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Original Research Article

A Double-Blind Randomized Sham Control Study to Assess the Effects of rTMS (Repetitive Transcranial Magnetic Stimulation) on Executive Functioning in Treatment Resistant Depression

Saadgi Jagawat[1], Tushar Jagawat[2], Savita Jagawat[2], Mukesh Sandu[3], Mausumi Sinha[4], Nandita Hazari[5]

[1]Formerly at VIMHANS, New Delhi
[2]NIMS University, Jaipur, Rajasthan
[3]BMCHRC, Jaipur, Rajasthan
[4]Sr. Consultant Psychiatrist, VIMHANS, New Delhi
[5]Consultant Psychiatrist, VIMHANS, New Delhi

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Corresponding author: Dr. Savita Jagawat
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Abstract

Background: Up to fifteen percent of patients with Depression eventually present with Treatment Resistant Depression (TRD). Executive functions, in general, are a part of the cognitive process which includes fluency, working memory, set-shifting ability, set maintenance, planning, response inhibition, error detection, abstraction, strategizing and organization. Cognitive impairment / executive functions have found to be associated with depression. The Food and Drug Administration (FDA) has approved Repetitive Transcranial Magnetic Stimulation (rTMS) for the treatment of both MDD (Major Depressive Disorder) and TRD in adolescent and adult populations.

Aims and Objectives: To examine the effects of active and sham rTMS on executive functioning in patients of treatment resistant depression by comparing pre and post rTMS effects on mood symptoms, executive functioning for both groups (active and sham) and assessing the correlation between the effects on executive functioning and mood changes due to rTMS.

Material and Methods: The study-included 20 individuals (10 in each arm) of either gender, aged between 18-50years suffering from mild to moderate depression (assessed by HAM-D). The executive functioning was assessed by using NIMHANS Neuropsychological Battery (Digit Symbol Substitution Test-DSST, Digit Sequencing Test-DST, Colour Trail making B test, and Stroop test), 10 sessions of either active HF-rTMS (10Hz) or sham rTMS (allocated by random sampling) were applied to the left DLPFC over two weeks.

Results: The mean age was found to be 42.62 years with 60 % males and 40 % females. On DSST Positive effects of rTMS were found for information processing speed in the active group compared to sham. On other tests, DST, CTB and Stroop test, the findings were not statistically significant. Significant positive correlation was present between HAM-D and Stroop tests scores in active group. The severity of depression reduced significantly due to rTMS treatment.

Conclusion: The important finding of this study is the decrease in time on DSST after treatment with rTMS in the active group showing improvement in visuomotor coordination, attention and information processing speed in patients with TRD.

Keywords: Repetitive Transcranial Magnetic Stimulation, Treatment Resistant Depression, Executive Functioning.

Introduction

Depression is one of the most leading causes of disability according to World Health Organization (WHO). Almost, more than 300 million people of all age groups suffer from depression throughout the globe. Comparatively, females suffer more from depression. The burden of depression is on the rise globally. [1]

Up to fifteen percent of patients with depression eventually present with treatment resistant depression. Depression is usually considered refractory when two drug trials of different classes of antidepressants (adequate in terms of duration, dosage, and adherence) fail to give a significant symptomatic improvement. [2] Generally, these patients are highly demanding of their families. It is costly as their total depression related expenses were found 19 times greater than those of patients in the compression group. TRD is also associated with extensive health care services in terms of general medical and extensive use of depression-related treatment. [3]

Cognition is defined as the mental process of comprehension, judgment, memory, and reasoning. Executive functions in general are a part of the cognitive process. Executive functions include fluency, working memory, set-shifting ability, set maintenance, planning, response inhibition, error detection, abstraction, strategizing, and organization. [4]

rTMS (Repetitive Transcranial Magnetic Stimulation) is a newer development in the field of neuro-psychiatry. It was introduced in 1985 as a non-invasive procedure for imposing motor movement by stimulation of the brain by the magnetic method. [5] This technique was mainly used for the management of depression.

TMS (Transcranial magnetic stimulation) is a form of brain stimulation, non-invasive in which changing magnetic field is used to generate electric current in a specific area of the brain. The Food and Drug Administration (FDA) has approved repetitive transcranial magnetic stimulation (rTMS) for the treatment of both MDD (major depressive disorder) and TRD (treatment resistant depression) in adolescent and adult populations. [6]

More than half of depressive patients who did not respond to antidepressants may show significant benefits with rTMS. Out of this percentage, patients who get full improvement are found to be about one-third of these individuals. Hence rTMS has the potential in improving symptoms of depression and also executive functioning in depression. TMS can, however, exert long-lasting effect when pulses are repeated at regular intervals in a process of rTMS. This procedure is non-convulsive, non-invasive, requires no anaesthesia, and safe in terms of side effects and is not associated with cognitive side effects. [7]

This study is planned to examine the effects of active and sham rTMS on executive functioning in patients of treatment resistant depression and to compare pre and post rTMS effects on depressive symptoms & executive functioning for both groups. (Active and sham) and to assess the correlation between the effects on executive functioning and mood changes with rTMS in patients with treatment resistant depression.

Aims and Objectives:

To examine the effects of active and sham rTMS on executive functioning in patients of treatment resistant depression by comparing pre and post rTMS effects on

mood symptoms, executive functioning for both groups (active and sham) and assessing the correlation between the effects on executive functioning and mood changes due to rTMS.

Null hypothesis:

There is no change in depressive symptoms and executive functioning test scores pre and post rTMS treatment, in the two groups under study.There is no association between the changes in executive functioning and severity of depression after 10 sessions of rTMS between the active and sham groups.

Materials and Methods

The study was done at Psychiatry outpatient and inpatient department of VIMHANS hospital, New Delhi. It was Prospective Interventional Randomized Comparative Sham Control Double-Blind Study. Patients with Treatment Resistant Depression (diagnosed by 2 consultant psychiatrists) were taken from OPD and IPD, VIMHANS hospital, New Delhi.

Inclusion criteria:

Age between 18-50 years of any gender. Patient's minimum education up to middle school (8th standard). Patients were ready to give written consent and willing to participate in the study. Cases fulfilling the diagnostic criteria for Treatment Resistant Depression: Thase and Rush staging method [8] stage II i.e, an adequate trial of 2 or more antidepressants of different classes, taken for minimum of 8 weeks and not improved clinically. Criteria for selecting the patients were according to HAM-D (Hamilton Depression Rating Scale) [9] scores. Patients with HAM-D scores within 8 to 18 (mild to moderate level) were selected for the study. Medication was unchanged for a month before rTMS until the end course of rTMS.

Exclusion criteria:

Patient with a history of intellectual disability, epilepsy, head injury with loss of consciousness, substance abuse (except nicotine), cerebrovascular disease, neurodegenerative disorders, systemic illnesses with known cerebral consequences. Presence of intracranial implants, any other metal object inside or near the brain or cardiac pacemaker. Pregnant or breastfeeding women. Patients who have undergone ECT within a month. Patients with bipolar disorder/ other psychiatric disorders. Patients refusing written consent.

Sampling technique:

Randomization Technique - A computer-generated randomization list was used - patients were either selected for active or sham rTMS randomly as per the list. Both the patient and the investigator rating the scales were blind to the allocation (double-blind).

Tools:

Socio-demographic Data, ICD-10 to diagnose Depression [10], Hamilton Rating Scale for Depression [9], Transcranial Magnetic Stimulation Adult Safety Screen (TASS) [11].

Tests for Executive Functioning - NIMHANS Neuropsychological battery used for assessing information processing speed, focused attention, working memory, response inhibition was administered before and after 10 sessions of rTMS. The tests selected for these 4 domains are based on the area stimulated (i.e., left Dorso-lateral prefrontal cortex - DLPFC). It is a validated battery and the tests have been standardized on the Indian population with an age 15-65 for both literate males and females and normative data has been established. [3] The following tests have been used in the study:

i. Digit Symbol Substitution Test for assessing Information Processing Speed. (DSST) [12]

ii. Color Trail Making B Test for assessing focused attention [13]

iii. Digit Sequencing Test for assessing working memory. (DST) [14]

iv. Stroop test for assessing response inhibition. [15]

The study design is sham-controlled RCT. Patients were given either real or sham rTMS which was allocated by random sampling. Patients and researchers were blind, only the technician was aware of real and sham allocation.

According to Protocol A, 10 sessions of either active HF-rTMS (10 Hz) or sham rTMS to the left DLPFC over the course of two weeks were given. A Figure of 8 coils (air-cooled) with weight 800 gm, length 185 meters, a width of circle 180mm outer and 75mm inner was used. For both the groups, on the first day, the resting motor threshold (RMT) was estimated from the right abductor pollicis brevis muscle based on a standardized method. The treatment intensity was fixed at 100 % of the individual resting MT throughout the experiment. Each rTMS session consisted of 75 trains, administered at 10 Hz pulse, 40 pulses with the intertrain interval of 26s in between. This indicated a total stimulation time of 37 min with 3000 pulses per session for 5 sessions per week for two consecutive weeks added to a total of 60,000 pulses. Sham rTMS was applied by tilting the coil 45^{o} away from the scalp. They both look alike and produced similar sounds when stimulated. Auditory protection in the form of earplugs was given during the treatment session.

Results

The table 1 shows the comparison of mean age between the two groups. The mean age of patients in the Active rTMS group was higher than the mean age of patients in Sham rTMS group. However, the difference was not statistically significant.

Table 1: Socio-demographic variables in the study population (N=20)

Comparison of Socio - Demographic Domains between the two groups.	Variables	Numbers	Active rTMS (n = 10)	Sham rTMS (n = 10)	p-value*
Age	Age of the patient (in years)		45.38 (10.29)	39.86 (13.27)	0.381
Gender	Male	12	6 (60.0%)	6 (60.0%)	
	Female	8	4 (40.0%)	4 (40.0%)	0.0
Education status	10th Grade and Below	2	1 (10%)	1 (10%)	
	Intermediate	6	2 (20%)	4 (40%)	
	Graduate and Above	12	7 (70%)	5 (50%)	1.00
Marital Status	Married	15	7 (70%)	8 (80%)	0.267
	Unmarried	5	3 (30%)	2 (20%)	
Occupation	Employed	11	5 (50%)	6 (60%)	
	Unemployed	2	2 (20%)	0	
	Student	1	0	1 (10%)	3.09
	Homemaker	6	3 (30%)	3 (30%)	
Family Types	Nuclear	15	7 (70%)	8 (80%)	0.267
	Joint	5	3 (30%)	2 (20%)	

According to the gender between the two groups, the proportion of male and female patients in the study was comparable between the true and sham group.

As can be observed from the above table, the comparison of patients according to education status between the two groups where there was a higher proportion of participants who had attained graduation or a higher degree of education in both groups. The difference in proportion of patients was not significantly different between the two groups.

The above table shows the comparison of patients according to marital status between the two groups. As can be observed from the above table, the proportion of married participants in our study was more than the unmarried in both groups. There was no statistically significant difference between the two groups.

The above table shows the comparison of patients according to occupation status between the two groups. As can be observed from the above table, majority of participants in both groups. The difference between the two groups was not statistically significant.

The above table shows the comparison of patients according to type of family between the two groups. As can be observed from the above table, majority of participants in both groups lived in a nuclear family. The difference between the two groups was not statistically significant.

Table 2: Comparison of Hamilton Depression Scale Scores (HAM-D) between the two groups at baseline and after rTMS administration. (N = 19)

HAM-D	**Mean (SD)**		**t value; p-value***
	Active rTMS (n = 10)	**Sham rTMS (n = 9)**	**(inter-group at each interval***
Pre-rTMS	15.00 (2.67)	14.57 (2.30)	0.330; 0.746
Post-rTMS	9.63 (4.31)	11.29 (3.04)	-0.850; 0.411
Change in score	-5.37	-3.28	
t value; p-value± (intra-group change over rTMS)	3.585; 0.009	3.683; 0.010	
p-value** (inter-group comparison of change over rTMS administered) = 0.665			

** Independent t-test was used. ± Paired t-test was used. ** Between-subjects repeated measures ANOVA was used*

The above table shows the comparison of mean Hamilton-D Test scores between the two groups. As can be seen from the above table, the baseline HAM-D scores were comparable between the true and sham groups. The mean HAM-D score was higher at baseline in the Active rTMS and Sham rTMS group compared to post rTMS. The decrease in HAM-D score was statistically significant in both Active and Sham rTMS group after administration of rTMS. However, the comparison of change in the score between the two groups was not statistically significant.

As can be seen from the table 3, the increase in DST scores shows improvement in the test performance. The mean DST score was higher at baseline and after rTMS administration in the Sham

rTMS group, although the difference was not statistically significant. DST scores increased in the active group and the change was higher in the active rTMS group, even though the difference was not statistically significant.

The mean DSST score was higher at baseline and after rTMS administration in the Sham rTMS group, although the difference was not statistically significant. DSST scores decreased in both groups but the change was higher in the active rTMS group and the difference was statistically significant, compared to Sham rTMS group. In addition, the comparison of change in the score between the two groups was not statistically significant. In the DSST test, score is the total time measured to do the test, and decrease in time shows improvement in the test.

Table 3: Comparison of Executive Functioning Tests (DST, DSST, Stroop Test, CTMB) score between the two groups at baseline and after rTMS administration. (N = 19)

Executive Functioning Tests	Score	Mean (SD)		t value; p-value* (inter-group at each interval*	t value; p-value± (intra-group change over rTMS)
		Active rTMS (n = 10)	Sham rTMS (n = 9)		
DST	Pre-rTMS	9.63 (2.97)	11.14 (3.34)	-0.932; 0.368	-0.734; 0.487
	Post-rTMS	10.13 (2.36)	11.00 (2.71)	-0.670; 0.515	0.097; 0.926
	Change in score	0.50	-0.04		
DSST	Pre-rTMS	202.95 (71.91)	315.94 (148.79)	-1.915; 0.078	2.902; 0.023
	Post-rTMS	164.17 (43.14)	306.17 (266.41)	-1.493; 0.159	0.179; 0.864
	Change in score	-38.78	-9.84		
Stroop Test	Pre-rTMS	196.05 (63.23)	158.91 (54.36)	1.210; 0.248	0.090; 0.931
	Post-rTMS	193.35 (104.48)	132.51 (52.13)	1.392; 0.187	4.348; 0.005
	Change in score	2.70	-26.40		
CTMB	Pre-rTMS	129.37 (63.61)	168.08 (99.25)	-0.912; 0.378	-0.248; 0.831
	Post-rTMS	132.45 (85.05)	174.68 (117.99)	-0.803; 0.476	-0.501; 0.634
	Change in score	3.08	6.60		

** Independent t-test was used. ± Paired t-test was used. ** Between-subjects repeated measures ANOVA was used*

The mean Stroop score was higher at baseline and after rTMS administration in the Active rTMS group, although the difference was not statistically significant at either intervals. Stroop scores decreased in Sham group and the change was statistically significant, in contrast to Active group, where the Stroop score

increased but was not statistically significant. In addition, the comparison of change in the score between the two groups was not statistically significant. Same as in DSST, here also decrease in score (time) shows that there is improvement in the test.

The mean time to do CTMB was higher at baseline and after rTMS administration in the Sham rTMS group, although the difference was not statistically significant at either interval. Mean time to do CTMB increased in Active and Sham rTMS but the difference was not statistically significant within either group. Increase in scores (time calculated) shows worsening in the test performance.

Table 4: Correlation between change in HAM-D scores with change in Executive functioning test scores following rTMS administration. (N = 19)

Mood Changes	**Executive Functioning**	**Active rTMS** (correlation coefficient)	**p-value***	**Sham rTMS** (correlation coefficient)	**p-value***
pre-rTMS – post rTMS					
∆HAM-D	∆DST	-0.131	0.757	0.231	0.619
	∆DSST	0.572	0.139	0.067	0.886
	∆Stroop	0.714	**0.047**	0.026	0.955
	∆CTBM	0.509	0.198	0.383	0.396

**Pearson correlation coefficient test used*

The above table shows the correlation between change in Mood scores with change in executive functioning scores in both Active and Sham rTMS groups. As can be observed from the above table, change in HAM-D score was significantly correlated with change in Stroop scores in the Active rTMS group.

Discussion

The mean age was 45.38 (S.D. 10.29) in the true group which was comparable to the sham group having mean age of 39.86 (S.D. 13.27). Data reveals normal age distribution of the population in two groups. This was similar to other studies with the mean age of 43.5 in previous studies (Moser et al. 2002, [16] Martis et al. 2003) [17]. The difference in the proportion of patients' education was not significantly different between the two groups. It is comparable with the previous studies (Nongpiur et al. 2011) [18]. There were 70% married in active group and 80 % were married in sham group. This difference is not statistically significant between the two groups. The difference between the married participants compared to unmarried in both groups were not statistically significant. In the present study, true, and sham groups were comparable in age, gender and education status. (Table 1)

A greater decrease from baseline scores on HAM-D was found to be present in the active group after administration of rTMS however the difference was not statistically different.

Our findings are consistent with many previous studies where HAM-D was used to assess the severity of depression. McLoughlin et al. (2007) [19] did a single blind study, found no difference in HDRS scores from baseline after 15 daily sessions at the end point (after 6 months of treatment) between two groups. Mosiman et al, 2002 [20] also reported no difference in active and sham group after rTMS.(Table 2)

The study conducted by Brunoni et al., 2014 [21] showed improvements in

depressive symptoms which were observed in 53 % of subjects. Salcini et al., in 2018 [22] studied the effect of high-frequency rTMS on cognitive executive functioning of TRD patients who were not taking any medicine. 26.3% met the criteria for remission of depression after the rTMS treatment. LF-rTMS over the right DLPFC was found to be effective in 42.9% of treatment resistant subjects (Pallanti et al. 2012). [23]

In the study done by Avery et al (2006) [24], Rating Scale (HAM-D) score at both 1 and 2 weeks following the final repetitive TMS treatment was found 20 % greater than the rate in the sham group. Studies done by Furtado et al (2013) [25], Eijndhoven et al (2020) [26] and Lingeswaran et al (2011) [27] ssuggested no difference in post depressive symptoms. The study done by Verma et al 2018 [28] concluded in TRD patients with HF-rTMS applied over left DLPFC showed improvement in 50% of participants. The authors suggest that rTMS is an effective add-on treatment strategy.

Based on the main findings, most of the selected studies done by Moser et al (2002) [16], Martis et al (2003) [17], Fitzerald et al (2009) [29], Tateishi et al (2019)30, Garnaat et al (2018) [31] Corlier et al (2020)32, Benadhira et al (2017) [33], Kedzior et al (2012) [34], Lingeswaran et al (2011)27 and Jha et al (2018) [35] supported the positive effect of rTMS on depression.

Digit sequencing test (DST)

DST measures verbal working memory, mental manipulations, cognitive flexibility, rote memory, learning, encoding, and attention. There is a link established between prefrontal cortex functions and working memory. It can be seen from Table 3, the scores from baseline were increased more in the active group on DST after rTMS but the change in performance in neither group was statistically significant. McLoughlin et al, (2007) [36] assessed global cognitive functions including domains of immediate short-term memory, attention and working memory, and frontal/executive function by applying HF-rTMS on left DLPFC. He found no difference between pre and post rTMS on measures of cognition. Furtado et al, (2012) [37], reported that there was no difference in attention, working memory and speed processing after rTMS stimulation. Hoy et al, (2012) [38] and Bloch et al, (2008) [39] also did not find a positive effect of rTMS applied on left DLPFC on verbal working memory assessed by the DST test. Our finding is not in keeping with few earlier studies Martis et al, (2003) [17], (Douglas et al, 2009) [40], (Avery et al, 2006) [24] who have found rTMS to be effective in improving executive functions with the similar domains.

Digit symbol substitution test (DSST)

The DSST scores decreased in both groups but the change was higher in the active rTMS group and this change in ‘readings’ was statistically significant. This is an important finding of our study indicating a decrease in time taken on DSST by the active group after ten sessions of rTMS revealing that rTMS treatment helped in improving visuomotor coordination, attention and speed in patients with TRD. This finding is consistent with previous studies (Moser et al, (2002) [16], Martin et al, (2017) [41], Hoy et al, (2012) [38], Garnnat et al, (2018) [31], Tateishi et al, (2019) [30]. The fine motor speed domains were reported to be increased after rTMS treatment in the study by Martis et al, [17] (2003), Fabre et al, (2004) [42] reported that 45.4% of patients showed specific improvements in verbal fluency and visuospatial memory after 2 weeks of HF rTMS on left DLPFC.

Stroop test

Stroop effect is a sign of cognitive interference where delay in the reaction time of the task takes place. Scores decreased in both groups from baseline to the endpoint with HF rTMS but the change was higher and significant in the Sham rTMS group indicating less Stroop effect which is an unexpected finding. It shows an adequate improvement in cognitive interference and increases in reaction time in the sham group, which could be due to the practice effect. Corlier et al, in 2020 [43] did a study on the effect of rTMS treatment on cognitive control and found improvement in both accuracy and reaction times on the Stroop test suggesting a decreased interference-effect.

Color trail making test B (CTMB)

In our study, we did not find any improvement in the Color trail making test B in both the groups post rTMS performance. It suggested psychomotor speed, visual scanning, and set-shifting ability had no positive change with rTMS treatment. Our findings are consistent with some previous studies. MSchulze-Rauschenbach et al, (2005) [44], Jorge et al, (2004) [45], McLoughlin et al, (2007) [19], and Furtado et al, (2013) [25] reported no cognitive improvement by HF-rTMS on left DLPFC in TRD patients on Color trail making B test. The results of this test were not consistent with the review done by Martin et al, (2017) [41] where 13 studies were analysed, which included 383 participants. It showed a significant difference in the performance of active rTMS over sham post-treatment. Results from the meta-regression analyses also showed that for the included studies, neither number of sessions ($F(11) = 1.81$, $P = .21$), pulses per session ($F(11) = 0.77$, $P = .40$), or frequency of stimulation ($F(11) = 0.91$, $P = .36$) significantly accounted for between trial variability.

Analysis of correlations between changes in the depressive symptoms and the effect on executive functions post rTMS showed a significant correlation between Stroop test score and Hamilton Depression Scale score post rTMS in the true group. This indicates that with improvement in depression, cognitive interference decreases, and reaction time for doing the task increases. There was no significant correlation between changes in depressive symptoms on HAM-D and domains of other executive functions that are attention, verbal working memory, visuomotor coordination, motor persistence, sustained attention and response speed, psychomotor speed, visual scanning, and set-shifting ability which were assessed by the tests DST, DSST and Color Making Trail Test B in our study. The findings in the present study are consistent with previous studies done by Martis et al, (2003) [17], David et al, (2011) [46,47], Salcini et al, (2018) [22] and, Corlier et al, (2020) [32] where they found the variables on Stroop color/word and Stroop color naming tests were associated with changes in depressive severity assessed by HAM-D.**(Table 4)**

Limitation of the study

This study had a small sample size, mostly from the urban areas of Delhi making the population homogeneous. More sessions of rTMS could produce better effects on cognitive functions. 10 sessions of rTMS might have less effect. Effects of medication and its compliance could not be ruled out as they might have an impact on cognitive functioning and depression.

Conclusion

The important finding of our study is the decrease in time on DSST after treatment with rTMS in the active group showing improvement in visuomotor coordination, attention, and speed in patients with TRD. The positive effect of rTMS was found to be present only on one (DSST) out of four tests of executive functions under this study. Depression severity scores (on HAM- D reduced in both groups and were

not significantly different between the groups.)—Positive correlations between improvement in depressive symptoms on HAM-D scores and the effect of rTMS on Stroop test parameters were present.

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