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Adjunctive repetitive transcranial magnetic stimulation therapy's effectiveness in treating a sample of patients with major depressive disorder refractory to first-line drug treatment

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Abstract

Background The usefulness of repetitious transcranial magnetic stimulation (rTMS) and its protocols in the treatment of major depressive disorder (MDD) remains controversial. This study aimed to evaluate the efficacy of rTMS in treating a sample of patients with MDD who did not respond to conventional treatment.

Results The Hamilton Depression Rating Scale (HDRS) scores for the active rTMS group were 19.66 ± 6.70 at baseline, 12.50 ± 6.69 at 2 weeks, and 11.23 ± 6.59 at 4 weeks. The average HDRS scores for the sham rTMS group were 20.03 ± 7.40 at baseline, 19.36 ± 6.86 at 2 weeks, and 18.53 ± 7.10 at 4 weeks ($F = 5.98$; $p < 0.01$). The Clinical Global Impression-Severity Scale (CGI-S) scores were significantly lower in the second and fourth weeks than the baseline due to the significant interaction between time effects and the groups ($F = 9.95$, $p = 0.002$). This condition was also similar to the CGI-Improvement Scale and Brief Illness Perception Questionnaire (Brief IPQ), and the intervention group showed a significantly lower score than the control group ($p < 0.05$).

Conclusions This study showed that rTMS using the employed protocol was promising for patients with MDD resistant to first-line drug therapy. Further studies are required to ensure our observation.

Trial registration Trial registration number: IRCT20190612043877N1

Trial registry Record URL: https://irct.behdasht.gov.ir/trial/63919

Keywords Depressive disorder, Surveys and questionnaires, Perception, Control groups

Background

Major depressive disorder (MDD) presents a significant challenge for healthcare systems across the globe [1]. Recent studies on antidepressants have changed our views on the effects of these drugs [2, 3]. Given the global burden of the disease and variabilities in response to pharmaceutical interventions between individuals, alongside the side effects of drugs, developing new therapeutic strategies seems essential [4].

Despite remarkable achievements in pharmaceutical therapy with neurotropic drugs, there is a major problem with these drugs. They influence neurochemical mechanisms in large brain parts, including areas not linked to depression. Focused and targeted therapeutic approaches can affect specific neural networks in the brain involved in the pathogenesis of the disease, boosting the efficacy

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of treatment, especially in patients resistant to first-line pharmaceutical therapy [2, 3].

Dealing with persistent symptoms of depression can be frustrating, especially when treatment with multiple first-line antidepressants proves ineffective. In such cases, the term TRD or treatment-resistant depression comes into play. TRD is used when symptoms continue despite trying at least two first-line antidepressants, such as SNRIs (serotonin and norepinephrine reuptake inhibitors), SSRIs (selective serotonin reuptake inhibitors), bupropion, or mirtazapine [5, 6]. This conceptualization has led to new ideas for treating depression, which are based on modifying cerebral neural networks. Brain stimulation techniques are capable of targeting a specific area of the brain. Among the new therapeutic strategies, repetitive transcranial magnetic stimulation TMS may stimulate a distinct brain area with focused magnetic pulses [7]. The primary target of rTMS in MDD is the dorsolateral prefrontal cortex (DL-PFC), which regulates vital processes such as decision-making, attention, and working memory [8].

In order to optimize the effectiveness of treatment with rTMS, it has been emphasized in recent years that there should be individualization of parameters and paradigms for rTMS therapy [9, 10]. In the first approach, the exact area of the stimulation is targeted, and individual descriptive data are included. The second approach involves several daily sessions of accelerated rTMS (arTMS) with accelerated intermittent theta-burst stimulation (aiTBS), decreasing the total time of stimulation within a few days [10–12]. Interestingly, there is no significant difference in remission rate or reduction in depression severity scores between accelerated and classic daily rTMS treatments when the left DLPFC is stimulated with rTMS [13]. Fitzgerald and colleagues discovered that there were no variations in clinical outcomes between the two protocols [13].

A meta-analysis has been conducted to evaluate the efficacy and tolerance of eight active and sham rTMS methods. The study analyzed 81 studies and 4233 patients. The study revealed that while some active rTMS techniques were more effective than shams, none showed significant superiority. This finding indicates that most rTMS protocols have noticeable variations in effectiveness and underlines the necessity for further clinical trials in this field [14]. Schilberg et al. attributed the lack of response to rTMS in some patients to demographic and clinical variabilities among individuals [15].

Although rTMS was FDA-approved for treating depression in 2008 [16], the optimal stimulation parameters are still under debate [17, 18]. Among the factors affecting rTMS efficacy are the coil type and its location, stimulation frequency, and the number of therapeutic sessions [4, 7]. Despite numerous parameter adjustments, rTMS effect rates are relatively modest [19]. Therefore, more studies are needed to optimize stimulation parameters for better effectiveness than electroconvulsive therapy (ECT).

This study aimed to assess the efficacy of ten sessions of rTMS on the left DLPFC at a ten-Hz frequency in a sample of patients with MDD resistant to first-line pharmaceutical therapy. Given the ongoing problem of resistance therapy in this disorder, it is worth considering whether this treatment protocol may benefit patients who do not respond to medication.

Materials

This was a double-blind, sham-controlled, randomized, prospective clinical trial conducted at 22 Bahman Hospital in Qazvin from 2022 to 2023. The Qazvin University's Ethics Committee has approved this study, Code IR.QUMS.REC.1398. 211. All participants provided informed consent before participation. The study design followed the CONSORT guidelines for eHealth interventions [20]. Inclusion criteria were those determined by a psychiatrist based on DSM 5 criteria and included people aged 18 to 70 years with a preliminary diagnosis of MDD. In other words, patients with MDD who had received specialist approval and treatment with adequate doses of antidepressants for at least six weeks but unfortunately did not respond were included in the study. The patients were required to take the same medication 6 weeks before the study and throughout the study. This study had specific exclusion criteria, which included any previous rTMS therapy, patients with chronic (medical) conditions, programming of pacing parameters, history of episodes, history of suicide attempt, gestation, neurosurgery, reluctance to participate in the research, and substance use.

Study procedure

To determine the sample size required for our study, we used the effect size ($f = 0.4$) obtained from previous research [21] and set the critical p-value at 0.05 and the power level at 0.95. The sample size has been estimated to be 58 based on these considerations. However, to meet the inclusion and exclusion criteria, we first studied 80 patients. A total of 60 patients were included from 80 participants recruited by physicians or online advertisements and social networks after screening and applying inclusion and exclusion criteria. Out of the participants, 16 had at least one exclusion criterion, 2 left the study, and 2 refused to participate. The 60 patients were randomly assigned to either the intervention group, which received active rTMS, or the control group, which received sham rTMS ($n = 30$ per

group). Eligible patients were assigned to groups with nearly the same number of people through a block randomization technique. The allocation was made using the sealed envelope technique to hide the contents. In other words, the study was conducted using a double-blind methodology to maintain the integrity of the results. The participants and the researchers assessing depression were blinded to group assignments during the allocation process. As a result, neither the participants nor the investigators knew which therapy or intervention each participant was receiving until the clinical trial was over.

The rTMS session was performed using a MagVenture instrument with figure-eight coils. As part of the study, each participant's MT (motor threshold) was determined before each session. This was achieved by identifying the lowest excitation energy level needed to excite the motor cortex and creating five subsequent contractions of the abductor of the thumb or the abductor pollicis brevis (APB) muscle. This information was crucial in ensuring that each participant's session was customized to their needs and abilities. It also helped ensure that the data collected and analyzed was accurate. The left DLPFC was where the stimulation was applied. Based on the project details provided, it seems that stimulation areas were determined by driving the coil to an optimal texture position for anterior activation of the right APB muscle in each person. This method was presumably used to ensure accuracy and consistency in the stimulation procedure across all participants. It is important to note that the stimulation location may vary depending on the specific muscle being targeted and the individual characteristics of each participant. Overall, this approach appears to be a well-thought-out and carefully executed study method. The active group received ten sessions of rTMS over 2 weeks, while the control group received fake rTMS for the same duration. The study conducted a meticulous examination of the coil's position using stereotactic systems to ensure accuracy. After that, stimulation sessions were carried out, which consisted of 75 trains of magnetic pulses with 3750 pulsings applied in each session, with a frequency of ten Hz, a 5-s stimulus, and a 10-s interval period between trains of stimulation.

The sham stimulation employing an rTMS instrument with a sham coil did not produce any touch sense at the desired area nor cause any stimulation of the cerebrum's outer layer. A similar acoustical impression was made by the sham instrument. In 2 weeks, each participant participated in ten rTMS sessions. Active and sham rTMS were delivered using the same equipment to reduce external factors and prevent bias. The device's voice could be heard by the patients, but the magnetic field was not transferred to the brain.

Research instruments and data collection tools

Participants' demographic and clinical data, including gender, age, education, and episodes of depression, were collected by self-report. The participants were evaluated by independent evaluators who were blinded to their therapeutic status.

The Hamilton Depression Rating Scale (HDRS) is a clinical appraisal scale used to measure depression and consists of 17 items that measure the behavioral, physical, and mental symptoms of depression. HDRS is the most popular scale for measuring depression, known as the Gold Scale. The cut-off point of this scale is 7. A score below 7 indicates no depression. A score between 8 and 13 exhibits mild depression, 14–18 shows moderate depression, 19–22 for severe depression, and above 23 for very severe depression [22–24]. The Persian version of this questionnaire has a reliability coefficient of 0.89 and has good validity [20].

The study's primary outcome was a change in depression symptoms, which was assessed using HDRS. For this purpose, at baseline, the questionnaire was completed before the intervention and again in the second and fourth weeks after. This questionnaire's response rate to treatment was based on a 50% reduction in HDRS scores after the intervention (fourth week) compared with the baseline. The remission rate was also considered based on the reduction of 7 and below 7 in HDRS scores in the final session compared with the baseline.

The secondary outcomes of the study were evaluated using the Clinical Global Impressions (CGI), which assesses the severity of symptoms, response to therapy, and the efficacy of treatments in patients with mental disorders. This tool has 2 items that evaluate disease severity and overall improvement, and each item is scored based on a seven-point Likert scale. Regarding the CGI-Severity Scale (CGI-S), the physician is asked during the clinical examination to rate disease severity in the patient relative to other patients with similar diagnoses according to the physician's previous experiences. Regarding the CGI-Improvement scale (CGI-I), the physician is asked to determine the rate of disease improvement compared with the start of the intervention [25].

To assess the effect of rTMS on patients' perceptions, the Brief Illness Perception Questionnaire (Brief IPQ) was employed. This questionnaire has 9 items and was developed by Broadbent et al. A higher score in this tool indicates a greater risk for the patient's perception of the disease [26]. This questionnaire has shown good validity and reliability in patients with psychological disorders [27]. In a study by Bazzazian et al., the Persian version of Brief IPQ showed the results of good internal consistency, construct validity, and concurrent validity with other criteria. The results showed that the scale had intercultural

validity [4]. The data of the mentioned research tools were collected and analyzed at 3-time points (i.e., before the intervention and 2 and 4 weeks afterward).

Statistical analysis

The analysis was performed with the SPSS software. Version 26 was developed by SPSS Inc., headquartered in Chicago, IL, USA. The data's normal distribution was assessed using the Kolmogorov-Smirnov test. The study used the chi-square and independent *t*-test to compare categorical and continuous variables. On the other hand, to compare mean depression scores (based on the CGI-S scale) between different time points (i.e., baseline and eighth and tenth weeks), the repeated-measure analysis of variance (ANOVA) test was utilized. The method's main advantage is its ability to control for unrelated group variance. The mean and SD were calculated considering the interaction between the time and groups. To check if the variances are equal, the researchers used the Levene test for homogeneity of variances. The statistical significance level was $p < 0.05$, indicating a 95% confidence interval (CI).

Results

The study conducted had a total of 60 participants, with 56.7% being male and 43.3% being female. The age range of the participants varied from 20 to 58 years, with a mean of 33.96 ± 7.47. Table 1 presents the participants' demographic and clinical features. As it can be seen, there was no significant difference between the intervention and sham groups in terms of gender, age, level of education, marital status, medications received, and duration of depression episode ($p > 0.05$).

Regarding the depression score or HDRS (Table 2), the 2 groups had non-homogeneous variances, and the result of the sphericity test was statistically significant. The interaction between the group (active or sham rTMS) and time (baseline, 2 weeks, and 4 weeks) was significant ($F = 5.98$; $p = 0.01$). The analysis of the main effects was significant in terms of time ($F = 10.87$; $p = .001$), indicating a reduction in the score of depressive symptoms over time in both groups; thus, the score was the lowest in the fourth week after the intervention compared with other times (Fig. 1 and Table 2).

Regarding CGI-S, sphericity was statistically significant; thus, the Greenhouse-Geisser test was used. The interaction between the time and group was significant ($F = 9.95$; $p = 0.002$), reflecting the main effects of time on the overall score ($F = 20.36$; $p < 0.001$); thus, CGI-S was significantly lower in the second and fourth weeks than in the baseline (Table 2).

In the fourth week after the intervention, the active rTMS group showed a significantly lower CGI-I score compared with the sham rTMS group (1.66 ± 0.71 vs. 2.73 ± 0.45; $p < 0.001$). Since CGI-I was measured only after the intervention in both groups, the relevant data are not presented in Table 2. Regarding the Brief IPQ score, the interaction between the time and group was significant ($F = 3.99$; $p = 0.03$), reflecting the main effects of time on the overall score ($F = 15.75$; $p < 0.001$); thus, CGI-S was significantly lower in the second and fourth weeks than in the baseline (Table 2).

Table 1 Demographic and clinical features in the intervention and control groups

Variable	Sham rTMS ($n = 30$)	Active rTMS ($n = 30$)	*p* value
Age (year)	35.60 ± 5.19	32.33 ± 9.01	0.09
Gender (female)	14 (16)	20 (10)	0.11
Marital status			
Single	20 (58.8%)	14 (41.2%)	0.16
Married	4 (28.6%)	10 (71.4%)	
Widowed	6 (50%)	6 (50%)	
Education			
Illiterate	18 (56.3%)	14 (43.8%)	0.57
Middle-school and lower than the diploma	8 (44.4%)	10 (55.6%)	
Academic	4 (40%)	6 (60%)	
Duration of depression episode (weeks)	25.53 ± 15.99	23.13 ± 16.28	0.07
Drugs used			
Citalopram	10 (50%)	10 (50%)	0.63
Sertraline	14 (58.3%)	10 (41.7%)	
Venlafaxine	2 (33.3%)	4 (66.7%)	
Fluoxetine	4 (40%)	6 (60%)	

Table 2 Clinical outcomes in the intervention and sham groups

Variable		Sham rTMS ($n = 30$)	Active rTMS ($n = 30$)	ANOVA[a]		ANOVA[b]	
				F	*p*	*F*	*p*
HDRS	Baseline	20.03 ± 7.40	19.66 ± 6.70	10.87	0.001	5.98	0.01
	Week 2nd	19.36 ± 6.86	12.50 ± 6.96				
	Week 4th	18.53 ± 7.10	11.23 ± 6.95				
GGI-S	Baseline	4 ± 0.83	3.80 ± 0.76	20.36	$p < .001$	9.95	$p = 002$
	Week 2nd	3.86 ± 0.89	3.30 ± 1.13				
	Week 4th	3.83 ± 0.98	2.86 ± 1.27				
B-IPQ	Baseline	56.60 ± 11.26	55.23 ± 12.90	15.75	$p < .001$	3.99	0.03
	Week 2nd	55 ± 11.25	48 ± 14.22				
	Week 4th	53.13 ± 14.24	46.66 ± 12.93				

[a] Repeated-measures analysis of variance (ANOVA), consider the effect of time

[b] Repeated-measures analysis of variance (ANOVA), interaction of group and time (active vs. sham)

Brief IPQ, Brief Illness Perception Questionnaire; *CGI-S*, the Clinical Global Impression-Severity scale

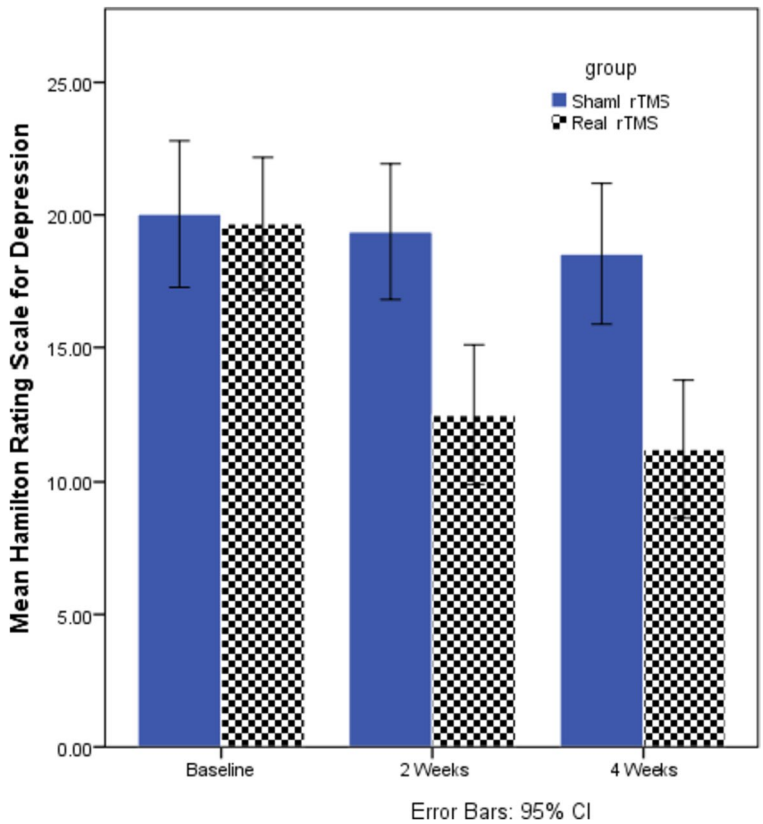

Fig. 1 Graphic representation of depression scores in the 2 groups at different times

Response and remission rates

Based on HDRS -17 scores, 14 (46.6%) participants in the active rTMS group and 2 (6.6%) participants in the sham rTMS group achieved a response. Response rates were significantly higher in the active rTMS group than in the sham group ($\chi^2 = 12.27$; $p < 0.001$). Similarly, the remission rate in the active rTMS group was 11 (36.6%), and in the sham rTMS group, it was 1 (3.3%). The rate of remission was significantly higher in the active rTMS group compared with the sham rTMS groups ($\chi^2 = 10.42$; $p = 0.001$).

During the study, no serious side effects were observed. Three participants reported mild headaches, two in the active group and one in the sham group. Two of the 3 participants who reported headaches were treated with nonsteroidal anti-inflammatory drugs. One participant in the active group declared mild discomfort in the prescribing area.

Discussion

Although primary evidence suggests the efficacy of high-frequency rTMS [28, 29], there are controversies on different specific protocols used to manage MDD. The present study was conducted to evaluate the efficacy of 10 sessions of rTMS on the left DLPFC at 10-Hz frequency in patients with MDD resistant to the first-line pharmaceutical therapy. The results showed that this method significantly reduced patients' depression scores. It seems that administration of high-frequency rTMS to left DLPFC improved depression scores due to increased blood flow to limbic and prefrontal areas [30, 31].

In the present study, rTMS was well-tolerated without severe side effects. These results are consistent with the findings of Jhanwar et al. [32]; they have also shown a significant reduction in HAMD scores with a high frequency of 10 Hz rTMS at 110% MT on the left DLPFC. In their study, rTMS treatment was performed on 5 consecutive days each week, resulting in 20 treatment sessions over 4 weeks [32]. One of the advantages of our study protocol compared with the study of Jhanwar et al. is that the present protocol, with a duration of 18 min per session for 10 sessions, improved the HDRS response rate by 46.7%. Prolonged stimulation times lead to increased discontinuation rates. This may be another obstacle to continuing treatment for patients; therefore, optimizing the stimulation parameters in a shorter time is a practical approach.

In the present study, in addition to the fourth week, the scales were measured in the second week, and the results showed a significant decrease in the studied scales in the second week. Some studies have shown that 2 weeks of rTMS treatment rapidly reduces HAMD-17 scores in patients with MDD [33, 34].

It appears that individuals with refractory depression have a lower response and remission rate compared with those with less resistant depression; for instance, Duprat et al. (2016) [35] showed a response rate of 35%, and Blumberger et al. (2018) [36] showed a response rate of 38% and remission rate of 30% on daily stimulation of the left DLPFC. In the present study, the rTMS protocol was different from the above studies. However, the remission and response rates were higher than the mentioned studies. Even though some studies have shown that delivering 100–110% MT has better outcomes [37], it is difficult to compare results due to variations in methodology, such as treatment duration, frequency, severity of illness, and resistance to medication in the study population.

This study showed that MDD patients' mean scores of disease perception were higher than the median score of the instrument (i.e., 53) in both groups. This indicates that the patients under study perceived a moderate risk of their disease. The score of the active rTMS group has been substantially reduced following the intervention, reflecting the positive effects of rTMS on the patients' health-related outcomes and probably their motivation for managing their disease. Barbosa et al. obtained similar findings in their study and showed that disease perception was linked to treatment outcomes in patients with TRD undergoing rTMS [38].

In addition, CGI-I and CGI-S improved significantly in the patients treated with active rTMS, reflecting the efficacy of the treatment process. Studies in this area have shown that this scale is sensitive to changes in the patient's clinical condition and can track the treatment process [39, 40]. In a study by Taylor et al. in 2017 [41], the CGI improvement rate was almost equal to that of our study. Likewise, Connolly et al. (2012) and Carpenter et al. (2012) obtained similar results [39, 40].

The present protocol could improve neural network balance and depression. Studies have indicated that the DLPFC region is highly involved in the development of MDD [42, 43]. This region seems to be involved in the development and progression of depression when individuals enter a phase of emotional repression; thus, an improvement in the depression score can be attributed to DLPFC cognitive functions in emotional engagement as well as the emotional roles of ventromedial prefrontal cortex (VMPFc) in the involvement to self-awareness and self-reflection [42, 43].

Another reason for achieving satisfactory outcomes in the present study can be the use of an optimized approach (i.e., stereotactic systems) for coil positioning. Stereotactic systems are frameless and allow for the online positioning of a predetermined cerebral area based on patients' neural imaging data. In addition, instead of old circular coils, we employed 8-shaped double-cone coils, which were separated from each other at a certain angle. It seems that the combination of these modifications, along with the optimal frequency and an adequate number of therapeutic sessions used, allowed for the modulation of deeper parts of the brain, such as DLPFC or anterior cingulate. In other words, choosing an optimal location and appropriate type of coils (with a special geometry) delivers a stronger current to the central fissure and, therefore, more efficient stimulation [44, 45].

Random selection and efficient blinding of participants and evaluators have been one of the strengths of this study. As a result, clinical and demographic variabilities between the participants did not have a significant

impact on the outcomes. Zhang et al. reported that rTMS results in better outcomes in elderly patients with depression [46]. In addition to demographic variables, the participants in the 2 groups did not differ significantly in terms of clinical variables. In other words, no significant differences were observed between the 2 groups regarding the medications used and the CGI-S and Brief IPQ scores at the baseline, which allowed for more realistic comparisons. Kaster et al. conducted a study which revealed that individuals with a higher depression score at the baseline were less likely to respond to rTMS. Furthermore, a faster response to rTMS was associated with more advanced age, lower baseline depression score, and lack of benzodiazepine use [47].

In the present study, patients undergoing rTMS continued to consume their antidepressants. This allowed us to assess patients in terms of the drugs used. Serotonin reuptake inhibitors were used by patients in both active and placebo rTMS groups, but there was no meaningful difference as regards the type of inhibitor compared with each other; thus, the study groups were clinically homogenous in this regard. Although the 2 groups were comparable in terms of the drugs used, we could not assess the possible interactions between specific pharmaceutical regimens and rTMS. Because the response and remission rates observed in the fourth week of the intervention could have been due to the synergistic effects of these 2 factors, it is recommended that this possible synergism be examined in future studies. It is important to note that a deeper understanding of the mechanisms of action of rTMS is necessary. We did not test the durability of the antidepressant effects of rTMS. Additional research is required to gain a thorough understanding of the effects of rTMS therapy. Specifically, more studies are needed to determine the optimal time gap between rTMS sessions and the effectiveness of combining rTMS with pharmaceutical therapy. It is essential to explore these factors further to ensure patients receive the most efficient and effective treatment possible. With further research, we can better understand the full potential of rTMS therapy and improve patients' overall care and treatment.

Conclusions

The present study showed the promising effects of rTMS on the left DLPFC (10-Hz frequency, 10 sessions) in treating MDD patients resistant to the first-line pharmaceutical therapy. This protocol delivered a high response rate (46.7%) in depression, improved clinical disease impressions, and improved illness perception without severe side effects. This clinical trial highlights the importance of efficacy and optimizing MDD treatment protocols. More studies are needed to confirm our observations.

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Authors' contributions
AHJ contributed to the original draft in mythology, visualization, conceptualization, investigation, software, data compilation, and creation. ARM was involved in the conceptualization, writing, reviewing, and editing. AAS has provided conceptualization, methodology, software, visualization, investigation, supervision, and writing for review and editing.

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Availability of data and materials
The published article and its accompanying data sets provide all the data produced or analyzed in this study.

Declarations

Ethics approval and consent to participate
The Ethics Committee of the Qazvin University of Medicine adopted this study by IR code QUMS. REC.1398.211.

Consent for publication
Not applicable

Competing interests
The authors declare no competing interests.

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References

1. Guidi J, Fava GA (2021) Sequential combination of pharmacotherapy and psychotherapy in major depressive disorder: a systematic review and meta-analysis. JAMA Psychiatr 8:261–269
2. Cosci F, Guidi J, Mansueto G, Fava GA (2020) Psychotherapy in recurrent depression: efficacy, pitfalls, and recommendations. Expert Rev Neurother 20(11):1169–75
3. Kazemi R, Ghazanfari F (2018) Effectiveness of bilateral repetitive transcranial magnetic stimulation on anhedonia and depression symptoms in major depressive disorder patients. J Clin Psychol 10(3):23–33
4. Bazzazian S, Besharat MA (2010) Reliability and validity of a Farsi version of the brief illness perception questionnaire. Procedia - Soc Behav Sci 5:962–5
5. Kekic A (2024) Pharmacogenomics in psychiatric diseases. InPharmacogenomics in clinical practice. Cham, Springer International Publishing. p. 147–185. https://doi.org/10.1007/978-3-031-45903-0_9
6. Steffens DCJNEJoM (2024) Treatment-resistant depression in older adults. 390(7):630–9
7. Lee JC, Wilson AC, Corlier J, Tadayonnejad R, Marder KG, Pleman CM et al (2020) Strategies for augmentation of high-frequency left-sided repetitive transcranial magnetic stimulation treatment of major depressive disorder. J Affect Disord 277:964–9
8. Schiena G, Franco G, Boscutti A, Delvecchio G, Maggioni E, Brambilla P (2021) Connectivity changes in major depressive disorder after rTMS: a review of functional and structural connectivity data. Epidemiol Psychiatr Sci 30:e59
9. Padberg F, Brem A-K, Palm U, Pogarell O, Hasan A, Brunelin J et al (2017) Discovering the individual brain: brain stimulation in psychiatry. Springer 267(Suppl 2):109–12
10. Baeken C (2018) Accelerated rTMS: a potential treatment to alleviate refractory depression. Front Psychol 9:2017
11. Wu G-R, Duprat R, Baeken C (2022) Accelerated iTBS changes perfusion patterns in medication resistant depression. J Affect Disord 306:276–280

12. Wu G-R, Baeken C (2022) Individual interregional perfusion between the left dorsolateral prefrontal cortex stimulation targets and the subgenual anterior cortex predicts response and remission to aiTBS treatment in medication-resistant depression: the influence of behavioral inhibition. Brain Stimulation 15(1):182–9
13. Fitzgerald PB, Hoy KE, Elliot D, McQueen S, Wambeek LE, Daskalakis ZJ (2018) Accelerated repetitive transcranial magnetic stimulation in the treatment of depression. Neuropsychopharmacology 43(7):1565–72
14. Brunoni AR, Chaimani A, Moffa AH, Razza LB, Gattaz WF, Daskalakis ZJ et al (2017) Repetitive transcranial magnetic stimulation for the acute treatment of major depressive episodes: a systematic review with network meta-analysis. JAMA Psychiatry 74(2):143–52
15. Schilberg L, Schuhmann T, Sack AT (2017) Interindividual variability and intraindividual reliability of intermittent theta burst stimulation-induced neuroplasticity mechanisms in the healthy brain. J Cogn Neurosci 29(6):1022–32
16. George MS, Taylor JJ, Short EB (2013) The expanding evidence base for rTMS treatment of depression. Curr Opin Psychiatry 26(1):13–8
17. Lefaucheur J-P, Aleman A, Baeken C, Benninger DH, Brunelin J, Di Lazzaro V et al (2020) Evidence-based guidelines on the therapeutic use of repetitive transcranial magnetic stimulation (rTMS): an update (2014–2018). Clin Neurophysiol 131(2):474–528
18. Zhang M, Wang R, Luo X, Zhang S, Zhong X, Ning Y, et al (2021) Repetitive transcranial magnetic stimulation target location methods for depression. Frontiers in Neuroscience. 15:1086. https://doi.org/10.3389/fnins.2021.695423
19. Baeken C (2018) Accelerated rTMS a potential treatment to alleviate refractory depression. Front Psychol. 9:2017
20. Baker TB, Gustafson DH, Shaw B, Hawkins R, Pingree S, Roberts L et al (2010) Relevance of CONSORT reporting criteria for research on eHealth interventions. Patient Educ Couns 81:S77–S86
21. Dell'osso B, Camuri G, Castellano F, Vecchi V, Benedetti M, Bortolussi S et al (2011) Meta-review of metanalytic studies with repetitive transcranial magnetic stimulation (rTMS) for the treatment of major depression. Clin Pract Epidemiol Ment Health 7:167–77
22. Eslami-Shahrbabaki M, Fekrat A, Mazhari S (2015) A study of the prevalence of psychiatric disorders in patients with methamphetamine-induced psychosis. Addict Health 7(1–2):37
23. Cheffi N, Chakroun-Walha O, Sellami R, Ouali R, Mnif D, Guermazi F et al (2022) Validation of the Hamilton Depression Rating Scale (HDRS) in the Tunisian dialect. Public Health 202:100–5
24. Sudhan H, Kumar SS editors (2022) Multimodal depression severity detection using deep neural networks and depression assessment scale. Proceedings of International Conference on Computational Intelligence and Data Engineering. Springer.
25. Busner J, Targum SD (2007) The clinical global impressions scale: applying a research tool in clinical practice. Psychiatry (Edgmont) 4(7):28–37
26. Broadbent E, Petrie KJ, Main J, Weinman J (2006) The brief illness perception questionnaire. J Psychosom Res 60(6):631–7
27. Bazzazian S, Besharat MA (2010) Reliability and validity of a Farsi version of the brief illness perception questionnaire. Procedia-Soc Behav Sci 5:962–5
28. Nguyen TD, Hieronymus F, Lorentzen R, McGirr A, Østergaard SD (2021) The efficacy of repetitive transcranial magnetic stimulation (rTMS) for bipolar depression: a systematic review and meta-analysis. J Affect Disord 279:250–5
29. McGirr A, Karmani S, Arsappa R, Berlim MT, Thirthalli J, Muralidharan K et al (2016) Clinical efficacy and safety of repetitive transcranial magnetic stimulation in acute bipolar depression. World Psychiatry 15(1):85–6
30. Cosmo C, Zandvakili A, Petrosino NJ, Berlow YA, Philip NS (2021) Repetitive transcranial magnetic stimulation for treatment-resistant depression: recent critical advances in patient care. Curr Treatment Options Psychiatry 8(2):47–63
31. Zhang F-F, Peng W, Sweeney JA, Jia Z-Y, Gong Q-Y (2018) Brain structure alterations in depression: psychoradiological evidence. CNS Neurosci Ther 24(11):994–1003
32. Jhanwar VG, Bishnoi RJ, Jhanwar MR (2011) Utility of repetitive transcranial stimulation as an augmenting treatment method in treatment-resistant depression. Indian J Psychol Med 33(1):92–6
33. O'Reardon JP, Solvason HB, Janicak PG, Sampson S, Isenberg KE, Nahas Z et al (2007) Efficacy and safety of transcranial magnetic stimulation in the acute treatment of major depression: a multisite randomized controlled trial. Biol Psychiatry 62(11):1208–16
34. Bakim B, Uzun UE, Karamustafalioglu O, Ozcelik B, Alpak G, Tankaya O et al (2012) The combination of antidepressant drug therapy and high-frequency repetitive transcranial magnetic stimulation in medication-resistant depression. Klinik Psikofarmakoloji Bülteni-Bulletin of Clinical Psychopharmacology 22(3):244–53
35. Duprat R, Desmyter S, van Heeringen K, Van den Abbeele D, Tandt H, Bakic J et al (2016) Accelerated intermittent theta burst stimulation treatment in medication-resistant major depression: a fast road to remission? J Affect Disord 200:6–14
36. Blumberger DM, Vila-Rodriguez F, Thorpe KE, Feffer K, Noda Y, Giacobbe P et al (2018) Effectiveness of theta burst versus high-frequency repetitive transcranial magnetic stimulation in patients with depression (THREE-D): a randomised non-inferiority trial. Lancet 391(10131):1683–92
37. George MS, Nahas Z, Molloy M, Speer AM, Oliver NC, Li X-B et al (2000) A controlled trial of daily left prefrontal cortex TMS for treating depression. Biol Psychiatr 48(10):962–70
38. Barbosa Menezes R. (2021) Illness perception and its influence in outcome and disability in patients with treatment resistant depression receiving rTMS treatment. University of British Columbia. https://doi.org/10.14288/1.0396936. http://hdl.handle.net/2429/77941
39. Connolly KR, Helmer A, Cristancho MA, Cristancho P, O'Reardon JP (2012) Effectiveness of transcranial magnetic stimulation in clinical practice post-FDA approval in the United States: results observed with the first 100 consecutive cases of depression at an academic medical center. J Clin Psychiatr 73(4):e567-73
40. Carpenter LL, Janicak PG, Aaronson ST, Boyadjis T, Brock DG, Cook IA et al (2012) Transcranial magnetic stimulation (TMS) for major depression: a multisite, naturalistic, observational study of acute treatment outcomes in clinical practice. Depress Anxiety 29(7):587–96
41. Taylor SF, Bhati MT, Dubin MJ, Hawkins JM, Lisanby SH, Morales O et al (2017) A naturalistic, multi-site study of repetitive transcranial magnetic stimulation therapy for depression. J Affect Disord 208:284–90
42. Zhang T, Huang Y, Jin Y, Ma X, Liu Z (2021) Treatment for major depressive disorder by repetitive transcranial magnetic stimulation in different parameters: a randomized double-blinded controlled trial. Front Psychiatry 12:304
43. Fitzgerald PB, Daskalakis ZJ (2013) Repetitive transcranial magnetic stimulation treatment for depressive disorders: a practical guide. Springer Science and Business Media, Berlin.
44. Sparing R, Hesse MD, Fink GR (2009) Neuronavigation for transcranial magnetic stimulation (TMS): where we are and where we are going. Cortex 46(1):118–20
45. Sack AT, Kadosh RC, Schuhmann T, Moerel M, Walsh V, Goebel R (2009) Optimizing functional accuracy of TMS in cognitive studies: a comparison of methods. J Cogn Neurosci 21(2):207–21
46. Zhang T, Sun W, Zhu J, Tang Y, Hui L, Zhou L et al (2019) Effect of adjunct repetitive transcranial magnetic stimulation in elderly patients with acute depressive episode: supporting evidence from a real-world observation. Am J Geriatr Psychiatry 27(1):91–2
47. Kaster TS, Downar J, Vila-Rodriguez F, Thorpe KE, Feffer K, Noda Y et al (2019) Trajectories of response to dorsolateral prefrontal rTMS in major depression: a THREE-D study. Am J Psychiatry 176(5):367–75

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