

Review Article

Repetitive Transcranial Magnetic Stimulation (rTMS) Research: Indian Scenario

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Abstract

rTMS involves non-invasive repetitive stimulation of specific brain areas using magnetic pulses for both diagnostic and therapeutic purposes in a number of neuropsychiatric conditions. Most of the research contribution has come from western countries. The current narrative review aims to provide a comprehensive overview of Indian research on rTMS as a therapeutic modality. One of the maximum research contributions in this field from lower- and middle-income countries (LAMIC) have come from India. Some groups are actively involved in rTMS research but percolation is still low. Due to the limited extent and varied foci of the studies along with methodological heterogeneity, it is difficult to derive any conclusions from the available studies. High frequency rTMS over dorso-lateral pre-frontal cortex (DLPFC) holds promise both in cases of depression and alcohol craving, while that over left frontal area corresponding to the hotspot for the right abductor digiti minimi may have some role in migraine prophylaxis. A number of different sites of stimulation and rTMS protocols have been tried for Obsessive Compulsive Disorder (OCD) and Schizophrenia with varying results. Extensive research in future is required to generate credible evidence base for this modality.

INTRODUCTION

The last few decades have seen a rapid progress in the understanding of the structure and function of the normal human brain as well as the nature of its various pathophysiologicals. The exponential surge in technology has contributed to a number of novel methods of investigating as well as treating the brain and neural structures, among which various brain stimulation modalities have come to the forefront. Transcranial magnetic stimulation (TMS) is one such tool which was initially introduced as a diagnostic modality and later on a whole new arena of its therapeutic implications was unearthed. In contrast to other methods of brain stimulation such as electro-convulsive therapy (ECT), deep brain stimulation (DBS) and Transcranial direct current stimulation (tDCS), which function by invasive or non-invasive application of electrical current to brain areas, TMS works on the principle of electromagnetic induction in which flow of current through a copper wire coil results in induction of a magnetic field, which is delivered as a brief pulse, which can penetrate into superficial brain areas without any invasive procedures [1]. rTMS involves repeated delivery of such magnetic pulses to a specific brain area and holds therapeutic potential in a number of neuropsychiatric conditions. This technique requires an elaborate and expensive set up and as such its affordability in Lower- and Middle-income countries like India is limited. Most of the research on rTMS has come from the western literature.

India is home to almost one-sixth of the world population and it is desirable that any major healthcare intervention should be studied in this region to be able to make any credible claims about its utility. This review aims to provide a comprehensive overview of therapeutic rTMS research conducted in the Indian population.

Approach

This narrative review focuses on the literature available from India. Two search engines were used for this review: PubMed and IndMED, with the search terms as “rTMS OR TMS OR repetitive Transcranial magnetic stimulation OR Transcranial magnetic stimulation.” Additionally, “AND India*” was added to the search algorithm while searching PubMed. All relevant search results were sorted by the authors to include only original studies or case studies on rTMS from India. Only treatment and adverse effects related studies were selected for the review. Studies about the diagnostic or measurement utilities of TMS were not considered.

Treatment studies

Mood disorders: Depression is one of the most researched indications for rTMS with the maximum available evidence base. In 2008, rTMS was approved for use by the FDA as a treatment for major depression for patients who do not respond to at least one antidepressant medication in the current episode [2]. But there are only few studies evaluating the role of rTMS

among Indian patients having depression. One RCT tested the efficacy of adjunctive high frequency rTMS of left dorsolateral prefrontal cortex (DLPFC) in 41 patients with severe depression who were drug naive or drug free for at least one month, who were randomized to either treatment arm (n=21) or sham control arm (n=20) administered over 10 days. 70% patients in the active group and 65% in the sham group had psychotic symptoms. Intent to treat analysis was not done. Significantly more improvement in depression and psychosis scores was found in treatment arm as compared to sham stimulation arm [3]. Contrary to this finding, another randomized, double-blind, sham-controlled trial with 9 patients of depression in active arm with 6 sessions of high frequency rTMS at left DLPFC over two weeks and 14 patients in sham group, found no statistically significant difference in depression scores between the groups at the end of the treatment. Notably, the sample size of this study and the number of rTMS sessions was much less compared to the previous one [4].

Udapa et al., in two studies evaluated the antidepressant efficacy and effect on heart rate variability (HRV) of 12 sessions of high-frequency rTMS, applied over a point which was 5 cm anterior to the hotspot of abductor pollicis brevis on the parasagittal line, against that of SSRI and TCAs. Post-treatment assessment was done at the end of two weeks for rTMS groups and four weeks for antidepressant groups. The antidepressant efficacy of rTMS was found to be similar to SSRIs and TCAs. The HRV showed improvement in the rTMS group, remained the same in SSRIs treated group and worsened in the TCAs treated group [5,6].

Two other studies focused on some add ones to the rTMS technique. One RCT compared patients with moderate to severe depression receiving low frequency rTMS with theta pattern frequency modulated priming (n=20) over right DLPFC in 10 sessions with those receiving rTMS with sham priming (n=20). Patients in the theta pattern frequency modulated priming arm performed significantly better on depression scores than the sham priming group [7]. The other study, a clinical trial, demonstrated that high frequency rTMS over SPECT identified areas of hypo perfusion in prefrontal cortex (PFC) in patients with treatment resistant major depression delivered in 20 sessions over 4 weeks fared better in terms of mean depression scores as compared to those receiving similar rTMS therapy over DLPFC without any prior identification of hypoperfused areas [8].

Apart from these studies, two case reports of rTMS in cases of depression were found. One reported the successful use of rTMS in maintenance treatment of a patient with treatment resistant depression, and the other reported the successful use of high-frequency rTMS at DLPFC in treatment augmentation in a patient with bipolar depression. [9,10].

Praharaj et al, in a RCT compared patients with bipolar mania receiving adjunctive right pre-frontal high frequency supra-threshold rTMS (n=21) over 10 days with those receiving sham stimulation (n=20). The study found that significantly more number of patients in rTMS arm had remission [11]. But when

the same group evaluated the efficacy of similar rTMS therapy (same location, frequency, threshold, duration) against sham stimulation in adolescent patients with mania, it was found to be ineffective [12].

Overall, it appears that high frequency rTMS over DLPFC may have some efficacy for depression, while no such conclusions can be drawn in cases with mania.

Obsessive compulsive disorder: Among patients having medication refractory OCD (n=11), Kumar & Chadda in an open label study demonstrated that augmentation with 15 sessions of low frequency rTMS over supplementary motor area (SMA) led to significant improvement in mean YBOCS scores [13]. In a similar study, Verma et al., found significant reductions in mean YBOCS scores among 41 patients with medication refractory OCD using adjuvant rTMS over SMA. The same study found no differences in response rates between males and females, concluding that response to rTMS is not a function of gender endotypic expression [14].

Other than the above reported positive outcomes in OCD using high frequency rTMS over SMA, not much efficacy for the therapy has been found when applied to different sites. One case series of 19 patients found no beneficial effects in OCD when low frequency rTMS was delivered over pre-SMA over 1 month as adjunctive treatment. Only one patient met the criteria for response [15]. Another RCT done primarily to evaluate the role of adjunctive right prefrontal high-frequency rTMS in OCD among 42 patients who were assigned to either active rTMS group or sham control group found no significant effect of rTMS in the treatment of OCD, rather depression scores modestly improved in the rTMS group compared to the sham control group [16].

A single reported case demonstrated the use of extended course of rTMS therapy (initially, 5 sessions per week over 6 weeks, and subsequently 1 session per week over 30 weeks, i.e., a total of 60 sessions) leading to significant improvement in a patient with treatment refractory OCD, which was maintained for more than 3 months after stopping rTMS [17].

Schizophrenia: One group working in the field of rTMS in schizophrenia has tried a number of sites of stimulation in their research. One such study was a double blind clinical trial which evaluated the efficacy of high frequency supra-threshold adjuvant rTMS (antipsychotics were started at the start of the study) over left prefrontal area (10 sessions over 2 weeks) compared to sham stimulation on positive and negative symptoms in patients with schizophrenia who were either drug naive or drug free for at least 2 months (n=5 in each arm). Compared to sham treatment, the rTMS arm showed significant improvement in negative symptoms irrespective of changes in depressive symptoms, but no group effects in positive symptoms were seen [18].

The same group have also studied high frequency theta patterned rTMS at the cerebellar vermal area delivered in 10 sessions over two weeks in a randomized double blind trial with active (n=20) and sham stimulation (n=20) arms. Significantly more improvement in negative and depressive symptoms was

seen in the active stimulation arm compared to sham stimulation [19]. Though, they had previously reported a case of worsening of auditory hallucinations with cerebellar vermal rTMS in a patient with schizophrenia [20]. Furthermore, they have tried to elucidate the response marker of cerebellar rTMS in a similar protocol in schizophrenia by studying its effect on resting state gamma activity in an open label study. Percentage reduction in psychopathology scores (negative syndrome and depression) were found to have significant positive correlation with percentage reduction in gamma spectral power, thus highlighting the potential role of resting state gamma activity as a biomarker for rTMS treatment response [21].

Another study by the same group evaluated the role of high frequency priming stimulation followed by low frequency rTMS at the left temporo-parietal region in the treatment of auditory hallucinations in recent onset schizophrenia patients in a RCT involving two arms- rTMS with priming and without priming (n=20 in each group) in 10 sessions over two weeks. The scores for auditory hallucinations decreased significantly in both the groups compared to the baseline. No significant difference was seen between the groups except for greater improvement in loudness of hallucinations in the priming group [22]. Using the same priming protocol in a patient with treatment resistant schizophrenia improvement in auditory hallucinations was reported which was maintained for 8 weeks after rTMS [23].

Subsequently, an investigation by this group was also done into the efficacy of MRI-navigated, adjunctive continuous theta burst stimulation (cTBS)-rTMS to right inferior parietal lobule in schizophrenia patients with first rank symptoms, over two weeks in a sham controlled, pilot exploratory study. This study failed to demonstrate any efficacy of cTBS in schizophrenia patients, though it was found to be safe [24].

A single blind (rater was blind to intervention) RCT evaluated the role of adjuvant low frequency left temporo-parietal rTMS (10 sessions) compared to antipsychotic treatment alone on auditory hallucinations in patients with schizophrenia (n=20 in each arm). The study found significant improvement in auditory hallucinations in experimental group as compared to the control group [25].

Substance use: Two RCTs have demonstrated the anti-craving efficacy of high-frequency rTMS over DLPFC (10 sessions over 2 weeks) in patients with alcohol dependence. One of them, a single blind RCT (subject was blinded), compared rTMS over right DLPFC (n=30) to sham stimulation (n=15) in a single blind trial and found significantly more improvement in craving scores in the treatment arm [26]. The other was a double blind RCT which compared patients receiving rTMS over right vs left DLPFC (n=10 in each arm). Both arms showed significant reduction in craving scores compared to baseline, but no significant group differences were seen [27]. The same group has further tried to study the mechanism involved in rTMS action among patients with alcohol dependence. In a randomized single-blind sham controlled study comprising of three arms, one each of alcohol dependent patients receiving active high frequency supra-

threshold rTMS in 10 sessions per day (n=25) or sham rTMS (n=25), and the third of healthy controls (n=25), the authors found that cerebral hemodynamic parameters were significantly different in alcohol dependent subjects as compared to healthy controls at the baseline, i.e., mean velocity (MV) of both middle cerebral artery (MCA) and anterior cerebral artery (ACA) was significantly reduced, and pulsatility index (PI) of MCA and resistance index (RI) of ACA were significantly increased in alcohol-dependent subjects in comparison with healthy controls. Significant differences were observed in values of MV, PI, and RI of both MCA and ACA following rTMS intervention, while such changes were not evident in the sham rTMS group. The changes in mean difference in MV of L-MCA and L-ACA were statistically significant in the active rTMS group, in comparison with the sham group. The results seemed to suggest that alcohol dependence may result in altered cerebral hemodynamic parameters, which can be improved with high-frequency rTMS [28].

Migraine: Two studies by the same group from India have evaluated the role of rTMS in migraine. Both used high frequency rTMS (3 sessions on alternate days) over left frontal area corresponding to the hotspot for the right abductor digiti minimi, and the migraine prophylaxis drugs were withdrawn prior to the study. The earlier one was an open label trial involving 51 subjects with migraine and reported improvement in 98% patients at the end of treatment which persisted till 4th week in 80.4%. [29]. The other was a randomized single blind placebo controlled study with 50 patients in each arm, which used sham stimulation in the control group. This study did not perform an intention to treat analysis. The frequency and severity of headache improved significantly in both groups at one month compared to baseline. But the improvement was significantly more in the rTMS group compared to the sham group [30]. Further the same group has tried to study the potential mechanism of action of rTMS in patients with migraine. In a RCT, the authors studied the somatosensory evoked potentials (SEP) 94 patients having migraine who were randomized to either active rTMS (n=56), as used in previously mentioned studies, or sham stimulation (n=38). The impaired habituation of SEP significantly improved in the active rTMS group compared to sham stimulation and correlated with a reduction in the severity of headache, possibly highlighting the biological basis of headache relief [31]. Furthering their research, the group also tried to evaluate the efficacy of single (n=52, two sham sessions) vs. three sessions (n=46) of similar protocol of rTMS therapy in chronic migraine and tension-type headache patients. The two groups did not differ significantly in terms of frequency or intensity of headache at 1 month, 2 month and 3 month follow ups [32].

Other disorders: One author reported two patients with severe Huntington's chorea having no improvement with bilateral low frequency rTMS over SMA as against the common notion of improvement in choreiform movements shown in studies from other countries [33].

Another report highlighted a case of hypersexual disorder who failed to respond to conventional pharmacological treatment but responded well with rTMS augmentation over SMA [34].

Table 1: Studies reporting adverse effects of rTMS.			
Author/year	rTMS characteristics	Patient characteristics	Adverse effects
Garg et al., 2016	High frequency theta patterned rTMS at the cerebellar vermal area delivered in 10 sessions over two weeks	Schizophrenia (n=20)	5 patients had transient headache which responded to analgesics 1 patient had excessive sleepiness after each session
Hegde et al., 2016	Low frequency rTMS was delivered over pre-SMA over 1 month	OCD (n=19)	4 patients reported mild transient headache
Jha et al., 2016	High frequency supra-threshold rTMS over PFC in 20 sessions over 4 weeks	Treatment resistant major depressive disorder (n=20)	Mild headache and tingling sensation over scalp in 3 patients
Kumar et al., 2016 [case report]	Low-frequency supra-threshold rTMS of right DLPFC	Ischemic infarct of left middle cerebral artery (n=1)	Seizure occurred 18 hours after the 4 th session
Pathak et al., 2015	Right pre-frontal high frequency supra-threshold rTMS over 10 days	Adolescents with mania (n=21)	Transient headache in 2 patients which lasted 1-4 hours
Mishra et al., 2015	High frequency rTMS over DLPFC in 10 session over 2 weeks	Alcohol dependence (n=20)	1 patient developed nightmares and middle insomnia after 8 th session
Garg et al., 2013 [case report]	High frequency cerebellar vermal rTMS	Treatment resistant schizophrenia (n=1)	Exacerbation of auditory hallucinations
Misra et al., 2013	High frequency rTMS over left frontal area corresponding to the hotspot for the right abductor digiti minimi in 3 sessions on alternate days	Migraine (n=50)	1 patient developed drowsiness in one session which lasted 12 hours and did not recur on subsequent rTMS
Misra et al., 2012	High frequency rTMS over left frontal area corresponding to the hotspot for the right abductor digiti minimi in 3 sessions on alternate days	Migraine (n=51)	3 patients had aggravation of headache during the sessions 1 patient had transient rhinorrhoea during the 2 nd session
Nongpiur et al., 2011	Low frequency rTMS over right DLPFC in 10 sessions, with or without theta priming	Depression (n=40)	Theta priming group: 2 had transient headache 4 had scalp tenderness Non-priming group: 1 had transient headache 3 had scalp tenderness 1 had discomfort due to twitching of temporalis muscle
Kumar & Chadda, 2011	Low frequency rTMS over SMA in 15 sessions	Treatment refractory OCD (n=11)	1 patient with history of bipolar disorder developed mania after the 3 rd session 2 patients reported moderate pain and feeling of discomfort at the site of stimulation
Ray et al., 2011	High frequency rTMS of left DLPFC over 10 days	Severe depression (n=21)	5 patients found the procedure painful 1 had transient headache that improved with paracetamol 1 had diminution of hearing after 1 st session which resolved spontaneously within one hour
Mishra et al., 2010	High frequency rTMS over right DLPFC in 10 session over 2 weeks	Alcohol dependence Active arm, n=30 Sham stimulation arm, n=15	The most common complaint was pain during stimulation which improved when session was over 5 patients had transient headache, 3 required analgesics 1 patient developed scalp pain and withdrew consent 1 patient in sham stimulation arm developed a seizure after 3 rd session (also within 6 days of stopping lorazepam for detoxification)

Sarkhel et al., 2010	Right prefrontal high-frequency rTMS, 10 sessions per day on 5 days per week	OCD (n=21)	Pain during stimulation was the most common side effect 3 patients reported headache which resolved spontaneously in 2 in few hours while persisted for 2 weeks in one patient and paracetamol was required
Praharaj et al., 2009	Right pre-frontal high frequency supra-threshold rTMS over 10 days	Bipolar mania (n=21)	Transient headache was reported in 6 patients
Tharayil et al., 2005 [case report]	Single pulse TMS for motor threshold estimation	Bipolar disorder (n=1)	Seizure

Adverse effect studies

Most of the reporting of adverse effects of rTMS has come from the above mentioned treatment related studies along with a few case reports of adverse events [35,36]. See Table (1), transient headache and local pain and discomfort were the most common side effects reported. The uncommon reported adverse effects included drowsiness, insomnia, transient diminution of hearing, seizures, mania and aggravation of auditory hallucinations.

CONCLUSIONS

Indian research on TMS, in comparison to that available from the western world, is very limited both in terms of the number of studies and sample sizes. TMS requires an expensive setup which only a few centres in India can afford, and as such only a few groups are active in this area. Moreover, there is lack of awareness of the potential that this technology holds, and the percolation among the limited number of neuro-psychiatric professionals is less. Recruitment of patients is also difficult since repeated sessions of rTMS may mean loss of work hours for patients, which is an important factor in a LAMIC state such as India. Despite that, India has been able to produce one of the maximum numbers of research papers on this subject among the LAMIC countries. A brief search for similar studies among the other ten countries of the WHO SEARO region yielded only two studies, both from Thailand [37,38]. This highlights the importance of the evidence base generated from India which has been presented in this review. But, because of the limited extent and varied foci of the studies along with methodological heterogeneity, it is difficult to derive any conclusions. From the reviewed studies, it appears that high frequency rTMS over DLPFC holds promise both in cases of depression and alcohol craving. These results are similar to what has been found in the international literature [39,40], but the Indian studies are mostly limited to DLPFC as the region of interest, and no comparisons have been made with rTMS given over other areas, or with other treatment modalities, which has been done by several studies globally [41,42,40]. Moreover, no Indian studies have explored varying protocols and stimulus parameters of rTMS, in order to find the most adequate one, which has been done by some studies from other countries [43]. The reviewed studies on migraine seem to suggest that rTMS over left frontal area corresponding to the hotspot for the right abductor digiti minimi may have some role in migraine prophylaxis. This is a unique finding as this brain area has not been studied at other centres where DLPFC is mostly focused upon [44]. Furthermore, studies from India could not yield any conclusions for rTMS in

OCD and schizophrenia as several different sites of stimulation and protocols have been tried with inconsistent results, while the international literature has yielded more consistent patterns [45-47,45]. From the current review, it is evident that a huge effort is required to build up the evidence base from India, both in terms of quantity and quality. The current literature can be, at best, seen as a stepping stone for future research with the hope of contributing subsequently to the global evidence base.

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