critical power level of 0.80, a sample size of 30 was calculated. At first, 47 patients were studied to comply with the inclusion and exclusion criteria. Patients with a history of OCD referred to one of the university psychiatric clinics who, based on an interview with a psychiatrist, met the DSM5 (Diagnostic and Statistical Manual of Mental Disorder 5th Edition) criteria for obsessive-compulsive disorder and had no other psychiatric disorders, were studied. According to the Beck Depression questionnaire, participants should not have a history of depression. In this study, we used the Persian version of Y-BOCS because the participants were Iranian. It is a clinical standard for assessing the severity of OCD and has good reliability and validity for this purpose (test-retest reliability (0.99)). At the beginning of the study, the Y-BOCS questionnaire was completed for all patients, and patients with a score equal to or greater than 16 entered the research project [25].

Inclusion criteria included being aged 18 to 60 years old, histories of moderate to severe OCD (score greater than or equal to 16 of the Y-BOCS questionnaire), and a score less than 17 according to the Beck Depression questionnaire and receiving standard OCD drug treatment for the last 4 weeks.

Exclusion criteria included association with other psychiatric illnesses, having an intellectual disability, history of epilepsy or seizures, documented substance use disorder, documented severe head trauma, severe neurosurgical procedure, having any type of metal implant, having a pacemaker in situ, and receiving any type of electroconvulsive therapy in the previous month.

The final sample included in the analyses consisted of 30 patients: 15 in the active group and 15 in the sham group. A personal checklist was used to collect patients' characteristics. Before obtaining written informed consent, the objectives of the study were explained to the potential patients. Besides, they were ensured that the treatment would not harm them and their information would be kept confidential. Also, they were informed that they can withdraw at any time.

The recruited subjects ($n$=30) were divided into two groups of A or B using a randomized block table. Group A was treated with magnetic rapid stimulator (Magstim Rapid Stimulator; Magstim Company, Ltd., Whitland, UK), 20 min per day and 5 days per week (a total of 1200 pulses/day) with an intensity of 110% of the motor threshold and with standard medications for OCD. Those in group B were only treated with standard medications for OCD and a sham device for the same number of times and duration as group A.

The target area of rTMS in all patients was the Left DLPFC, which is an extensive region. Hence, a 70-mm circular coil was applied. The coil was kept in a manner to be superior to the inferior frontal sulcus. Also, it was anterior to the precentral sulcus.

Patients were blinded to the applied intervention. At the end of each week, an examiner was obliged to reexamine the patients' clinical symptoms as well as to fill the Y-BOCS questionnaire. The questionnaire was filled in blindly. The mean scores of the questionnaire as well as the observations and clinical evaluations of both groups were compared before and after providing the intervention. Besides, intra-group comparisons were also performed. These comparisons intended to evaluate the effectiveness of each treatment regimen independently and in comparison with the other group were addressed.

All subjects signed the informed consent form. Also, all data were kept confidential and analyzed anonymously. The participants were allowed to leave the trial at any step. All interventions and assessments were free for the subjects. Additionally, the current study has been designed and performed in agreement with the Helsinki declaration with no patient being deprived of essential treatment. This study is confirmed by the Ethical Committee of Qazvin University of Medical Sciences (IR.QUMS.REC.1396.63). Moreover, the current study is documented at the Iranian Registry of Clinical Trials (IRCT ID: IRCT20200728048240N1).

## Results

Of the 30 patients initially recruited for the present study, 8 (26/7%) were male and 22 (54/3%) were female. Twenty-five participants (83/3%) were married. The mean age of patients was 39.3 years. The youngest and oldest participants were 20 and 59 years old, respectively. Most patients were married and had severe diseases. The active and sham groups did not significantly differ in terms of any clinical or demographic characteristics (Table 1).

**Table 1** Demographic information in both groups

| Variables | Group received rTMS | Group received sham | *P* value |
|---|---|---|---|
| Gender | | | |
| Female | 10 | 12 | 0.68 |
| Male | 5 | 3 | |
| Age average | 37.13 | 41.4 | 0.27 |
| Marital status | 13 | 12 | 1 |
| Married | | | |
| Single | 2 | 2 | |
| Severity of the disease | | | |
| Mild | 0 | 1 | 1 |
| Severe | 15 | 14 | |

**Table 2** Comparison Y-BOCS scores in the beginning of the study and 5th, 10th, and 15th sessions in both groups

| Groups | YB-0 | YB-5 | YB-10 | YB-15 |
|---|---|---|---|---|
| rTMS | 21.8 | 16.4 | 15 | 13.2 |
| Sham | 23.6 | 16.6 | 14.93 | 12.7 |
| *P* value | 0.37 | 0.94 | 0.97 | 0.82 |

Comparison of the mean score of the Y-BOCS questionnaire before treatment in the two groups showed no significant difference between the scores ($p$ value= 0.27). Considering all patients, the mean score of the questionnaire before treatment was 22.7 $\pm$ 5.6. In group A, that received rTMS, the mean score of the questionnaire after 5 sessions was 16.53 $\pm$ 5.3. The mean score of the questionnaire after 10 sessions was 14.97 $\pm$ 5.3. The mean score of the questionnaire after 15 sessions was 13 $\pm$ 6.35 (Table 2).

The ANOVA analysis, which was performed after the last session between each group, showed no statistically significant difference ($p$ value = 0.82). It is worth noting that none of the patients showed any serious complications, such as seizures, severe headache, neurological complications, or cognitive impairment during treatment.

## Discussion

This study demonstrated that low-frequency rTMS on the left dorsolateral prefrontal cortex, compared to the sham, could not improve the severity of OCD. As a result, one of the effective factors is the time spent on treatment.

We performed the first evaluation after five sessions, while some studies in the early hours reported the effectiveness of this treatment in improving OCD symptoms [26]. Although this suggests that rTMS may speed up patients' recovery, it does not appear to have a significant effect on the final result.

Other factors influencing the outcome of the treatment include the area being treated and the intensity and frequency of rTMS. In this study, we investigated all OCD types; hence, separating different types of OCD may have affected the results.

Most previous studies have focused on patients with a history of drug resistance, but in the present study, rTMS was used to treat the patients responding to medication.

Numerous studies have used rTMS in refractory OCD. Meanwhile, research on the lateral posterior prefrontal cortex reported conflicting findings. So that six research on cranial electrical stimulation (CES), electroconvulsive therapy (ECT), transcranial direct current stimulation (tDCS), transcranial magnetic stimulation (TMS), and magnetic seizure therapy (MST). The surgical methods contain cortical brain stimulation (CBS), deep brain stimulation (DBS), and vagus nerve stimulation (VNS), which applied low-frequency stimulation, achieved similar findings indicating that treatment was effective on OCD symptoms [24, 27–32]. However, in this study, which was performed on OCD responders, treatment with rTMS was not different from Sham, but the disease process improved.

Hence, it can be argued that 1 Hz rTMS may be an adjunct therapy for refractory OCD patients but may not be effective in treating OCD. According to the evidence, rTMS aimed at targeting SMA (supplementary motor area) may be positively associated with better health status in OCD patients, although the association between SMA neuromodulation and the OCD as well as the effect of rTMS on it has not yet been elucidated [30, 31]. To clarify this issue, it is important to understand the concept of obsession as a form of thinking disorder and compulsion as a behavior. In studies that reported positive effects of rTMS on OCD, the advancement in Y-BOCS score can be attributed to the enhanced compulsion, in the meantime, no decline was observed in obsession. Greenberg and colleagues reported that a high-frequency rTMS session on the Left lateral peripheral cortex greatly reduced the urge to compulsion but did not affect obsession [33].

Neuroimaging studies have reported a probable association between hyperactive SMA in OCD individuals and impaired inhibitory management of behavior. Thus, SMA is an interesting goal for manipulating subcortical areas, which can affect OCD presentations, particularly in compelling behaviors [34].

We did not find any adverse effects (e.g., seizure, intense headache, and delirium). The findings of the present study are in line with most research approving that rTMS is safe and tolerable. Small sample size, short-term follow-up, lack of cognitive structural assessment, and lack of total blindness are the main limitations of the trial.

Because rTMS is not approved by the FDA for the treatment of anxiety, this led us to consider anxiety as an exclusion criterion. The severity of anxiety may have differing effects on the efficacy of the standard drug treatment for OCD in each group. Furthermore, different levels of anxiety can cause various degrees of neurotransmitters, like dopamine and norepinephrine, as well as a variety of hormones like cortisol. These, in turn, may have different effects on the neuro-excitability and neuro-biochemistry of the neural tissues targeted by rTMS producing differing responses. Similar to previous studies, in the present study, the Y-BOCS questionnaire was used to measure the severity of OCD, Therefore, the symptoms of obsession and compulsion were not evaluated separately [35]. In future studies, it is suggested that the sample size be larger so that the exact effects of rTMS can be determined through such research.

## Conclusions

In this study, after 15 sessions of 1 Hz rTMS with no cognitive side-effect or intense adverse consequences, the symptoms of OCD patients were markedly reduced, although the treatment process was the same in the control group. Despite these limitations, the results of this study are still valuable, as we evaluated the effectiveness and safety of the aforementioned technique in patients with OCD, albeit some differences were observed compared to previous studies.

#### Abbreviations

OCD: Obsessive-compulsive disorder; rTMS: Repetitive transcranial magnetic stimulation; SSRI: Selective serotonin reuptake inhibitors; CBT: Cognitive-behavioral therapy; SNRI: Selective serotonin-norepinephrine reuptake inhibitor; DLPFC: Dorsolateral prefrontal cortex; Y-BOCS: Yale-Brown Obsessive-Compulsive Scale; OFC: Orbitofrontal cortex; MPF: Medial prefrontal; ACC: Anterior cingulate cortex; SMA: Supplementary motor area; BG: Basal ganglia; PET: Positron emission tomography; BS: Brain stimulation; CES: Cranial electrical stimulation; ECT: Electroconvulsive therapy; tDCS: Transcranial direct current stimulation; TMS: Transcranial magnetic stimulation; MST: Magnetic seizure therapy; CBS: Cortical brain stimulation; DBS: Deep brain stimulation; VNS: Vagus nerve stimulation; CES: Cranial electrical stimulation; ECT: Electroconvulsive therapy; tDCS: Transcranial direct current stimulation; IRCT: Iranian Registry of Clinical Trials; FDA: Food and Drug Administration; DSM5: Diagnostic and Statistical Manual of Mental Disorder 5th Edition.

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**Authors' contributions**
We have the pleasure of sending you the manuscript entitled "The effect of low-frequency repetitive transcranial magnetic stimulation on left dorsolateral prefrontal cortex in patients with the obsessive-compulsive disorder: a double-blinded, sham-controlled clinical trial" authored by AAD and SAH to be considered for publication as a research article in your prestigious journal. All authors have seen and approved the manuscript and have contributed significantly to the paper. AAD: Conceptualization, visualization, investigation, supervision, and writing of the original draft. SAH: visualization, conceptualization, investigation, data curation, and writing reviewing, and editing the manuscript.

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**Availability of data and materials**
All data generated and analyzed during this study are included in this published article.

## Declarations

**Ethics approval and consent to participate**
This study was approved by the Ethics Committee of Qazvin University of Medical Sciences (Ethics Code: IR.QUMS. REC.1396.63); also, the current study is documented at the Iranian Registry of Clinical Trials (IRCT ID: IRCT20200728048240N1). A written consent form was also obtained from the patients for this study.

**Consent for publication**
Written informed consent was obtained from the patients for publication of this information and accompanying images.

**Competing interests**
The authors declare that they have no competing interests.

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## Publisher's Note