

Effect of Excitatory repetitive Transcranial Magnetic Stimulation over Left Dorsolateral Prefrontal Cortex on Depression and Motor-recovery in Ischemic Stroke Patients

Research Article

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Article Information: Submission: 23/09/2025; Accepted: 11/10/2025; Published: 14/10/2025

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Abstract

30 - 50% of stroke survivors develop depression during the first six months known as post-stroke depression (PSD). Repetitive transcranial magnetic stimulation (rTMS) is an FDA-approved therapy for the treatment of major depression in psychiatric cases. However, rTMS is being investigated for the treatment of post-stroke depression (PSD). Preliminary reports suggest that excitatory 10 Hz rTMS applied over left Dorsolateral Prefrontal cortex (L-DLPFC) area has a beneficial effect in reducing PSD symptoms. However, systematic meta-analyses of those studies suggest that they suffer from several drawbacks. Reducing PSD is important because it can enhance the post-stroke motor recovery. It can enhance motor recovery either due to motivational benefits or directly by strengthening the cortical connections, but this has not been tested in detail yet. Thus, in this work it is hypothesised that excitatory 10 Hz rTMS of L-DLPFC will reduce PSD symptoms and reduction of depression will enhance motor recovery either due to motivational or other benefits. To assess that in this work MCA ischemic stroke patients suffering from PSD and hemiplegia were recruited and provided the excitatory rTMS treatment. Our results suggest that the given rTMS treatment is effective in reducing PSD symptoms significantly but has no immediate impact on motor function in those patients. In future studies, it is planned to study the long-term impact of PSD reduction on motor-recovery.

Keywords: Post-stroke depression; rTMS; Middle Cerebral Artery (MCA) Occlusion; Ischemic stroke; Motor recovery

Introduction

Stroke is a common medical illness. In the United States, there are approximately 800,000 new cases each year [1]. Currently, an estimated 4.5 million stroke survivors reside in the United States. Stroke survivors in whom motor-weakness or paralysis of limbs develops, makes it difficult for them to perform the basic activities of daily living, which mostly leads to depression in them. This post-stroke depression (PSD) hampers their motor recovery. PSD has been

identified as a major challenge in stroke recovery. At stroke onset, patient's age, sex, marital status, number of children, occupation, family responsibilities, education, support from caregivers, laterality of stroke, financial status/load and other illnesses are important deciding factors in the development of PSD. It has been observed that around 30 - 50% of stroke patients develop depression within 6 months after stroke. Thus, it is important to evaluate and treat PSD as its recovery will improve the quality of life of stroke-survivors

[1]. It is believed that there is an association between depression and hypo-activity of left dorsolateral prefrontal cortex (L-DLPFC). Currently, drugs are used for PSD treatment which generates a lot of toxic effects. Repetitive transcranial magnetic stimulation (rTMS) is a relatively novel therapy which has shown preliminary, promising results in the treatment of PSD [2]. In rTMS, strong magnetic pulses are delivered utilizing a powerful magnet at a fixed frequency over a defined brain area. It has been observed that rTMS applied to any brain area at ≤ 1 Hz pulse frequency has inhibitory effect on that area and nearby neurons whereas at ≥ 5 Hz it has excitatory effect.

In one study, ten sessions of rTMS (10 Hz, 110% of the resting motor threshold, 20 trains of 5 seconds duration) applied over the L-DLPFC has been shown to have a significant reduction in PSD symptoms [3]. In another study on PSD patients (n=20) with either left or right hemispheric lesion at stroke onset, application of ten sessions of low frequency rTMS over left DLPFC (1 Hz, at 100% of resting motor threshold) showed 41.3% reduction of Hamilton Depression Rating Score (HAMD score) and this effect was maintained for one month [4]. Further, a sham-controlled study showed that five sessions of high frequency (10 Hz) rTMS for five consecutive days over the region spanning from the dorsal anterior cingulate cortex to medial prefrontal cortex led to a decline in the severity of apathy and degree of depression in chronic stroke patients [5]. A meta-analysis of 22 RCTs (n=1764 patients) reported beneficial effects of rTMS on post-stroke depression using HAM-D as primary outcome [6]. In addition to that, a sham-controlled, double-blind prospective study showed that ten sessions of 10 Hz rTMS (110% resting motor threshold, 5 s/train, 20 trains with 1 minute interval, total 1000 pulses) over left DLPFC in chronic post-stroke depression patients improved depression (measured by HAMD-17 and Beck Depression Inventory (BDI) scores) but no significant motor-recovery was reported [7]. Accelerated rTMS (20 Hz frequency, 110% of resting motor threshold, applied over DLPFC area (five sessions per day for four consecutive days for total 20 sessions) was given to ischemic stroke patients (n=6) (within 2 weeks to six months post-stroke) suffering from post-stroke depression identified using HAMD. Accelerated rTMS significantly decreased HAMD score but no significant difference was found in modified Rankin scale, functional independence measures and National Institute of Health Stroke Scales [8].

Although the above-mentioned preliminary studies suggests that excitatory 10 Hz rTMS applied over left DLPFC area has a beneficial effect on post-stroke depression but meta-analyses of different studies shows that they are highly heterogenous in terms of small or inadequate sample size and highly variable therapy assessment criteria in different studies etc. [9-12]. Dorsolateral prefrontal cortex is anatomically connected with the primary motor cortex (M1) and other associated motor areas, both being part of the frontal lobe, thus it is reasonable to hypothesize that rTMS stimulation of L-DLPFC can enhance post stroke motor-recovery. In addition to that, L-DLPFC stimulation can have motivational benefits to the patient which should enhance motor recovery. Keeping all this in view, in this work it was hypothesised that excitatory rTMS treatment provided in L-DLPFC area will reduce PSD symptoms and will enhance motor recovery.

Methodology

a. Subjects

Forty post-stroke depressed patients (≥ 6 months old) of Middle cerebral artery (MCA) Occlusion with left or right sided paralysis (hemiplegia) of similar degree were recruited from Neurology OPD, AIIMS, New Delhi using the below-mentioned inclusion and exclusion criteria. Patients were randomly recruited in the rTMS (n=20) or the Sham/control group (n=20). A patient with a BDI-II score > 17 was taken as clinically depressed [13].

Inclusion Criteria

Stroke patients with similar level of depression and motor-deficits as assessed by BDI and Barthel Index (BI score) were recruited in both the rTMS and Sham group [14].

Exclusion Criteria

Stroke patients with any type of seizure activity, any major head injury in the past or having daily headaches. Patients with MRI contraindications such as stents, aneurysm clips, and cardiac pacemaker or defibrillator. Patients with severe systemic disease, encephalitis, auto-immune disorders or tumors/cancers. Patients with neurodegenerative or psychiatric disorders like chronic headaches, Parkinson's, multiple sclerosis, Alzheimer's, cerebral palsy, CJD or bipolar disorders. Patients with rapidly progressing dementia and language comprehension deficits. Patients with movement disorders. Depressed patients who are actively suicidal. Currently breast feeding or pregnant females. Patients not willing to give consent.

Informed consent was taken from all the patients as and when it was decided that they can participate in the study.

b. Pre-rTMS BI and BDI-II scores

Before providing the rTMS treatment, BDI and BI scores were noted from all the patients by a neurologist not involved in this study.

c. rTMS procedure

rTMS was applied using Magstim rapid 2 stimulators. All the patients recruited in the rTMS group were given the same rTMS treatment using the below-mentioned procedure. Patients in the sham group were also provided the same rTMS treatment but the coil was kept at 90 degrees to the patient's scalp creating a placebo effect.

Procedure: A figure 8-shaped magnetic coil was placed over left DLPFC (F3 position) and repetitive magnetic pulses were delivered at a frequency of 10 Hz, at an intensity of 110% of the resting motor threshold, duration of 5 seconds and total of 20 trains (total 1000 pulses) separated by 40 s inter-train interval [7]. The procedure was repeated for 4 weeks, five times a week (Monday-Friday) at the same day time.

d. Post-rTMS BI and BDI-II scores

BI and BDI-II scores were again recorded on the last day of 4th week of rTMS treatment. All the scores were noted by a neurologist not involved in this study. Mean \pm standard deviation of the values in the two groups were calculated. Paired Student's t-test was used for the statistical comparison between the pre-post values in the two groups.

Results

Out of forty recruited patients, thirty patients only completed the entire procedure. (Table 1) shows mean \pm standard deviation of patients' demographic data in the two groups, sham (control group) and experimental rTMS group. The two groups were chosen in such a way that there was no statistically significant difference between the two groups in terms of demographic features. (Table 2) shows the pre- and post-rTMS BI and BDI-II scores of the sham and the rTMS group. Our results suggest that excitatory rTMS over L-DLPFC significantly reduce PSD symptoms as suggested by the decrease in the BDI score. The decrease in the BDI score in the rTMS treatment group was found to be statistically significant at $p < 0.05$, however, in group with sham exposure, pre-post BDI scores were statistically non-significant. This suggests that the observed difference in BDI score or reduction of PSD symptoms in the rTMS group is because of the given rTMS treatment. Furthermore, the reduction in PSD symptoms in the rTMS group was same irrespective of the laterality of the stroke. No statistically significant difference was observed for the BI score between the Sham and the rTMS treatment group which suggests our rTMS treatment did not provide any motor recovery to the stroke patients.

Discussion

The aim of this study was to assess the impact of excitatory rTMS applied over the left dorsolateral prefrontal cortical area (DLPFC) on depression and motor recovery in post-stroke depression (PSD) patients. Several investigations have been carried out to study the effect of rTMS on PSD and has shown positive outcome. Also, several mechanisms have been proposed explaining the beneficial effects of excitatory rTMS such as increase in the BDNF levels [15]. PSD results in reduction of BDNF levels. Low levels of BDNF results in mood dysregulation and loss of hippocampal function. In rats, high frequency rTMS (20 Hz) has been shown to trigger BDNF expression. Apart from increasing BDNF expression, it can activate the BDNF/ERK signalling, which is important for hippocampal cell proliferation [15]. Glucose metabolism is known to decrease in the ischemic hemisphere, especially in patients with PSD. Using FDG-PET imaging it has been shown that rTMS increases glucose uptake in rat cortex and striatum [15]. It also inhibited apoptosis in the ischemic brain. Similarly, rTMS has been shown to induce neurogenesis. Stroke can

lead to abnormal changes in the concentration of neurotransmitters and cytokines and excessive generation of free radical species. Experimental evidence in rodents suggests that rTMS corrects for all these factors [15]. Studies conducted in the recent past, has analysed the effect of dual target rTMS (L-DLPFC and ipsilesional primary motor cortex) on serological markers such as Brain derived growth factor (BDNF) and Vascular Endothelial growth factor (VEGF) and also imaging techniques such as Transcranial Colored Doppler (TCD) have been assessed to address the effect of rTMS on Post stroke cognitive impairment (PSCI) recovery [16]. There are reports suggesting that 10 Hz rTMS applied over L-DLPFC area is effective in reducing post-stroke depressive symptoms but reducing PSD will have any functional outcome in stroke recovery has not been studied in detail yet. In this work, middle cerebral artery (MCA) ischemic stroke depressed patients were provided the 10 Hz L-DLPFC rTMS treatment for major depression. By comparing the effect of same rTMS treatment in same type of post-stroke depressed patients we can answer whether PSD treatment with rTMS can have any direct effect on motor recovery.

Our results suggest that 10 Hz rTMS over L-DLPFC area is effective in reducing BDI-II score of depression in post-stroke depressed patients but no major difference was noted in Barthel Index scores for motor recovery. This suggests that excitatory rTMS has no immediate beneficial effect on motor recovery. In a nut shell, these findings strongly suggest that L-DLPFC excitatory rTMS treatment is very helpful in PSD recovery but it is less likely to enhance motor recovery in ischemic stroke patients. We would like to mention that our findings are strongly in line with the previous findings on the effect of excitatory L-DLPFC rTMS treatment on PSD treatment and functional/motor recovery [7,8]. In conclusion, this study compliments earlier studies on the beneficial role of rTMS in PSD recovery. Future studies will be conducted to check the long-term benefits of rTMS treatment on motor recovery.

Acknowledgements

Dr. Gupta is thankful to Indian Council of Medical Research (ICMR) for providing him the Research Associate fellowship (Ref. No. 3/1/3/92/Neuro/2018-NCD-I) and Prof. Achal Kumar Srivastava for providing the lab facility.

Conflict of Interest

All authors declare no conflict of interest.

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Table 1: Patients' demographic (baseline) data

	Sham group (n=15)	Depressed group (n=15)
Age, years	56.8 +/- 12.28	44.27 +/- 12.65
Sex (M:F), n	10:5	8:7
Handedness (Right:Left)	15:0	15:0
Lesion side (Right: Left)	(10:5)	(9:6)

Table 2: Patients' pre and post-rTMS treatment data

	Sham group (n=15)	rTMS group (n=15)
Pre-rTMS BI score	58 +/- 23.94	58.63 +/- 18.31
Pre-rTMS BDI-II score	27.2 +/- 3.88	28 +/- 2.85
Post-rTMS BI score	62 +/- 25.18	65.45 +/- 18.36
Post-rTMS BDI-II score	25.8 +/- 3.88	14.36 +/- 2.44

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