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Original Research Article

EFFICACY AND SAFETY OF ADJUNCTIVE LOW-FREQUENCY REPETITIVE TRANSCRANIAL MAGNETIC STIMULATION OVER THE SUPPLEMENTARY MOTOR AREA IN PHARMACORESISTANT OBSESSIVE-COMPULSIVE DISORDER: A RANDOMIZED, SHAM-CONTROLLED TRIAL

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ABSTRACT

Background: Obsessive-compulsive disorder (OCD) is a chronic, disabling psychiatric illness in which 40–60% of patients fail to achieve adequate response to selective serotonin reuptake inhibitors (SSRIs) and cognitive-behavioural therapy. Repetitive transcranial magnetic stimulation (rTMS) of the supplementary motor area (SMA) has emerged as a potential adjunctive strategy, but controlled data from Indian populations remain limited. **Materials and Methods:** In this single-centre, randomized, single-blind, sham-controlled trial, 60 adults (18–60 years) with DSM-5 OCD who had failed two adequate SSRI/clomipramine trials and had baseline Yale-Brown Obsessive Compulsive Scale (Y-BOCS) scores ≥16 were allocated 1:1 to active or sham low-frequency rTMS over the bilateral SMA (1 Hz, 110% resting motor threshold, 1,200 pulses/session, 20 sessions over 4 weeks). Assessments with Y-BOCS, Beck Depression Inventory-II (BDI-II), Beck Anxiety Inventory (BAI), and Clinical Global Impression-Severity (CGI-S) were performed at baseline, 2 weeks and 4 weeks. Per-protocol analysis included 26 active and 16 sham completers. **Result:** Groups were comparable at baseline on sociodemographic, clinical, and symptom-severity variables (all $p>0.05$). At week 4, mean Y-BOCS reduction was 8.04 points in the active group versus 1.32 in the sham group (between-group $p<0.01$). BDI-II, BAI and CGI-S also improved significantly in the active group relative to sham (all $p<0.01$ at 4 weeks). A strong negative correlation between number of sessions and Y-BOCS reduction was observed in the active group ($r = –0.762$, $p<0.01$) but not in sham ($r = –0.243$, $p=0.096$). Adverse events were mild and transient—most commonly headache (76% early, 50% by week 4) and scalp discomfort—and declined in frequency across the treatment course. No seizures or serious adverse events occurred. **Conclusion:** Adjunctive low-frequency SMA rTMS produced statistically significant and clinically meaningful reductions in obsessive-compulsive, depressive and anxiety symptoms in pharmacoresistant OCD, with a favourable safety profile. These findings support rTMS as a viable augmentation strategy and provide much-needed sham-controlled data from an Indian tertiary-care setting.

INTRODUCTION

Obsessive-compulsive disorder (OCD) is a chronic, heterogeneous neuropsychiatric illness with a lifetime prevalence of approximately 2-3% and a marked impact on functioning and quality of life [1,2]. First-line interventions-selective serotonin reuptake inhibitors (SSRIs), clomipramine and exposure and response prevention (ERP)-produce

meaningful benefit in many patients, yet 40-60% show only partial response or no response even after adequate trials [3,4]. Such pharmacoresistance drives considerable disease burden and has motivated the exploration of neuromodulatory strategies that more directly target the cortico-striato-thalamo-cortical (CSTC) circuitry implicated in OCD pathophysiology [5,6].

Functional neuroimaging consistently demonstrates hyperactivity within orbitofrontal cortex, anterior cingulate cortex, caudate and thalamus in OCD, together with altered connectivity along CSTC loops [6]. The supplementary motor area (SMA) is a key cortical node within this network, contributing to the motor-initiation and response-inhibition deficits underlying compulsive behaviour. Low-frequency (≤1 Hz) repetitive transcranial magnetic stimulation (rTMS) produces lasting inhibition of cortical excitability, making the SMA an attractive target for normalising aberrant motor-inhibitory processing in OCD [7,8].

Early randomized sham-controlled trials over the SMA reported encouraging but modest reductions in Yale-Brown Obsessive Compulsive Scale (Y-BOCS) scores [7,9]. In 2018, the United States Food and Drug Administration cleared deep TMS of the medial prefrontal and anterior cingulate cortex for treatment-resistant OCD, following a pivotal multicentre trial [10]. Subsequent meta-analyses and network meta-analyses have confirmed a small-to-moderate overall effect of rTMS across multiple cortical targets, with SMA and dorsolateral prefrontal cortex (DLPFC) protocols showing the most consistent signals of efficacy [11-14]. However, considerable heterogeneity persists across trials in stimulation frequency, intensity, number of sessions, target localisation, and sham method.

Indian data on rTMS for OCD remain sparse, and the few published studies have been limited by small samples, open-label designs, or variable targeting [11,15]. Cultural differences in symptom presentation, help-seeking behaviour, and access to advanced neuromodulation justify locally conducted, methodologically rigorous trials. The present study was therefore designed to evaluate, in a randomized, sham-controlled design, the efficacy and safety of 4 weeks of adjunctive low-frequency rTMS (1 Hz, 110% motor threshold, 1,200 pulses/session) over the bilateral SMA in adults with pharmacoresistant OCD, using validated clinician- and self-rated measures of obsessive-compulsive, depressive and anxiety symptoms.

MATERIALS AND METHODS

This single-centre, randomized, single-blind, parallel-group, sham-controlled trial was conducted in the Department of Psychiatry, Jawaharlal Nehru Medical College and Hospital, Aligarh Muslim University, Aligarh, India, between June 2024 and January 2025. The protocol was approved by the Institutional Ethics Committee (IECJNMC/1436) and prospectively registered with the Clinical Trials Registry-India (CTRI/2024/12/077787). Written informed consent was obtained from all participants before enrolment.

Participants

Adults aged 18-60 years with a primary DSM-5 diagnosis of OCD, confirmed by a consultant psychiatrist, were eligible if they met operational criteria for pharmacoresistance: Y-BOCS ≥16 with <35% improvement after at least two adequate (6-8 weeks, maximum tolerated dose) first-line drug trials, including SSRIs and/or clomipramine [3]. Medications were required to be stable for ≥6 weeks before enrolment and were continued unchanged throughout the trial. Exclusion criteria comprised comorbid psychiatric disorders other than mild anxiety (BAI 8-15) or mild depression (BDI-II <19); neurological disorder, head injury or loss of consciousness; history of seizures; pregnancy; and presence of pacemaker or metallic intracranial implants, in accordance with international TMS safety guidelines [16].

Randomization and blinding

Seventy-two patients were assessed for eligibility; 10 were excluded after screening and 2 declined participation. Sixty participants were randomly allocated 1:1 to active or sham rTMS using a computer-generated randomization sequence. Outcome assessors were blinded to group allocation. Participants were blinded to the extent achievable with current sham methodology (perpendicularly positioned coil producing comparable auditory and scalp sensations without effective cortical stimulation).

Intervention

Active participants received low-frequency rTMS delivered at 1 Hz and 110% of individually determined resting motor threshold, with 1,200 pulses per session. The SMA was localized using the 10-20 EEG system, defined as 15% of the nasion-inion distance anterior to the vertex in the sagittal plane [7]. Twenty sessions were administered 5 days per week over 4 weeks (cumulative dose: 24,000 pulses). Sham stimulation used the same coil positioned perpendicularly over the SMA, preserving auditory and tactile cues while minimizing effective stimulation. Self-reported side effects were elicited after each session.

Outcome measures

The primary outcome was change in Y-BOCS total score [17], with clinically significant response defined a priori as ≥35% reduction from baseline. Secondary outcomes included BDI-II, BAI [18], CGI-S, treatment-emergent adverse events, and the correlation between number of sessions and Y-BOCS reduction. Assessments were performed three days before the first session (baseline), after the 10th session (2 weeks), and after the 20th session (4 weeks).

Sample size and statistical analysis

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Sample size was estimated using G*Power for detection of a clinically meaningful between-group Y-BOCS difference with α=0.05 and power=0.80, yielding a minimum of 30 participants. Analyses were performed in SPSS v.26 on the per-protocol population. Continuous variables are reported as mean ± SD and categorical variables as frequency (%). Between-group comparisons used independent-samples t-tests or χ^2 tests; within-group changes across timepoints used repeated-measures ANOVA. The relationship between number of sessions and symptom reduction was assessed using Pearson correlation. A two-tailed $p<0.05$ was considered statistically significant.

RESULTS

Participant flow and baseline characteristics: Of 60 randomized participants, 42 completed the trial and were analysed: 26 in the active group (dropouts: 1 headache, 4 financial/logistical, −) and 16 in the sham group (dropouts: 2 headache, 2 financial, 9 lack of perceived benefit by week 3). Sociodemographic and clinical characteristics were comparable between groups; the majority in both arms were aged 18–29 years, reported an illness duration of 1–5 years, and had no identified precipitating factor [Table 1]. Baseline symptom severity did not differ significantly between groups on any scale [Table 2].

Primary outcome: Y-BOCS: Active rTMS produced progressive reductions in Y-BOCS scores, from 33.92 ± 2.67 at baseline to 30.19 ± 2.89 at 2 weeks and 25.88 ± 2.96 at 4 weeks. In contrast, the sham group showed minimal change (33.13 → 32.19 → 31.81). Between-group differences favored active rTMS at both 2 weeks (mean difference –2.00, t = –2.27, p = 0.03) and 4 weeks (mean difference –5.93, t = –6.94, p<0.01). Within the active group, repeated-measures ANOVA confirmed a significant effect of time (F = 52.02, p<0.01), representing a mean reduction of 8.04 points (23.7%) over 4 weeks, whereas within-group change in the sham arm was not significant (F = 1.51, p = 0.23).

Secondary outcomes: Depressive symptoms (BDI-II) decreased significantly in the active group (15.46 → 9.65; F = 70.65, p<0.01) but not in sham (14.63 → 13.44; p = 0.42); the between-group difference at 4 weeks was –3.78 (t = –3.96, p<0.01). Anxiety symptoms (BAI) showed a similar pattern, falling from 12.77 to 6.81 in the active group (F = 21.71, p<0.01) versus 12.19 to 10.69 in sham (p = 0.38), with a between-group mean difference of –3.88 at 4 weeks (t = –4.29, p<0.01). CGI-S improved from 5.19 to 3.73 in the active group (F = 17.86, p<0.01) but remained essentially unchanged in sham (5.63 → 5.19; p = 0.44); between-group difference at 4 weeks was –1.46 (t = –5.52, p<0.01). A summary of outcomes is presented in [Table 3].

Table 1: Baseline sociodemographic and clinical characteristics.

Variable	Active (n=26)	Sham (n=16)	p-value
Age 18–29, n (%)	13 (50.0)	9 (56.2)	0.91
Female, n (%)	16 (61.5)	8 (50.0)	0.46
Married, n (%)	15 (57.7)	10 (62.5)	0.37
Rural residence, n (%)	17 (65.4)	8 (50.0)	0.32
Illness duration 1–5 y, n (%)	13 (50.0)	9 (56.2)	0.06
Precipitating factor present, n (%)	6 (23.1)	6 (37.5)	0.32
Family history of psychiatric illness, n (%)	10 (38.5)	6 (37.5)	0.95

Table 2: Baseline clinical rating scale scores (mean ± SD).

Scale	Active (n=26)	Sham (n=16)	t	p
Y-BOCS	33.92 ± 2.67	33.13 ± 1.86	1.05	0.30
BDI-II	15.46 ± 2.19	14.63 ± 3.28	0.90	0.38
BAI	12.77 ± 4.12	12.19 ± 3.04	0.49	0.63
CGI-S	5.19 ± 0.98	5.63 ± 0.89	–1.44	0.16

Table 3: Between-group comparison of outcome measures at 4 weeks.

Scale	Active (mean ± SD)	Sham (mean ± SD)	Mean diff.	t	p
Y-BOCS	25.88 ± 2.96	31.81 ± 2.17	–5.93	–6.94	<0.01
BDI-II	9.65 ± 3.11	13.44 ± 2.83	–3.78	–3.96	<0.01
BAI	6.81 ± 2.69	10.69 ± 3.07	–3.88	–4.29	<0.01
CGI-S	3.73 ± 0.78	5.19 ± 0.91	–1.46	–5.52	<0.01

Dose–response relationship: In the active group, a strong negative correlation was observed between number of rTMS sessions received and reduction in Y-BOCS score (Pearson r = –0.762, p<0.01), indicating that greater session exposure was associated with larger symptom improvement. The corresponding correlation in the sham group was weak and non-significant (r = –0.243, p = 0.096), consistent with the absence of a true therapeutic effect.

Safety and tolerability: Adverse events were predominantly mild and transient [Table 4]. Headache was most frequent, reported by 20/26 participants (76%) during the first 2 weeks and decreasing to 13/26 (50%) by week 4. Scalp discomfort (58% → 8%), tingling (38% → 19%), neck pain (30% → 0%), difficulty concentrating (35% → 19%), burning sensation (11% → 0%) and mild skin redness (11% → 0%) all attenuated over time. Transient mood changes were noted in 2 participants (8%) early on and resolved without

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intervention. No seizures or other serious adverse events were recorded, in line with established rTMS safety data [15].

Table 4: Treatment-emergent adverse events in the active group.

Adverse event	Weeks 1–2, n (%)	Weeks 3–4, n (%)
Headache	20 (76)	13 (50)
Scalp discomfort	15 (58)	2 (8)
Tingling	10 (38)	5 (19)
Neck pain	8 (30)	0 (0)
Trouble concentrating	9 (35)	5 (19)
Burning sensation	3 (11)	0 (0)
Skin redness	3 (11)	0 (0)
Transient mood changes	2 (8)	0 (0)
Seizures	0 (0)	0 (0)

DISCUSSION

In this randomized, sham-controlled trial, adjunctive low-frequency rTMS over the bilateral SMA produced statistically significant and clinically meaningful improvement across all assessed domains-obsessive-compulsive symptoms, depression, anxiety, and global clinical severity-in adults with pharmacoresistant OCD. A mean Y-BOCS reduction of approximately 8 points over 4 weeks in the active group, contrasted with negligible change in sham, corresponds to one of the larger effects reported in the contemporary SMA literature and aligns with the magnitude of improvement described in several earlier controlled studies [7,9].

Our findings are concordant with the seminal sham-controlled trial by Gomes and colleagues, who reported a 35% Y-BOCS reduction after bilateral SMA 1 Hz rTMS versus 6.2% with sham in treatment-resistant OCD [9]. Mantovani and colleagues similarly demonstrated normalisation of hemispheric excitability and symptomatic improvement following SMA rTMS [7]. Subsequent meta-analyses have consistently supported the efficacy of low-frequency SMA stimulation, albeit with substantial between-study heterogeneity arising from differences in pulse dose, number of sessions, motor-threshold targeting, and sham methodology [11,12]. The more recent network meta-analysis by Vinod and colleagues, which ranked bilateral SMA with 1 Hz and DLPFC high-frequency protocols among the most effective cortical targets, adds external support to our chosen approach [13]. The magnitude of change in our cohort may reflect the relatively high cumulative dose (24,000 pulses over 20 sessions), adherence to 110% motor-threshold stimulation, and the inclusion of a relatively severe population (baseline Y-BOCS ~34).

Parallel improvements in depressive and anxiety symptoms in the active group merit discussion. The mean BDI-II reduction of 5.81 points and BAI reduction of 5.96 points are consistent with the meta-analytic anxiolytic and antidepressant effects of rTMS in OCD reported by Thatikonda and colleagues, who estimated pooled Hedges' g of 0.30 and 0.24 for anxiety and depression respectively [12]. Because anxiety symptoms in OCD are often phenomenologically intertwined with obsessive distress, part of the BAI reduction likely reflects secondary improvement as obsessions declined. The BDI-II change, however, was of similar magnitude and may indicate direct mood-regulatory effects mediated by SMA-medial prefrontal connectivity, which has been implicated in affective processing within OCD networks [5,6]. The consistent improvement in CGI-S further suggests broad functional benefit rather than isolated symptom reduction.

The strong negative correlation between number of sessions and Y-BOCS reduction in the active group ($r = -0.762$), with no comparable relationship in sham, supports a genuine dose-response effect rather than regression to the mean or non-specific expectancy. This is in keeping with the observation that trials delivering ≥20 sessions tend to yield more robust and sustained outcomes [11,14,19]. The similarity of our correlation to values reported in earlier SMA rTMS work strengthens external validity. Safety and tolerability in our sample were consistent with international experience: headache and scalp discomfort predominated, decreased over successive sessions, and no seizures occurred, reinforcing the favourable risk profile outlined in established safety guidelines [16].

This study contributes several features relevant to the Indian and low- and middle-income country context. It is among a small number of sham-controlled SMA rTMS trials conducted at an Indian tertiary-care centre, with a standardised protocol, prospective clinical-trial registration, validated outcome measures, and systematic adverse-event tracking. A predominantly rural, lower-middle socioeconomic sample broadens the generalisability of rTMS data beyond the largely urban, Western populations that dominate the existing literature.

Several limitations must be acknowledged. First, the sample size-though consistent with most published SMA trials-limits statistical power, particularly for subgroup analyses. Second, the asymmetric dropout rate (active 13%, sham 47%, driven largely by perceived lack of improvement in sham) raises the possibility of attrition bias; per-protocol analysis without intention-to-treat imputation may have inflated apparent between-group differences. Future trials should employ mixed-effects modelling or multiple imputation and more credible sham

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methodologies to mitigate these concerns. Third, follow-up was limited to 4 weeks, providing no information on durability; OCD is chronic and longer-term data are essential. Fourth, the single-centre design, exclusion of patients with substantial psychiatric comorbidity, and reliance on self-reported adverse events constrain generalisability. Finally, the absence of neuroimaging or neurophysiological biomarkers precluded mechanistic inference.

CONCLUSION

Adjunctive low-frequency rTMS (1 Hz, 110% motor threshold, 1,200 pulses/session, 20 sessions) over the bilateral SMA produced statistically significant and clinically meaningful improvement in obsessive-compulsive, depressive and anxiety symptoms, as well as global illness severity, in adults with pharmacoresistant OCD. Treatment was well tolerated, with only mild and self-limited adverse events. Dose-dependent symptom reduction in the active group but not the sham group supports a genuine therapeutic effect. Larger, multicentre, intention-to-treat trials with longer follow-up, improved sham methodology, and integration of neuroimaging biomarkers are warranted to confirm these findings, define optimal protocols, and evaluate cost-effectiveness in routine Indian clinical practice.

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