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# Effect of high-frequency repetitive transcranial magnetic stimulation (rTMS) in patients with comorbid panic disorder and major depression

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## Abstract

**Objective:** To explore the role of dorsolateral prefrontal cortex (DLPFC) stimulation in the treatment of panic disorder with comorbid depression.

**Methods:** The present study reports findings from retrospective analysis of 13 treatment-resistant patients diagnosed with comorbid panic disorder and depression, given 20 sessions of high-frequency transcranial magnetic stimulation (rTMS) over left-DLPFC over a period of 1 month.

**Results:** There was a significant reduction in both the panic and depressive symptom severity, assessed by applying Panic Disorder Severity Scale (PDSS) and Hamilton Depression Rating Scale (HDRS) at baseline and after 20 sessions of rTMS. There was a 38% and 40% reduction of PDSS and HDRS scores, respectively, in the sample. The changes in PDSS and HDRS scores were not significantly correlated ($\rho = -0.103$, $p = 0.737$).

**Conclusions:** High-frequency rTMS delivered at left-DLPFC may have a potential role in treatment of comorbid panic disorder and depression. Future studies done on a larger sample in a controlled environment are required to establish its role.

**Keywords:** rTMS, panic disorder, depression, DLPFC, magnetic stimulation

Panic disorder is a relatively common psychiatric disorder leading to significant distress and disability.[1] Major depressive disorder is a commonly comorbid condition, resulting in poorer treatment outcomes among patients with panic disorder.[2] About one-third of patients with panic disorder continue to experience panic attacks and other symptoms even after receiving first line treatments.[3] Repetitive transcranial magnetic stimulation (rTMS) is a novel non-invasive brain stimulation technique that can modulate underlying cortical activity depending upon the parameters of stimulation, with high-frequency stimulation (>5 Hz) increasing and low-frequency stimulation (<1 Hz) decreasing cortical excitability.[4]

Neuroimaging studies have consistently shown lateral asymmetry in dorsolateral prefrontal cortex (DLPFC) activity among patients with panic disorder, which reduces after successful treatment with cognitive behavior therapy or antidepressants.[5] The prefrontal cortex has been shown to regulate emotions by inhibiting the activation of subcortical limbic structures; therefore, applying rTMS over prefrontal cortex may have a potential anxiolytic effect.[6] This has also been supported by the clinical effectiveness of low-frequency rTMS (applied on right DLPFC) in treatment of panic disorder comorbid with depression.[7,8] Moreover, high-frequency rTMS over left DLPFC is a well-established treatment strategy for patients with depression.[9] Although, most studies assessing the effect of rTMS in panic disorder have used low-frequency stimulation over right DLPFC, there are a few case reports of high-frequency rTMS given over left DLPFC resulting in improvement of panic disorder symptoms.[10,11] The present study attempted to determine if the well-established rTMS treatment protocol

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(high-frequency rTMS over left DLPFC) for major depressive disorder can also be effective in treatment of panic disorder, as both conditions are highly comorbid.

## Methods

The study reports findings from a retrospective record-based review of clinical case files of patients treated at the rTMS laboratory, Department of Psychiatry of a tertiary care treatment center in India between August 2010 and December 2015. The study included participants of either gender with diagnosis of major depressive disorder and panic disorder without agoraphobia (made by a psychiatrist according to ICD-10 diagnostic criteria), resistant to at least two medications of different class taken at optimum dosage and duration (at least 8–12 weeks), and who had completed 20 sessions of rTMS. The adequacy of dosage and duration was determined by careful review of medical records. Patients with any comorbid psychiatric disorder other than depression and panic disorder, history of seizures, neurosurgical metallic implant, cardiac pacemaker or inner ear prosthesis, pregnancy, or unstable medical condition were excluded from the study.

High-frequency rTMS was administered in accordance with the updated safety guidelines, using a Magstim Rapid device (Whitland, UK) with a 70-mm figure-of-eight air-film coil.[12] The resting motor evoked potential (MEP) was determined using an electromyogram recording from the right-sided abductor pollicis brevis (APB) in accordance with the International Federation of Clinical Neurophysiology recommendations.[12] The resting motor threshold (RMT) was defined as the minimum stimulus intensity that produced a MEP (about 50 µV in 5 out of 10 trials) at rest. The coil was placed over the left DLPFC, as per the standard procedure, determined by moving the TMS coil 5.0 cm rostrally from the right APB motor threshold (MT) area, along a left superior oblique plane with a rotation point about the tip of the patient's nose.[13] The stimulation parameters used were 20 Hz frequency, stimulation intensity at 110% of RMT, 5-sec train duration, inter-train interval of 20 sec, and 10 trains per session. Each session of rTMS consisted of 1000 pulses/day delivered in 250 sec. A total of 20 rTMS sessions was given, 5 days per week (from Monday to Friday) over a period of 4 weeks. The patients were continued on the last drug combination that they had received for at least 8–12 weeks before and during the entire study period.

A semi-structured proforma was used for recording details of socio-demographics and clinical profile of patients. The Hamilton Depression Rating Scale (HDRS) and Panic Disorder Severity Scale (PDSS) were applied at baseline (before starting rTMS) and at post-intervention (after 20 sessions of rTMS) to assess depression and panic disorder symptoms respectively.[14,15] They were applied by a trained psychiatrist supervising treatment sessions at the rTMS laboratory.

Statistical analysis was done using SPSS version 23.0 (Chicago, IL, USA). Descriptive statistics were used to describe the demographic and clinical characteristics of the sample. The frequency distribution of the percentage changes in PDSS and HDRS score was analyzed to determine the proportion of responders. Data was analyzed for statistically significant differences by first checking that there is a normal distribution and then using paired t-test, otherwise using Wilcoxon signed-rank test to assess the change in mean PDSS and HDRS score from baseline to final session. Correlation analysis was used to examine whether changes in scores of panic and depression rating scales correlate. For all statistical analyses, the alpha level of significance was set at 0.05.

The study was approved by Institute Ethics Committee (IEC-133/04.03.2016, RP-8/2016) and informed written consent was taken before the administration of rTMS.

## Results

The mean age of the sample was 38.23 ± 6.52 years (range: 28–52 years). The mean total duration of illness for panic disorder and depression was 6.85 ± 4.93 and 7.46 ± 4.11 years, respectively. There was a significant reduction in the mean PDSS and HDRS scores after completion of 20 sessions of rTMS from baseline (Table 1). The changes in PDSS and HDRS scores were not significantly correlated ($\rho = -0.103$, $p = 0.737$).

There was a 38% and 40% reduction of PDSS and HDRS scores, respectively, in the sample. Overall, 7 out of 13 patients (53.8%) had PDSS score reduction of more than 40% and met the criteria for response in panic disorder.[14] Out of 13 patients, 6 (46.2%) had a reduction of HDRS score of more than 50% and met the criteria for response in depression.

The main side effects reported were of headache and localized scalp discomfort in one and two patients, respectively. There were no serious adverse effects reported by any patient during or after rTMS, and it was well tolerated by all the patients.

## Discussion

This is the first study to report the effects of high-frequency rTMS applied over left DLPFC among patients with comorbid panic disorder and depression. Our study suggests that high-frequency rTMS over left DLPFC might be an effective treatment strategy for this group of patients. Almost half of the patients reported a significant clinical improvement in their panic disorder and depression symptom severity. Further, the change in severity of panic disorder was not correlated with change in depression severity, possibly indicating an independent effect of rTMS on panic symptoms. Since the conventional treatments are not effective for many patients with comorbid panic disorder and depression, if our findings are replicated in a larger sample under controlled conditions, rTMS might prove to be a valuable treatment strategy for treatment-resistant patients with comorbid panic disorder and depression. This is especially vital considering that previous studies have reported depression comorbidity and side effects to be the most common reasons for the failure of treatment in panic disorder.[16]

**Table 1. Change in PDSS and HDRS scores after 20 repetitive transcranial magnetic stimulation (rTMS) treatment sessions (*n*=13)**

| *Scale* | *At baseline* | *After 20 sessions* | *Mean difference* | *Wilcoxon sign-rank test* | |
|---|---|---|---|---|---|
| | *Mean ± SD (Median)* | *Mean ± SD (Median)* | | *Z-score* | p-*value* |
| PDSS | 16.08 ± 2.56 (17.00) | 9.92 ± 3.63 (10.00) | 6.16 | –3.016 | 0.001* |
| HDRS | 22.77 ± 4.62 (22.00) | 13.54 ± 4.21 (12.00) | 9.23 | –3.194 | 0.003* |

PDSS: Panic Disorder Severity Scale; HDRS: Hamilton Depression Rating Scale.

*$P$-value < 0.05.

Although the Food and Drug Administration approved the use of rTMS for treatment of depression in 2008, the optimal stimulation parameters to be used are still debatable. The recent evidence suggests use of higher frequency (20Hz vs 10Hz) rTMS and longer treatment durations (4weeks vs 2weeks) to be more effective in treatment of depression.[17,18] Thus, we delivered 1000 pulses/session at 20Hz instead of the standard protocol of 3000 pulses/session at 10Hz stimulation frequency for a total of 20 sessions over the course of 4weeks.[19] The use of a 20-Hz stimulation frequency might have increased the seizure risk, and in order to decrease that risk, fewer pulses/session were given.

Our study supports the findings of previous studies that used low-frequency rTMS over the right DLPFC for treatment in panic disorder.[7,8] We postulate that obtaining a more symmetrical frontal pattern either by stimulatory effect of high-frequency rTMS over the left DLPFC or by inhibitory effect of low-frequency rTMS over the right DLPFC, might be responsible for the decrease in panic symptoms.[11]

However, our findings must be interpreted with caution considering the limitations of the study. The small sample size, open study design and absence of control group prevents us from ruling out placebo response and limits the generalizability of results. Further, the classic method used for positioning of the TMS coil might not be able to accurately localize DLPFC when compared with neuro-navigation guided localization.[20] This could not be done in the present study as such a facility is not available at our center. Despite these limitations, our study suggests that high-frequency rTMS delivered at left DLPFC may have a potential role in treatment of comorbid panic disorder and depression. Future studies done on a larger sample under controlled conditions are required to establish its role.

## Disclosure

The authors report no conflict of interest. The authors alone are responsible for the content and writing of the paper.


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