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Original Article

The Effectiveness of Repetitive Transcranial Magnetic Stimulation (rTMS) on Attention and Short-Term Memory in Patients with Major Depressive Disorder

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Abstract

Background: Major Depressive Disorder (MDD) often presents with cognitive deficits, including impairments in attention and short-term memory, which can significantly impact patients' quality of life.

Objectives: This study investigated the effectiveness of repetitive Transcranial Magnetic Stimulation (rTMS) on attention and short-term memory in patients with MDD.

Methods: This study adopted a quasi-experimental, pretest-posttest control group design, conducted in Yazd, Iran, during 2023. A convenience sample of thirty patients, aged 20-50 years, diagnosed with MDD, was recruited and subsequently randomized into either an intervention or a control group (n=15 per group). All participants received antidepressant medication (SSRI); however, the intervention group also underwent ten sessions of 5Hz rTMS at an intensity of 120% of the motor threshold, targeting the left dorsolateral prefrontal cortex (DLPFC), while the control group received sham rTMS. Cognitive function, specifically attention and short-term memory, was evaluated using the Wechsler Memory Scale. Statistical analysis was performed using SPSS-27, with analysis of covariance (ANCOVA) employed to assess treatment effects.

Results: Participants in the study included 30 individuals with MDD (male and female), with a mean age of 43.65 ± 6.49 years. The findings indicated that rTMS yielded statistically significant changes in attentional and short-term memory performance among these patients (P<0.01). This outcome demonstrates a beneficial impact of rTMS on cognitive domains affected by MDD, providing empirical evidence for its potential therapeutic role.

Conclusion: This study demonstrates that rTMS targeting the DLPFC significantly enhances attention and short-term memory in MDD patients. Consequently, these results suggest rTMS as a valuable adjunctive therapy for mitigating cognitive deficits associated with MDD through its neuromodulatory effects, offering a potential strategy to improve patients' daily functioning and overall quality of life.

Keywords: Depressive Disorder, rTMS, Attention, Memory, Neuroplasticity, Cognitive Remediation

1. Background

Major Depressive Disorder (MDD) is a widespread and severely debilitating mental disorder, demanding substantial clinical and research attention.[1,2] The World Health Organization (WHO) identified MDD as the third leading contributor to the global burden of disease in 2008, with projections indicating it will become the foremost contributor by 2030.[3] MDD profoundly influences cognition, affect, and behavior,[4] and for numerous individuals, symptom severity impedes daily functioning across various domains.[5] A fundamental cognitive domain implicated in MDD,[6,7] is frequently reported as impaired, manifesting as concentration difficulties that detrimentally affect daily functioning, often persisting despite conventional first-line treatments.[8] While MDD is conventionally classified as a mood disorder, cognitive dysfunction represents a significant comorbid feature. Accumulating evidence substantiates the presence of cognitive impairments in MDD, encompassing executive function, memory, attention, and psychomotor speed.[9] Notably, attention is inextricably linked to human intellectual performance and core cognitive processes, including perception, learning, memory, and executive function. Numerous facets of cognitive functioning, such as short-term memory and higher-order cognitive processes essential for goal-directed behavior, rely heavily on attentional resources.[10,11]

Short-term memory is acknowledged as a significant cognitive domain affected by depression.[12,13] Short-term memory encompasses systems responsible for the transient maintenance of limited stimulus information, typically lasting seconds. The most extensively studied short-term memory subsystems include phonological, spatial, and visual components, with evidence also

indicating the existence of short-term storage within other sensory modalities, such as the somatosensory system.[14] Deficits in short-term memory can manifest as difficulty remembering instructions, forgetting details of conversations, struggling to follow multi-step tasks, and frequently misplacing items. These impairments can significantly hinder daily functioning in various domains, including work, academics, and social interactions. Clinical observations suggest a frequent association between depressive symptomatology and deficits in short-term memory, although other memory systems, such as long-term and procedural memory, which governs motor skill acquisition, are generally less affected. Nonetheless, depression can exert a detrimental impact on overall memory function.[15-17]

Neurotransmitter systems, the brain's endogenous chemical messengers, are implicated in the pathophysiological mechanisms underlying depression, as evidenced by numerous studies.[17,18] Contemporary research posits that perturbations in the functional dynamics and efficiency of these neurotransmitters, along with their interactions within neural networks regulating mood, significantly contribute to the manifestation and treatment of depressive disorders.[19] Repetitive Transcranial Magnetic Stimulation (rTMS) modulates cortical excitability and can influence neurotransmitter function, particularly the glutamatergic and GABAergic systems, which play a crucial role in synaptic plasticity and cognitive processes. Specifically, 5Hz rTMS applied to the left DLPFC is thought to enhance cortical excitability and induce long-term potentiation-like effects, facilitating the strengthening of neural connections and improving cognitive functions such as attention and short-term memory.[20]

While pharmacotherapy and psychotherapy remain standard clinical interventions for depression management, a substantial proportion of patients exhibit incomplete therapeutic responses or experience adverse effects.[21] Consequently, rTMS, a non-invasive and well-tolerated neuromodulatory technique, has attracted considerable scholarly and clinical interest.[22] By selectively modulating targeted brain regions, notably the prefrontal cortex, rTMS has demonstrated potential to ameliorate cognitive and affective symptoms in patient populations.[23] rTMS employs magnetic stimulation to precisely modulate activity within circumscribed neural circuits, with the direction of modulation (excitation or inhibition) determined by the specific stimulation protocol.[24] Thus, rTMS represents a promising therapeutic avenue for modulating neurotransmitter function. Extensive research endeavors have investigated the therapeutic efficacy of rTMS in depression.[25,26] For example, Kazemi et al.,[27] in a randomized controlled trial, reported significant reductions in rumination and improvements in concentration following rTMS intervention compared to control conditions. Likewise, Asbaghi et al.[28] documented the efficacy of rTMS in enhancing working memory performance. Miron et al.[29] observed that rTMS exerts its therapeutic effects in major depressive disorder through the induction of sustained neuroplastic changes. Furthermore, Tang et al.[30] demonstrated the efficacy of rTMS in ameliorating executive dysfunction in individuals diagnosed with major depressive disorder.

MDD is commonly associated with cognitive deficits, particularly in the domains of attention and short-term memory, which profoundly compromise patients' daily functioning and overall quality of life. Despite the efficacy of conventional treatments in ameliorating affective symptoms, these interventions often yield suboptimal improvements in cognitive impairments, thus highlighting a critical unmet clinical need. While rTMS has shown promise for treating depressive symptoms and some cognitive domains in MDD, there remains a relative scarcity of research specifically examining the effects of rTMS on attention in this population. Considering the well-documented role of the DLPFC in both affective regulation and cognitive processing, rTMS, a technique that directly targets this neural substrate, presents a potentially efficacious therapeutic modality.

2. Objectives

This study was designed to evaluate the effectiveness of rTMS in enhancing attentional and short-term memory performance in individuals diagnosed with MDD, addressing this identified gap in the existing literature.

3. Methods

This research implemented a quasi-experimental, pretest-posttest control group design, conducted in Yazd, Iran, during 2023. The target population encompassed all individuals, aged 20 to 50 years, diagnosed with MDD, and residing within Yazd, Iran, during the year 2023. Participants were recruited from individuals attending clinics and rehabilitation centers in Yazd. A simple randomization method, using a computer-generated random number sequence, was employed to allocate participants to either the experimental or control group (n = 15 per group). The sample size was determined using a power analysis with G*Power software, setting the desired power at 0.80 and alpha at 0.05, which indicated a minimum sample size of 30 participants to detect a medium effect size.

Participants were selected based on the following inclusion criteria: age between 20 and 50 years, a psychiatrist-confirmed diagnosis of MDD according to DSM-5 criteria, provision of written informed consent, absence of concurrent therapies other than stable Selective Serotonin Reuptake Inhibitor (SSRI) treatment, and the absence of comorbid psychiatric disorders. Exclusion criteria included any neurological conditions (e.g., epilepsy, history of head injury), any contraindication to rTMS (e.g.,

metal implants in the head, pacemaker), pregnancy, substance use disorders, and unstable medical conditions.

To ensure ethical considerations, all prospective participants were thoroughly informed about the study's objectives, procedures, potential risks and benefits, and their right to withdraw without prejudice. Participants were provided written informed consent, affirming their full comprehension of this information and their voluntary decision to partake in the research. The study's design and procedures were approved by the University Ethics Committee.

The Wechsler Memory Scale was administered as a pretest to assess baseline short-term memory and attentional performance. Both the experimental and control groups continued their antidepressant medication (SSRI) regimen; however, the experimental group additionally underwent ten sessions of 5Hz rTMS targeting the left dorsolateral prefrontal cortex (DLPFC). The rTMS was administered at an intensity of 120% of the resting motor threshold, with each session consisting of 3000 pulses delivered in 20 trains of 150 pulses each, with an inter-train interval of 30 seconds. Each session lasted approximately 20 minutes. The sham rTMS procedure for the control group involved the same coil placement and session duration, but the coil was angled away from the scalp at 90 degrees, delivering a minimal amount of magnetic stimulation and producing the same clicking sound as the active rTMS to maintain blinding. Following the completion of the treatment sessions, a posttest assessment using the Wechsler Memory Scale was conducted.

3.1. Measure

The Wechsler Memory Scale (WMS) is a widely utilized neuropsychological assessment tool designed to evaluate various aspects of memory functioning, including attention and short-term memory, which are critical variables in cognitive research. Developed by David Wechsler, the WMS has undergone several revisions, with the most recent being the WMS-IV, tailored to assess memory capacities across diverse populations. In the context of attention and short-term memory, the WMS includes subtests such as the Digit Span, which measures an individual's ability to focus attention and briefly retain numerical sequences, and the Spatial Span, which evaluates visuospatial short-term memory and attentional control. These subtests provide quantitative data that researchers can analyze to understand how attention influences the encoding and retrieval processes of short-term memory.[31] The WMS's standardized format and robust psychometric properties make it a valuable instrument for both clinical and experimental studies, offering insights into the interplay between attentional mechanisms and short-term memory performance across age groups and neurological conditions.[32]

3.2. Statistical Analysis

The obtained data were analyzed using SPSS-27 software and employing analysis of covariance (ANCOVA).

4. Results

The participants in this study consisted of 30 individuals diagnosed with MDD, with a mean age of 43.65 ± 6.49 years. The sample included 18 females (60%) and 12 males (40%). Regarding education, 20 participants (66.7%) had completed at least a high school education, eight (26.7%) held a bachelor's degree, and two (6.7%) had postgraduate qualifications. At the pre-test, the experimental group showed a mean score of 15.31 (SD = 3.24) for attention and 41.35 (SD = 7.31) for short-term memory. Following the rTMS intervention, the post-test scores for the experimental group were 22.18 (SD = 4.41) for attention and 53.69 (SD = 9.12) for short-term memory. In the control group, the pre-test mean scores were 15.24 (SD = 3.07) for attention and 39.42 (SD = 6.65) for short-term memory, while the post-test mean scores were 14.89 (SD = 2.89) for attention and 40.77 (SD = 7.09) for short-term memory (Table 1).

Table 1. Means and SD of Attention and Short-term Memory in Experimental and Control Groups at Pre-test and Post-test

Variables	Phases	Experimental group		Control group	
		Mean	SD	Mean	SD
Attention	Pre-test	15.31	3.24	15.24	3.07
	Post-test	22.18	4.41	14.89	2.89
Short-term memory	Pre-test	41.35	7.31	39.42	6.65
	Post-test	53.69	9.12	40.77	7.09

Table 2. The Outcomes of the Kolmogorov-Smirnov Test

Variables	Phases	Experimental group		Control group	
		K-S	*P*	K-S	*P*
Attention	Pre-test	0.25	0.231	0.19	0.200
	Post-test	0.19	0.212	0.22	0.181
Short-term memory	Pre-test	0.26	0.211	0.18	0.172
	Post-test	0.23	0.274	0.22	0.181

To ascertain the normality of score distributions within the experimental and control groups, the Kolmogorov-Smirnov test was employed in this study. The outcomes of the Kolmogorov-Smirnov test, pertaining to the research variables, are detailed in Table 2. The Kolmogorov-Smirnov test results revealed non-significant

K-S statistics (P>0.05) for all study variables across both the experimental and control groups at both the pretest and posttest assessments, indicating that the score distributions did not significantly deviate from normality. This finding of normality is crucial as it supports the validity of using ANCOVA for subsequent statistical analysis, as ANCOVA assumes that the residuals are normally distributed. Furthermore, Levene's test was utilized to evaluate the assumption of homogeneity of variances between the experimental and control groups. The results demonstrated that the assumption of homogeneity of variances was satisfied.

Table 3. Analysis of Covariance (ANCOVA) Results for Attention and Short-term Memory

Variables	SS	df	MS	F	*P*	η^2
Attention	249.38	1	249.38	21.58	0.001	0.82
Short-term memory	273.80	1	273.80	21.86	0.001	0.87

Table 3 presents the results of an ANCOVA examining the effects of the intervention on attention and short-term memory, controlling the potential covariates. Findings reveal statistically significant differences between the experimental and control groups for both attention (F = 21.58, P = 0.001, η^2 = 0.82) and short-term memory (F = 21.86, P = 0.001, η^2 = 0.87). The large effect sizes (η^2), indicated by 0.82 for attention and 0.87 for short-term memory, demonstrate that a substantial proportion of the variance in these cognitive domains is attributable to the rTMS intervention. These large effect sizes signify a strong and meaningful impact of rTMS on attention and short-term memory, beyond mere statistical significance, suggesting that the intervention has a noteworthy practical influence on cognitive improvement in patients with MDD. These results demonstrate a clear and robust effect of the intervention on both attention and short-term memory performance.

5. Discussion

The present investigation sought to determine the extent to which rTMS could enhance attentional capacity and short-term memory performance in individuals with a diagnosis of MDD. The present findings revealed that rTMS significantly enhanced attentional performance in patients diagnosed with MDD. This result corroborates previous research, notably the work of Asbaghi et al.,[28] which demonstrated the capacity of rTMS to ameliorate cognitive deficits associated with depressive disorders. Previous studies[30,33] affirm the efficacy of rTMS interventions. Mechanistically, attention can be conceptualized as a cognitive and behavioral process that selectively prioritizes specific aspects of internal or external information, utilizing both top-down voluntary and bottom-up automatic mechanisms to facilitate the processing or inhibition of diverse sensory inputs. Attention critically influences other cognitive domains, including memory, language, and problem-solving, reflecting the intricate interplay of distributed neural networks. Frontal brain regions, particularly the DLPFC, are instrumental in attentional tasks. Neuroimaging studies have consistently implicated the DLPFC in executive functions, especially selective attention. Specifically, functional Magnetic Resonance Imaging (fMRI) investigations have shown that the posterior DLPFC is activated during dual-task divided attention conditions, suggesting its role in managing the increased working memory demands of divided attention compared to selective attention.

Repeated rTMS application can induce neuroplastic changes in brain function, particularly within neural circuits engaged in attentional processing. The precise mechanisms by which rTMS enhances attention and memory involve the modulation of synaptic plasticity and neural connectivity within the DLPFC. rTMS is thought to induce Long-Term Potentiation (LTP)-like effects, strengthening synaptic connections between neurons and facilitating more efficient neural communication. This enhancement of synaptic efficacy in the DLPFC can improve the processing and maintenance of information relevant to attentional tasks, as well as enhance working memory capacity. Furthermore, rTMS can modulate the release of neurotransmitters, such as glutamate and GABA, which are crucial for synaptic plasticity and cognitive function. By modulating cortical excitability and inducing lasting effects, rTMS has emerged as a valuable neuroscience tool for temporarily perturbing and investigating specific brain functions.[34]

The present study also demonstrated the efficacy of rTMS in enhancing short-term memory function among patients diagnosed with MDD. These results align with the findings reported by Kazemi et al.,[27] who observed that rTMS application facilitated improved concentration in MDD patients via magnetic stimulation. Similarly, Asbaghi et al.[28] documented rTMS-induced enhancements in working memory within a bipolar disorder population. Furthermore, the observed improvements in short-term memory are consistent with Tang et al.'s[30] report of rTMS's positive impact on executive function. To elucidate this finding, it is pertinent to note that MDD is a significant contributor to individual disability, characterized by cognitive impairments alongside affective and behavioral symptoms. These cognitive deficits, often manifested as impairments in domains such as working memory and attention, are frequently accompanied by a negative cognitive bias towards social or environmental stimuli. Notably, existing literature indicates that cognitive impairments associated with MDD can persist

even following the resolution of affective and behavioral symptoms.[35]

Cognitive impairments observed in MDD are significantly associated with functional limitations in activities of daily living, adversely affecting overall performance, diminishing work productivity, and reducing workplace efficiency. Prior research has consistently demonstrated that cognitive dysfunction in MDD patients can persist even following optimal symptom management and clinical recovery. While a universally accepted definition of treatment-resistant depression remains elusive, the most widely adopted criterion defines it as a condition where "there is no response to at least two distinct and appropriate antidepressant treatments administered at adequate doses and durations." rTMS represents a viable alternative therapeutic modality for treatment-resistant depression. The capacity of rTMS to modulate cortical excitability suggests its potential utility in remodeling cortical networks, thereby influencing cognitive function. Consequently, rTMS is recognized as a non-invasive neuromodulatory brain stimulation technique that specifically targets the glutamatergic neurotransmitter system.[36] Contemporary studies have provided evidence that rTMS can enhance cognitive performance across various domains, including concentration, executive functions, working memory, and long-term verbal memory. Given the pivotal role of the glutamatergic system in memory formation and consolidation, and the pronounced impact of rTMS on this system, it is plausible that rTMS can effectively improve the memory function in individuals with MDD.

This study investigating the rTMS effects on attention and short-term memory in MDD has several limitations. Firstly, using a convenience sample from Yazd clinics limits the findings' generalizability to diverse MDD populations with different demographics or cultural backgrounds. The small sample size also restricts statistical power, potentially obscuring subtle effects and further limiting generalizability. While SSRI use and comorbid psychiatric disorders were controlled, potential interactions between rTMS and SSRIs, and the influence of varying illness severity or duration, were not examined. Future research should explore these factors for a more comprehensive understanding of rTMS effects. The study's reliance on the Wechsler Memory Scale, though valid, offers a narrow assessment of cognitive function. Incorporating a broader range of neuropsychological tests in future research would provide a more complete cognitive profile. Crucially, the study design focused on immediate post-treatment outcomes, leaving the long-term sustainability of cognitive improvements unclear. Longitudinal studies with follow-up assessments are essential to determine the durability of rTMS effects on attention and memory, which is vital for informing clinical practice and treatment planning. Addressing these limitations will strengthen future research and enhance the clinical applicability of rTMS for cognitive enhancement in MDD.

6. Conclusion

In conclusion, this study provides compelling evidence that rTMS targeting the DLPFC can significantly improve attentional and short-term memory functions in patients with MDD. These findings support the hypothesis that rTMS exerts a beneficial neuromodulatory effect on cognitive circuits implicated in MDD, demonstrating its potential as a viable and targeted therapeutic intervention for addressing cognitive deficits associated with this disorder. Clinically, rTMS offers a non-invasive and generally well-tolerated treatment option. Patient suitability for rTMS involves considering factors such as the absence of contraindications (e.g., metallic implants, epilepsy), the patient's medical history, and their willingness to adhere to the treatment protocol. In terms of treatment sequencing, rTMS can be used as a monotherapy, adjunctively with pharmacotherapy or psychotherapy, or as a sequential treatment following inadequate response to other interventions. However, it is important to acknowledge the study's limitations, including the convenience sampling method, relatively small sample size, and lack of long-term follow-up. Despite these limitations, the significant cognitive enhancements observed following rTMS highlight its promise as a clinical tool for improving cognitive function in MDD.

Research Highlights

What Is Already Known?

MDD is known to cause cognitive deficits, including impaired attention and short-term memory, alongside mood symptoms. rTMS is an established treatment for improving mood in MDD, particularly when targeting the dorsolateral prefrontal cortex (DLPFC), but its cognitive effects are less studied.

What Does This Study Add?

This study demonstrates that 5Hz rTMS targeting the left DLPFC significantly enhances attention and short-term memory in MDD patients. Using a controlled design and the Wechsler Memory Scale provides evidence that rTMS can mitigate cognitive impairments, suggesting a broader therapeutic role beyond mood improvement.

Author Contributions

Authors contributed equally to this work.

Conflict of Interest Disclosures

All authors declared that they have no conflict of interest.

Ethical Approval

This study was approved under the ethical approval code of IR.IAU.YAZD.REC.1403.043.

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