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Investigating the impact of adjunctive priming repetitive transcranial magnetic stimulation in late-life depression: a pilot single-blind randomized control study

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Abstract

Background. Conventional treatment methods have limited effectiveness in addressing late-life depression (LLD) that does not respond well. While a new approach called priming repetitive transcranial magnetic stimulation (rTMS) has shown promise in treating depression in adults, its effectiveness in LLD has not been explored. This study aimed to investigate the impact of priming rTMS on LLD.

Methods. This study investigated the effectiveness of priming rTMS in 31 patients with LLD who did not improve after an adequate trial of antidepressants. Patients were randomly assigned to receive either active priming rTMS or sham priming rTMS. Active priming rTMS was delivered over the right dorsolateral prefrontal cortex for 10 sessions, lasting 31 minutes each, over a period of 2 weeks.

Results. The group receiving active priming rTMS demonstrated greater improvements in scores on the Hamilton Rating Scale for Depression ($p < 0.037$; partial η^2 0.141) and the Geriatric Depression Rating Scale ($p < 0.045$; partial η^2 0.131) compared to the sham priming group, with a mild effect size. At the end of the second and fourth weeks, the priming rTMS group achieved a response rate of 50%, while the sham priming group had response rates of 26.7% and 6.7%, respectively. No adverse effects requiring intervention were observed.

Conclusion. Priming rTMS is well-tolerated for the treatment of LLD and not only reduces the severity of depression but also maintains the achieved response over time.

Introduction

The prevalence of depressive symptoms among older adults residing in the community ranges from 8% to 16%, with major depression in the range of 1% to 4%.[1-3] Depression accelerates brain aging, predisposes to medical illnesses, and increases the risk of obesity, frailty, cognitive impairment, and mortality.[4] Despite being a common mental disorder, up to 50 to 60% of patients do not respond adequately to antidepressant treatment in the general population,[5] and it gets even more challenging in older adults.[6] Prevalence of treatment resistance is higher in late-life depression (LLD) compared to major depression in the adult population,[6] possibly due to higher medical comorbidity, structural brain changes such as white matter hyperintensity and reduced receptors, and pharmacokinetic variability of the medications.[7-9] Although electroconvulsive therapy (ECT) is an effective and generally well-tolerated treatment option, vascular risk factors, medical comorbidities, risks related to anesthesia, and concern for cognitive side effects have been the limiting factors in older patients.[10] High prevalence of treatment resistance and limited alternate options for LLD highlight the need for novel therapies to overcome therapeutic nihilism. Transcranial magnetic stimulation (TMS) is a newer yet approved treatment option for treatment-resistant depression in the adult population.

The number of studies on the use of TMS in LLD is few, as compared to its use in adult depressed patients, and the results are inconclusive. High frequency (10 Hz) repetitive transcranial magnetic stimulation (rTMS) over the left dorsolateral prefrontal cortex (DLPFC) is the approved treatment protocol for depression in adults. Most available studies on TMS in LLD also have utilized high-frequency rTMS (HF rTMS) but have yielded mixed results.[11-13] Recent trials have focused on bilateral and accelerated protocols in LLD. A recent study which compared HF rTMS with bilateral rTMS combining HF rTMS over left DLPFC with low-frequency rTMS (LF rTMS) over right DLPFC in LLD found better efficacy with bilateral rTMS when compared to HF rTMS alone.[14] Similarly, another study examined the effect of bilateral deep TMS and found higher remission rates when compared to sham. However, study has also reported the poor tolerability of H1 coil which was used initially for left DLPFC stimulation.[15]

There is a higher risk of side effects with HF rTMS, especially in those with past history of cerebrovascular stroke or an existing electrolyte imbalance, as both these conditions can increase the likelihood of seizures.[16] LF rTMS has a comparative low risk for seizure and is generally better tolerated, but has less evidence of efficacy.[17] Apart from the combination or sequential bilateral rTMS, priming is another novel paradigm which can be used to enhance the effectiveness of LF rTMS while retaining its better tolerability. Priming is a pre-treatment stimulation, which involves a period of high-frequency stimulation at low intensity, preceding the low-frequency stimulation so as to enhance the neural response.[18] Brief pre-treatment with stimulation in the 5–6 Hz range greatly increases the ability of subsequent 1 Hz stimulation to produce a decrease in synaptic efficacy.[19,20] Importantly, the priming stimulation can be so brief or mild that it has no detectable effects of its own on synaptic transmission. Priming in rTMS has previously been used successfully in other clinical conditions like chronic tinnitus, stroke rehabilitation, and verbal auditory hallucinations, as well as in adult depressed patients.[21,22] Previously it has also been found to be equally efficacious as bilateral rTMS in adult patients with depression.[23] However, till date, no study has been published on the effect of priming rTMS in patients with LLD. So, this study was designed with the aim to assess the effect of priming on adjunctive LF (1 Hz) rTMS over right DLPFC in the treatment of LLD.

Material and methods

Study design

This single-blind, pilot randomized sham-controlled study was approved by the Institutional Ethics Committee (101st/ECM IIB Thesis/P2) and was registered prospectively with the Clinical Trial Registry of India, CTRI/2020/08/027230, dated 19/08/2020. The detailed protocol of this study has been published elsewhere.[24] As a time-bound pilot study conducted during the unprecedented COVID-19 pandemic, we have enrolled 31 patients after taking written informed consent between January 2021 and January 2022.

Study population

Participants included were patients suffering from depressive episode or recurrent depressive disorder, moderate (F32.1/F33.1) or severe without psychotic symptoms (F32.2/F33.2) as per International Classification of Diseases-10th edition (ICD-10) diagnostic criteria for research (DCR). The operational definition for treatment resistance was taken as an adequate dose of at least one antidepressant for 6 weeks or more and who continue to have Hamilton Rating Scale for Depression-17 (HAMD-17)[25] score of 15 and above, which is adapted with modification from Thase and Rush staging.[26] Considering the poor/partial response as less than 25% reduction on HAMD score from baseline and minimum cut-off score for moderate depression as 20 in HAMD 17,[25] we have included only those patients whose HAMD score was 15 and more even after at least 6 weeks of antidepressant treatment.[5] Age range of patients included was from 50 to 79 years which is similar to the criteria adopted by the recent meta-analysis on TMS in LLD.[27] Patients with any comorbid alcohol or other substance dependence (except for nicotine and caffeine) according to ICD-10 DCR and any comorbid severe medical or surgical illness were excluded from the study. Those patients who had any contraindication for rTMS were also excluded after applying a standard screening questionnaire for rTMS patients.[16] These patients did neither receive ECT nor any psychological interventions 6 weeks before the study enrolment. Patients were continued on stable dose of antidepressant(s) throughout the study period.

Process of randomization

Thirty-one patients fulfilling predefined inclusion and exclusion criteria were enrolled into the study. Details have been tabulated in the CONSORT diagram (Figure 1). Patients were randomized into 2 groups, that is, Active Priming rTMS (G1) and Sham Priming rTMS (G2) using block randomization technique with block size of 4, using freely available software, www.sealedenvelope.com. Patients remained blinded about the group allocation.

Study procedure and intervention

At baseline, all the patients were assessed using the HAMD-17 and Geriatric Depression Rating Scale (GDS).[28] Resting Motor Threshold (RMT) was assessed using right thumb movement visualization technique.[29] Then the patients in active priming group (G1) received priming stimulation, that is, 6 Hz rTMS over right DLPFC at 80% RMT for 10 minutes (600 stimulations; 20 trains of 5 seconds each) followed by 1 Hz rTMS over right DLPFC at 100% RMT for 21 minutes (1200 stimulations; 60 pulses, 20 trains with 5 seconds intertrain interval). Patients with sham priming rTMS group (G2) received 100% RMT, 1 Hz rTMS for a total of 21 minutes similar to G1 preceded by 10 minutes of sham stimulation using commercially available sham coil simulating the active rTMS coil. Both the groups received a total of 10 daily sessions, over 2 weeks. rTMS side effect scale[30] was applied after every session of rTMS.

Outcome measures

Change in the total scores of symptom severity scales from baseline to week 1, 2, and week 4 between the two groups are the primary outcome measures to achieve the objective of the study. Depression symptom severity scale HAMD 17 is used along with GDS in this study as the latter one being a scale which is specifically designed for geriatric population.[28] To see the efficacy of intervention in two groups response rate (defined as 50% reduction in HAMD score from baseline)[31] and remission rates defined as HAMD Score ≤ 10[32,33] were also calculated. This is being done as in geriatric depression, the first occurrence of achieving a score of HAMD≤10 has been proposed as definition of remission.[32]

Statistical analysis

The data was analyzed using the computer software program, statistical package for social sciences (SPSS) with an intention to treat (ITT) design and last observation carried forward (LOCF) approach. Description of sample characteristics was done with descriptive statistics: percentage, mean, and standard deviation. Baseline sociodemographic and clinical characteristics were compared between the groups with independent *t*-test and chi-square test. As repeated measures Analysis of Variance (ANOVA) was used to measure within-group and between-group interaction, normality of distribution was assessed, Mauchly's test of sphericity was done, followed by greenhouse Geiser correction as applicable. To test the effect size partial η^2 was calculated and a value of 0.2–0.5 was assumed as moderate and < 0.2 as mild effect size. Chi-square test was used to compare the response and remission rates between the groups. The level of significance was taken as <0.05.

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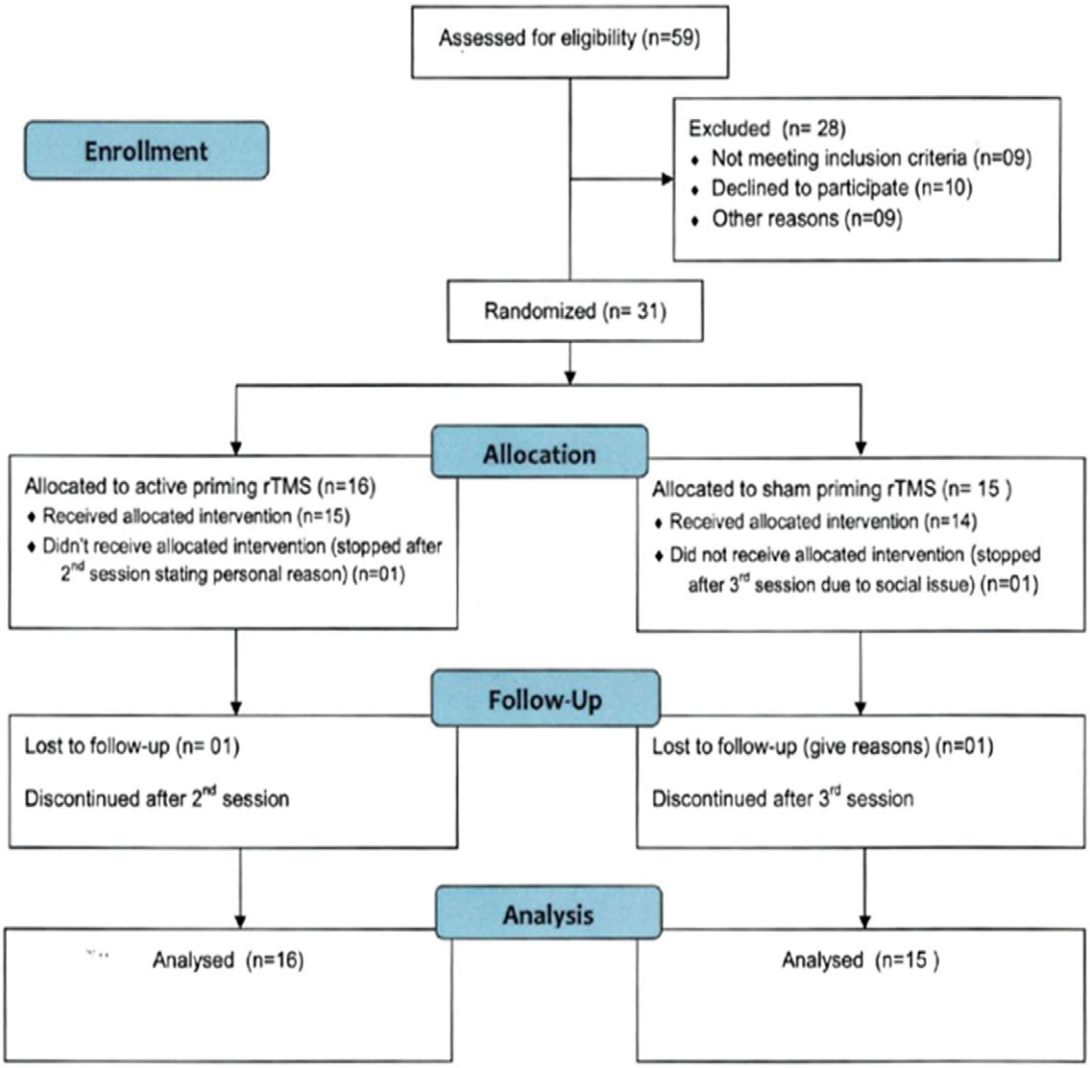

Figure 1. CONSORT flow diagram showing recruitment of the patients.

Results

The sociodemographic and clinical profile of both the groups were comparable with no significant difference as shown in Table 1. The treatment profile for the current episode of the patient population also did not differ significantly. The groups were similar in terms of the number of antidepressants trial, number of current antidepressants, or presence of benzodiazepine in the current regime (Table 1). The class of antidepressants used included selective serotonin reuptake inhibitor (SSRI), serotonin norepinephrine reuptake inhibitor (SNRI), noradrenergic and specific serotonergic antidepressant (NaSSA), tricyclic antidepressant, and atypical antidepressants.

Change in depression severity

Both groups showed statistically significant improvement over time in all domains ($p < 0.001$). Table 2 shows group × time interaction at the 4 points of assessment using repeated measures ANOVA with treatment as between-group factor and time as within-subject factor. On Bonferroni test for post hoc comparison for assessing the effect of treatment over 4 observations, it was found that HAMD score reduced significantly from baseline to week 1 with mean difference = 6.06, 95% CI [4.06 to 8.06], $p < 0.001$, from baseline to week 2 with mean difference = 8.21, 95% CI [5.53 to 10.89], <0.001 and from baseline to week 4 with mean difference = 6.81, 95% CI [4.48 to 9.14], <0.001. The score of HAMD reduced significantly between weeks 1 and 2 with mean difference = 2.15, 95% CI [0.75 to 3.56], $p = 0.001$, but HAMD score increased significantly between weeks 2 and 4 with mean difference = −1.40, 95% CI [−2.77 to −0.03], $p = 0.043$. Similarly, GDS score also reduced significantly from baseline to weak 1 with mean difference = 5.66, 95% CI [3.27 to 8.05], $p < 0.001$, from baseline to week 2 with mean difference = 8.21, 95% CI [5.21 to 11.21], $p < 0.001$ and from baseline to week 4 with mean difference = 6.39, 95% CI [3.57 to 9.21], $p < 0.001$. The score of GDS reduced significantly between weeks 1 and 2 with mean difference = 2.55, 95% CI [1.12 to 3.98], $p < 0.001$, but GDS score increased significantly between weeks 2 and 4 with mean difference = −1.82, 95% CI [−3.53 to −0.19], $p = 0.032$ (Figure 2).

Table 3 shows interaction between the two groups with change in symptom severity scores over time with the group as between-subject variable. On comparing between groups, HAMD ($p < 0.037$; partial $\eta^2 = 0.141$) and GDS ($p < 0.045$; partial $\eta^2 = 0.131$) improved better in

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Table 1. Sociodemographic and Clinical Profile of Patient Population

Sl. No.	Variable		Active priming G1 (n = 16) Mean ± SD n (%)	Sham priming G2 (n = 15) Mean ± SD n (%)	t/χ^2/df	*p*-value
1	Age in years		64.81 ± 6.98	62.80 ± 7.10	0.796/29	0.433
2	Education in years		8.56 ± 5.09	8.47 ± 5.48	0.051/29	0.96
3	Gender	Male	11 (68.8%)	9 (60%)	0259[a]/1	0.716
		Female	5 (31.3%)	6 (40%)		
4	Age of onset of illness in years		48.38 ± 12.55	49.40 ± 11.21	0.239/29	0.813
5	Duration of illness in months		206.63 ± 134.00	166 ± 114.97	0.326/29	0.383
	(in years)		(17.22 ± 11.17)	(13.83 ± 9.58)		
6	Duration of current episode in months		7.88 ± 4.65	11.80 ± 9.11	1.526/29	0.138
7	Number of episodes		3.69 ± 2.06	3.20 ± 1.61	0.731/29	0.471
8	ICD10 diagnosis	F33.2	12 (75%)	10 (66.67%)	0.483/2	0.785
		F33.1	3 (18.75%)	3 (20%)		
		F32.2	1 (6.25%)	2 (13.33%)		
9	Duration of treatment in months		6.63 ± 3.86	9.93 ± 7.56	1.549/29	0.132
10	Number of antidepressant trials		2.25 ± 0.68	2.60 ± 0.74	1.373/29	0.18
11	Current antidepressant	One	9 (56.3%)	9 (60%)	0.045[a]/1	1
		Two	7 (43.8%)	6 (40%)		
12	Benzodiazepine	Present	12 (75%)	10 (66.7%)	0.261[a]/1	0.704
	(BZD)	Absent	4 (25%)	5 (33.3%)		
13	Current	One antidepressant and BZD Combination	4 (25%)	5 (33.3%)	0.390/3	0.942
	Pharmacological	Two antidepressants and BZD combination	4 (25%)	4 (26.7%)		
	Regime	One antidepressant and other psycho-tropic combination	5 (31.3%)	4 (26.7%)		
		Two antidepressant and other psycho-tropic combination	3 (18.8%)	2 (13.3%)		

Abbreviations: BZD, benzodiazepine; F32.2, severe depressive episode without psychotic symptoms; F33.1, recurrent depressive disorder, current episode moderate; F33.2, recurrent depressive disorder, current episode severe without psychotic symptoms; SD, standard deviation.
[a]Cell count < 5-Fisher exact with yates correction done.

Table 2. Effect of Priming rTMS: Change in Symptom Severity Scores Over Time Between Active and Sham Priming Groups

Sl. no.	Variable	Group	Baseline[a] Mean ± SD	Week1[b] Mean ± SD	Week2[c] Mean ± SD	Week 4[d] Mean ± SD	F-value	*p*-value	Post hoc
1	HAMD-17	Active priming G1	19.75 ± 3.92	12.56 ± 4.91	10.13 ± 4.76	11.06 ± 5.34	57.62	<0.001	(b,c,d) <a, c < b, c < d
		Sham Priming G2	18.80 ± 3.51	13.19 ± 4.07	12.00 ± 4.42	13.87 ± 3.68			
2	GDS	Active priming G1	21.81 ± 4.26	15.56 ± 5.34	12.13 ± 5.57	13.50 ± 6.03	40.572	<0.001	(b,c,d) <a, c < b, c < d
		Sham Priming G2	22.53 ± 4.22	17.47 ± 4.37	15.80 ± 5.51	18.06 ± 5.15			

Note. a, baseline; b, Week 1; c, Week 2; d, Week 4.
Abbreviations: GDS, Geriatric Depression Scale; HAMD, Hamilton Rating Scale for Depression.

active priming group than the sham priming group with mild effect size.

Response and remission rates

There was a higher rate of response in active priming rTMS group (50%) after the completion of sessions, that is, at week 2 when compared to sham priming group (26.7%). When followed up after 2 weeks (at 4 weeks from baseline), response rate was statistically higher in active priming group (50%) when compared to sham priming group (6.7%; $\chi^2 = 7.051$, df = 1, $p < 0.05$). Similarly, remission rate was also found to be higher in active priming group (68.8%) when compared to sham priming (33.3%). Difference in the remission rate was found to be statistically significant again at 2 weeks follow-up (at week 4 from baseline) which was 56.3% and 23.3% respectively in active priming and sham priming groups ($\chi^2 = 6.227$, df = 1, $p < 0.05$).

The number needed to treat (NNT) for response at week 4, as well as remission in active priming group with 95% confidence interval (CI) was calculated using https://www.graphpad.com/

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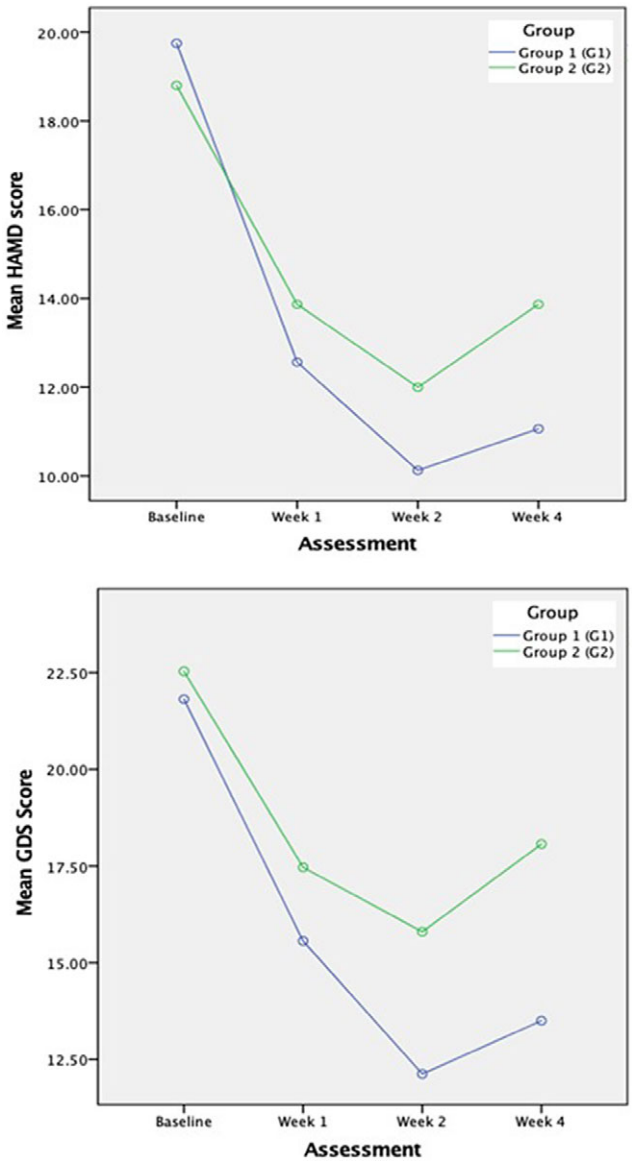

Figure 2. Comparison of change in depression severity (HAMD and GDS scores) between active priming rTMS (G1) and sham priming rTMS (G2) groups.

Table 3. Effect of Priming rTMS: Group* Time Interaction with Respect to Active and Sham Priming Groups with Group as Between-Subject Variables

Sl. no.	Group* Time	Greenhouse Geiser *F*	*p*-value	Partial η^2 (Effect size)
1	HAM D	4.757	**0.037***	**0.141**
2	GDS	4.368	**0.045***	**0.131**

Abbreviations: GDS, Geriatric Depression Scale; HAMD, Hamilton Rating Scale for Depression.
*$p < 0.05$.

quickcalcs/ NNT1/, 2022. NNT for response was 3 (CI = 1.4 to 6.3) and NNT for remission was 3 (CI = 1.4 to 7.6). The number needed to harm was 27.86, which was calculated with patients who experienced side effects anytime during the study period.

Side effect profile

Three patients (18.75%) in the active priming group (scalp discomfort = 2, lacrimation = 1) and 4 patients (26.67%) in sham priming group (scalp discomfort = 2 and 1 each for headache and sleepiness) reported side effects after the first session. At the end of 5 sessions, only 1 patient in sham priming reported side effect. All these side effects were mild in intensity, subsided within an hour of the completion of the treatment, and did not require any medical intervention. No patient reported any side effects after the completion of 2 weeks of rTMS protocol as well as in follow-up at week 4, both in active priming and sham priming group.

Discussion

This is a pilot randomized, single-blind, sham-controlled study done on 31 patients with LLD who had poor/partial response to antidepressant drug treatment. This is also first-ever study done on effects of TMS in patients with LLD from Indian subcontinent. The sociodemographic and clinical profiles of patients in both the groups were comparable; hence minimizing the confounding factors. Patients were on stable doses of medications at least 6 weeks prior to randomization and remained on the same dose throughout the study period, ensuring the elimination of treatment confounders. This step was similar to a recent previous study[15] and has overcome the limitation of few other previous TMS studies.[34]

Mean HAMD score was 19.75 ± 3.92 in G1 and 18.80 ± 3.51 in G2 which indicate moderate severity of depression despite being on standard antidepressant medications. Mean HAMD score was similar in previous studies which used HAMD-17 version.[11,35] Mean GDS score was 21.81 ± 4.26 in G1 and 22.53 ± 4.22 in G2 both of which are in the lower border of severe depression severity. Only one previous study used GDS along with HAMD which had a similar GDS mean score of 19.7 ± 3.9.[36]

Effect of active priming rTMS as compared to sham priming rTMS

Both groups showed statistically significant improvement over time in all domains. This is in agreement with the majority of the previous TMS studies. In the current study sham priming group also had its therapeutic effect of LF-rTMS as previously proven in the adult population with major depression.[37] However, it can also suggest a nonspecific effect of participation in the daily rTMS sessions as well as the daily interaction with the clinician delivering the sessions. Previous TMS studies which included exclusive sham groups also have observed nonspecific effects even in treatment-resistant cases of depression, which are attributed to close clinical surveillance, rigorous monitoring of medication compliance of study participants, and regular interaction with the clinical personnel.[12,15] On post hoc comparisons, it was evident that the highest reduction in the severity was at the end of treatment sessions, that is, at week 2. Further, during follow-up (at week 4 from baseline) there was an increase in severity scores indicating relapsing symptoms in both groups, although active priming group performed better compared to sham priming group. This possibly hints at the need for a greater number of overall sessions or maintenance sessions.

When it was compared between groups, active priming rTMS was better than sham priming in terms of reduction in depression scores namely HAMD and GDS with mild effect size. The effect size was modest (<0.2) when compared to the effect size of 0.36 (CI = 0.13 to 0.6) in the recently published meta-analysis.[27] However, this was the overall effect size and exclusive effect size for active rTMS was not calculated. Whereas, in our study, the comparison group also has therapeutic effects of its own which could be

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the reason for smaller effect size. The addition of an exclusive sham group could have given a clearer scenario.

Considering the superiority found in the active priming group with regards to response and remission rates at week 4, NNT was calculated for both response as well as remission at week 4 in the active priming group. NNT for response was 3 (CI = 1.4–6.3) and NNT for remission was also 3 (CI = 1.4–7.6). These values are similar to the only TMS study in LLD which has previously calculated NNT[15] to achieve remission as 4.0 (95% CI = 2.1–56.5) and to achieve response as 2.7 (95% CI =1.0–7.52). Considering the modest sample size, larger RCTs are needed before generalizing these findings.

Priming mechanism

Priming rTMS is a paradigm which is known to enhance the inhibitory effect of LF-rTMS at the same time preserving the favorable safety profile of this protocol.[21,23] The current study examined its effect in patients with LLD and found it to be significantly beneficial in reducing the depression severity at 2 weeks with 10 sessions and maintaining the lower scores till the end of fourth week. Relapse of symptoms after the rTMS sessions end, has been an issue not only in late life but also in general adult patients and because of this number of sessions needed also gets increased ranging from 20–30 daily sessions spreading across 4–6 weeks.[38] It is believed that priming rTMS alters the synaptic efficiencies of excitatory circuits and such prior history of neuronal activity alters subsequent long-term depression (LTD)-like plasticity through the metaplastic interplay with other cortical and subcortical areas.[39] This is the main mechanism upon which the current study also proposes its beneficial effects of priming rTMS in patients with LLD over sham priming rTMS or just LF-rTMS over right DLPFC.

However, there are certain questions which remain unanswered. It is believed that metaplastic effect can allow additional increments of LTD to be elicited later on, even after the sessions end.[39] That means the improvement which was observed at the end of second week should have continued with some intensity further. But in the current study, no significant improvement was found after the second week. Yet, the improvement achieved relatively sustained better in the priming group when compared to the sham priming group which showed greater deterioration after the end of sessions as depicted in Figure 2 in the result section. This perhaps indicates a mechanism of priming acting underneath which emphasizes the need for exploration of its biological underpinnings in future studies.

Limitations and future directions

This is a pilot study with modest sample size. Large multicentre studies with double-blind design are needed to generalize the study findings. Rater was not blind to the group allocation and so rater bias could have affected the results. In the absence of a complete sham group, placebo effect cannot be ruled out. Although patients were blinded to the group allocation, the effectiveness of blinding was not assessed. Hence detection bias cannot be ruled out. Follow-up period was short to make generalizable conclusions on sustained remission. Longer follow-up studies are needed to see whether the results obtained are maintained for long term. Stimulation was performed as adjunctive treatment to the ongoing antidepressant therapy and participants were on different combinations of psychotropic medications, although on a stable dose. This variation in medication combinations may have resulted in differences among the participants and potentially influenced the outcomes. Neuroimaging and neurophysiological techniques like fMRI and qEEG can be used in addition to clinical assessment, to demonstrate neural patterns associated with clinical improvement.

Conclusion

Based on the results of this single-blind randomized sham-controlled study, it can be concluded that adjunctive priming rTMS over right DLPFC seems to have favorable effects in LLD. It was well-tolerated by patients with LLD and did not cause any adverse effects requiring medical intervention. Priming rTMS appears to have a predominant effect not only in the reduction of depressive symptoms but also in maintaining the durability of response achieved. Hence, this pilot study opens an avenue for further investigations to look into the potential therapeutic applications of priming rTMS in LLD using large-scale double-blind RCTs.

Author contribution. Conceptualization: K.L.V., S.S., B.S., S.K.K.; Literature search: K.L.V., S.S., S.K.K.; Manuscript writing: K.L.V., S.S., B.S.; Manuscript editing: K.L.V., S.S., B.S., S.K.K.

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References

1. Beekman ATF, Copeland J, Prince MJ. Review of community prevalence of depression in later life. *Br J Psychiatry.* 1999;**174**(4):307–311. doi:10.1192/bjp.174.4.307.
2. Blazer D, Burchett B, Service C, et al. The association of age and depression among the elderly: an epidemiologic exploration. *J Gerontol.* 1991;**46**(6):M210–M215. doi:10.1093/geronj/46.6.M210.
3. Blazer DG. Depression in late life: review and commentary. *J Gerontol A Biol Sci Med Sci.* 2003;**58**(3):M249–M265. doi:10.1093/gerona/58.3.M249.
4. Alexopoulos GS. Mechanisms and treatment of late-life depression. *Transl Psychiatry.* 2019;**9**(1):188. doi:10.1038/s41398-019-0514-6.
5. Fava M. Diagnosis and definition of treatment-resistant depression. *Biol Psychiatry.* 2003;**53**(8):649–659. doi:10.1016/S0006-3223(03)00231-2.
6. Tedeschini E, Levkovitz Y, Iovieno N, et al. Efficacy of antidepressants for late-life depression: a meta-analysis and meta-regression of placebo-controlled randomized trials. *J Clin Psychiatry.* 2011;**72**(12):1660–1668. doi:10.4088/JCP.10r06531.
7. Knochel C, Alves G, Friedrichs B, et al. Treatment-resistant late-life depression: challenges and perspectives. *Curr Neuropharmacol.* 2015;**13**(5):577–591. doi:10.2174/1570159X13015151013200032.
8. Lenze EJ, Mulsant BH, Blumberger DM, et al. Efficacy, safety, and tolerability of augmentation pharmacotherapy with aripiprazole for treatment-resistant depression in late life: a randomised, double-blind, placebo-controlled trial. *The Lancet.* 2015;**386**(10011):2404–2412. doi:10.1016/S0140-6736(15)00308-6.
9. Lenze EJ, Sheffrin M, Driscoll HC, et al. Incomplete response in late-life depression: getting to remission. *Dialogues Clin Neurosci.* 2008;**10**(4):419–430. doi:10.31887/DCNS.2008.10.4/jlenze.
10. Jurek L, Dorey J-M, Nourredine M, et al. Impact of vascular risk factors on clinical outcome in elderly patients with depression receiving electroconvulsive therapy. *J Affect Disord.* 2021;**279**:308–315. doi:10.1016/j.jad.2020.10.025.
11. Xie M, Jiang W, Yang H. Efficacy and safety of the Chinese herbal medicine shuganjieyu with and without adjunctive repetitive transcranial magnetic stimulation (rTMS) for geriatric depression: a randomized controlled trial. *Shanghai Arch Psychiatry.* 2015;**27**(2):8.

12. Yesavage JA, Fairchild JK, Mi Z, et al. Effect of repetitive transcranial magnetic stimulation on treatment-resistant major depression in US veterans. *JAMA Psychiatry*. 2018;**75**(9):884–893. doi:10.1001/jamapsychiatry.2018.1483.
13. Zhao X, Li Y, Tian Q, et al. Repetitive transcranial magnetic stimulation increases serum brain-derived neurotrophic factor and decreases interleukin-1β and tumor necrosis factor-α in elderly patients with refractory depression. *J Int Med Res*. 2019;**47**(5):1848–1855. doi:10.1177/0300060518817417.
14. Trevizol AP, Goldberger KW, Mulsant BH, et al. Unilateral and bilateral repetitive transcranial magnetic stimulation for treatment-resistant late-life depression. *Int J Geriatr Psychiatry*. 2019;**34**(6):822–827. doi:10.1002/gps.5091.
15. Kaster TS, Daskalakis ZJ, Noda Y, et al. Efficacy, tolerability, and cognitive effects of deep transcranial magnetic stimulation for late-life depression: a prospective randomized controlled trial. *Neuropsychopharmacology*. 2018;**43**(11):2231–2238. doi:10.1038/s41386-018-0121-x.
16. Rossi S, Hallett M, Rossini PM, et al. Safety, ethical considerations, and application guidelines for the use of transcranial magnetic stimulation in clinical practice and research. *Clin Neurophysiol*. 2009;**120**(12):2008–2039. doi:10.1016/j.clinph.2009.08.016.
17. Miron J-P, Sheen J, Mansouri F, et al. The role of low-frequency repetitive transcranial magnetic stimulation in major depression: a call to increase the evidence base. *Brain Stimulat*. 2020;**13**(5):1296–1297. doi:10.1016/j.brs.2020.06.013.
18. Tallabs FA, Hammond-Tooke GD. Theta priming of 1-Hz rTMS in healthy volunteers: effects on motor inhibition. *J Clin Neurophysiol*. 2013;**30**(1):79–85. doi:10.1097/WNP.0b013e31827ed0e3.
19. Abraham WC, Bear MF. Metaplasticity: the plasticity of synaptic plasticity. *Trends Neurosci*. 1996;**19**(4):126–130. doi:10.1016/S0166-2236(96)80018-X.
20. Abraham WC, Tate WP. Metaplasticity: a new vista across the field of synaptic plasticity. *Prog Neurobiol*. 1997;**52**(4):303–323. doi:10.1016/S0301-0082(97)00018-X.
21. Nongpiur A, Sinha VK, Praharaj SK, et al. Theta-patterned, frequency-modulated priming stimulation enhances low-frequency, right prefrontal cortex repetitive transcranial magnetic stimulation (rTMS) in depression: a randomized, sham-controlled study. *J Neuropsychiatry Clin Neurosci*. 2011;**23**(3):348–357. doi:10.1176/jnp.23.3.jnp348.
22. Ray P, Sinha VK, Tikka SK. Adjuvant low-frequency rTMS in treating auditory hallucinations in recent-onset schizophrenia: a randomized controlled study investigating the effect of high-frequency priming stimulation. *Ann Gen Psychiatry*. 2015;**14**(1):8. doi:10.1186/s12991-015-0046-2.
23. Fitzgerald PB, Hoy KE, Singh A, et al. Equivalent beneficial effects of unilateral and bilateral prefrontal cortex transcranial magnetic stimulation in a large randomized trial in treatment-resistant major depression. *Int J Neuropsychopharmacol*. 2013;**16**(9):1975–1984. doi:10.1017/S1461145713000369.
24. Vidya KL, Srivastava S, Singh B, et al. Effect of priming on adjunctive repetitive transcranial magnetic stimulation in treatment of late-life depression: protocol of a prospective randomized sham-controlled study. *CNS Spectr*. 2022;**7**:1–7. doi:10.1017/S1092852922001018.
25. Hamilton MA. Rating scale for depression. *J Neurol Neurosurg Psychiatry*. 1960;**23**(1):56–62. doi:10.1136/jnnp.23.1.56.
26. Thase ME, Rush AJ. When at first you don't succeed: sequential strategies for antidepressant nonresponders. *J Clin Psychiatry*. 1997;**58**(Suppl 13):23–29.
27. Valiengo L, Maia A, Cotovio G, et al. Repetitive transcranial magnetic stimulation for major depressive disorder in older adults: Systematic review and meta-analysis. *J Gerontol Ser A*. 2021;**77**:851. doi:10.1093/gerona/glab235.
28. Yesavage JA, Brink TL, Rose TL, et al. Development and validation of a geriatric depression screening scale: a preliminary report. *J Psychiatr Res*. 1982;**17**(1):37–49. doi:10.1016/0022-3956(82)90033-4.
29. Pridmore S, Fernandes Filho JA, Nahas Z, et al. Motor threshold in transcranial magnetic stimulation: a comparison of a neurophysiological method and a visualization of movement method. *J ECT*. 1998;**14**(1):25–27.
30. Slotema CW, Blom JD, Hoek HW, et al. Should we expand the toolbox of psychiatric treatment methods to include repetitive transcranial magnetic stimulation (rTMS)? a meta-analysis of the efficacy of rTMS in psychiatric disorders. *J Clin Psychiatry*. 2010;**71**(07):873–884. doi:10.4088/JCP.08m04872gre.
31. Frank E. Conceptualization and rationale for consensus definitions of terms in major depressive disorder: remission, recovery, relapse, and recurrence. *Arch Gen Psychiatry*. 1991;**48**(9):851. doi:10.1001/archpsyc.1991.01810330075011.
32. Alexopoulos GS. Depression in the elderly. *The Lancet*. 2005;**365**(9475):1961–1970. doi:10.1016/S0140-6736(05)66665-2.
33. Nierenberg AA, Wright EC. Evolution of remission as the new standard in the treatment of depression. *J Clin Psychiatry*. 1999;**60**(Suppl 22):7–11.
34. Dai L, Wang P, Zhang P, et al. The therapeutic effect of repetitive transcranial magnetic stimulation in elderly depression patients. *Medicine (Baltimore)*. 2020;**99**(32):e21493. doi:10.1097/MD.0000000000021493.
35. Jorge RE, Moser DJ, Acion L, et al. Treatment of vascular depression using repetitive transcranial magnetic stimulation. *Arch Gen Psychiatry*. 2008;**65**(3):268–276. doi:10.1001/archgenpsychiatry.2007.45.
36. Fabre I, Galinowski A, Oppenheim C, et al. Antidepressant efficacy and cognitive effects of repetitive transcranial magnetic stimulation in vascular depression: an open trial. *Int J Geriatr Psychiatry*. 2004;**19**(9):833–842. doi:10.1002/gps.1172.
37. Berlim MT, Van den Eynde F, Jeff Daskalakis Z. Clinically meaningful efficacy and acceptability of low-frequency repetitive transcranial magnetic stimulation (rTMS) for treating primary major depression: a meta-analysis of randomized, double-blind and sham-controlled trials. *Neuropsychopharmacology*. 2013;**38**(4):543–551. doi:10.1038/npp.2012.237.
38. Lefaucheur J-P, Aleman A, Baeken C, et al. Evidence-based guidelines on the therapeutic use of repetitive transcranial magnetic stimulation (rTMS): an update (2014–2018). *Clin Neurophysiol*. 2020;**131**(2):474–528. doi:10.1016/j.clinph.2019.11.002.
39. Hamada M, Terao Y, Hanajima R, et al. Bidirectional long-term motor cortical plasticity and metaplasticity induced by quadripulse transcranial magnetic stimulation: quadripulse stimulation of the human motor cortex. *J Physiol*. 2008;**586**(16):3927–3947. doi:10.1113/jphysiol.2008.152793.