



Repetitive Transcranial Magnetic Stimulation Bilateral as Adjuvant Therapy for Improvement of Cognitive Function in Patients with Bipolar Disorder

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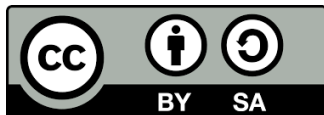
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Abstract

Cognitive impairment in bipolar disorder can persist despite mood stabilization, highlighting the need for adjunctive interventions targeting cognitive difficulties. This study evaluated the effectiveness of bilateral repetitive transcranial magnetic stimulation (rTMS) as an adjunctive treatment for reducing subjective cognitive complaints in patients with bipolar disorder. This quasi-experimental study with repeated assessments included 28 hospitalized patients at Dr. Arif Zainudin Hospital, Surakarta, between January and March 2026. Participants were recruited using purposive sampling and allocated alternately to the intervention and control groups, with 14 patients in each group. The intervention group received standard therapy plus 10 sessions of sequential bilateral rTMS targeting the dorsolateral prefrontal cortex (DLPFC), whereas the control group received standard therapy alone. Subjective cognitive complaints were assessed using the Cognitive Complaints in Bipolar Disorder Rating Assessment (COBRA) at baseline, midpoint, and treatment completion; depressive and manic symptoms were also assessed. Repeated-measures analyses, between-group comparisons, and regression analyses were performed. Mean COBRA scores decreased from 22.64 to 12.50 in the rTMS group and from 22.57 to 19.07 in the control group. The between-group difference in improvement was 6.64 points ($p < 0.001$; Cohen's $d = 3.027$). Changes in depressive and manic symptoms were not significantly associated with improvements in cognitive complaints. One participant reported a headache. These findings suggest that bilateral rTMS may reduce subjective cognitive complaints in patients with bipolar disorder. However, baseline differences in depressive symptoms, nonrandom allocation, reliance on subjective cognitive assessment, and the short follow-up period warrant larger randomized controlled trials incorporating objective neurocognitive assessments before definitive clinical recommendations can be made.



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INTRODUCTION

Bipolar disorder is a chronic mental disorder characterized by recurrent episodes of mania, hypomania, and depression and is a major cause of disability worldwide (World Health Organization, 2025). Epidemiologically, its global prevalence has been estimated at approximately 2.4% (Léda-Rêgo et al., 2024). Global data indicate that bipolar disorder affects millions of individuals worldwide and contributes substantially to the burden of disease in terms of incidence, prevalence, and disability-adjusted life years (DALYs) (World Health Organization, 2025; Liu et al., 2026). In Indonesia, although epidemiologic data remain limited, reports from Bipolar Care Indonesia indicate an increasing number of reported cases in recent years (Jubail & Nadia, 2024). These findings underscore bipolar disorder as a significant mental health condition requiring comprehensive and sustained management.

Bipolar disorder is characterized not only by mood symptoms, which have traditionally been the primary focus of clinical management, but also by cognitive impairment that is increasingly recognized as a persistent and clinically relevant feature affecting patients' psychosocial functioning and quality of life (Huang et al., 2023; Sun et al., 2026). Cognitive deficits may involve working memory, executive function, attention, processing speed, and verbal memory and can persist even during euthymia (Huang et al., 2023; Tian et al., 2025). Consequently, some patients may not return to their premorbid level of functioning despite improvement in mood symptoms (Nicoloso-SantaBarbara et al., 2023). Nevertheless, the assessment and management of cognitive impairment are often overlooked because clinical practice tends to prioritize mood stabilization (Sun et al., 2026; Wu et al., 2024).

Standard pharmacologic treatments for bipolar disorder are effective in controlling mood symptoms, but their benefits for cognitive impairment remain limited (Johnson et al., 2023; Sun et al., 2026). Moreover, some treatment-related adverse effects may negatively affect cognitive performance, particularly memory, attention, and psychomotor speed (Johnson et al., 2023; Sabtiari et al., 2025). These limitations highlight the need for adjunctive nonpharmacologic interventions that specifically target cognitive symptoms without substantially increasing systemic adverse effects. In this context, repetitive transcranial magnetic stimulation (rTMS) represents a potential therapeutic approach. However, the 2018 Canadian Network for Mood and Anxiety Treatments and International Society for Bipolar Disorders (CANMAT/ISBD) guidelines classify rTMS as a third-line adjunctive treatment for acute bipolar depression, indicating the need for further research on its potential role in addressing cognitive impairment in patients with bipolar disorder (Yatham et al., 2018).

Neuroimaging studies of bipolar disorder indicate that dysfunction within frontal and frontolimbic neural networks plays an important role in cognitive impairment and emotion regulation across mood states. Functional magnetic resonance imaging (fMRI) studies have demonstrated altered activity in frontal regions involved in emotion processing, reward processing, and working memory, with patterns varying across manic, depressive, and euthymic states (Mesbah et al., 2023). In addition, ventral prefrontal dysfunction appears to persist across mood states, whereas dorsal prefrontal dysfunction may be more dependent on the current mood state (Colic et al., 2024). These findings suggest that bipolar disorder involves dynamic dysfunction of prefrontal neural systems underlying cognitive impairment and emotion regulation, providing a neurobiological rationale for targeting prefrontal regions with therapeutic neuromodulation.

Given the involvement of prefrontal neural systems in cognitive impairment associated with bipolar disorder, neuromodulation targeting the dorsolateral prefrontal cortex (DLPFC) has a plausible neurobiological rationale. One potential intervention is sequential bilateral rTMS of the DLPFC, combining low-frequency stimulation of the right DLPFC with high-frequency stimulation of the left DLPFC, an approach that has been investigated in patients with bipolar depression (Kazemi et al., 2018; Cai et al., 2025). This approach is intended to modulate cortical excitability and functional connectivity across prefrontal networks, while evidence suggests that high-frequency rTMS can modulate functional brain connectivity and neuroplasticity (Tian & Izumi, 2022; Guan et al., 2025).

Meta-analyses have indicated that bilateral rTMS may be effective and generally well tolerated as an adjunctive treatment for depressive disorders. However, evidence regarding its effects on cognitive outcomes in patients with bipolar disorder remains limited and inconsistent (Kazemi et al., 2018; Cai et al., 2025; Sun et al., 2026). Most previous studies have also employed unilateral stimulation protocols and focused primarily on mood symptoms rather than cognitive outcomes as the principal endpoint (Adu et al., 2022; Sciortino et al., 2021). Therefore, this study aimed to evaluate the effectiveness of bilateral rTMS as an adjunctive therapy for improving cognitive complaints in patients with bipolar disorder. The findings are expected to contribute to the evidence base for developing more comprehensive, multidomain therapeutic strategies for bipolar disorder.

METHOD

Design, Location, and Research Time

This quantitative study employed a quasi-experimental, two-group pretest–posttest control design with repeated measures. Cognitive complaints were assessed at three time points (T1, T2, and T3) in the sequential bilateral rTMS intervention group receiving rTMS as an adjunct to standard therapy and in the control group receiving standard therapy alone. The study was conducted at Dr. Arif Zainudin Hospital, Surakarta, from January to March 2026.

Research Subject

The target population was patients with a diagnosis of bipolar disorder who were hospitalized at Dr. Arif Zainudin Hospital Surakarta. Inclusion criteria: aged 18-60 years, diagnosed with bipolar disorder by a psychiatrist after the age of 18 years, cooperative undergoing rTMS procedures and repeated clinical evaluations, receiving standard treatment, and no rTMS contraindications. Exclusion criteria: history of epilepsy/seizures, incompatible metal/electronic implants in the head/neck/intracranial, significant neurological abnormalities, pregnancy, and uncooperative patients. The sampling technique used nonprobability sampling using the purposive sampling method; subjects with odd sequence numbers were allocated to the intervention group and even sequence numbers to the control group.

The sample size was calculated using a two-group comparative hypothesis test formula, resulting in 13 subjects per group which was rounded up to 14 subjects per group, resulting in a total of 28 subjects (14 intervention groups, 14 control groups).

Research Variables

The independent variable was bilateral rTMS as adjuvant therapy (alternating stimulation in right/inhibitory DLPFC 1 Hz and left/excitatory DLPFC 10 Hz, 10 sessions over 10 consecutive working days, intensity 100-110% motor threshold). The primary bound variable was cognitive function, measured by Cognitive Complaints in Bipolar Disorder Rating Assessment (COBRA; score 0-48, higher score = more severe cognitive complaints, score <14 = impaired cognitive function). Secondary bound variables were depressive symptoms (MADRS) and mania symptoms (YMRS). Confounding variables identified included age, sex, pharmacotherapy regimen, severity of initial symptoms, marital status, education, and length of illness.

Research Instruments and Procedures

The research instruments included informed consent sheets, identity and demographic data sheets, and COBRA, MADRS, and YMRS sheets. After obtaining ethical permission, subjects who met the criteria underwent screening, informed consent, and demographic-clinical data completion. Initial measurements (T1) were taken before the first rTMS session (intervention group) or on day 0 (control group). The intervention group received 10 sessions of bilateral rTMS (right DLPFC 1 Hz/1800 pulse then left DLPFC 10 Hz/2000 pulse, each session of 20-30 minutes), while the control group received standard therapy without rTMS but was monitored at comparable time intervals. Middle measurement (T2) was taken after 5 rTMS sessions were completed, and final measurement (T3) was taken 2 hours after the 10th session was completed (or day 10 in the control group). Side effects were systematically recorded at each evaluation session/visit.

Data Analysis Techniques

Data normality test was conducted using Shapiro-Wilk. The odds ratio (OR) to 95% CI was calculated from contingency table 2×2 to compare the proportion of achievement of unimpaired cognitive function (COBRA <14) between groups. Changes in COBRA scores over time (T1→T2→T3) in each group were tested by Repeated Measures ANOVA (normal data) or Friedman Test (abnormal data). The difference in score change (Δ C1-T2, Δ T2-T3, Δ T1-T3) compared between groups was using the Independent t-test (normal data) or the Mann-Whitney U test (abnormal data). The magnitude of the influence of bilateral rTMS on Δ T1-T3 was analyzed by simple linear regression (after testing the assumption of residual normality, homokedasticity, and homogeneity of variance/Levene). The effect of mood change (Δ MADRS, Δ YMRS) on Δ COBRA was analyzed by multiple linear regression. The $p < 0.05$ was considered statistically significant.

RESULTS AND DISCUSSION

Demographic and Clinical Characteristics of the Subject

The characteristics of the 28 study subjects (14 intervention groups, 14 control groups) are presented in Table 1 below.

Table 1. Demographic and Clinical Characteristics of Research Subjects

Characteristics	Intervention (n=14)	Control (n=14)	p
Age (years), mean±SD	29.5 ± 10.2	29.1 ± 5.7	0,891
Gender: Female	50,0%	64,3%	0,704
Status: Unmarried	78,6%	57,1%	0,420
Education: The most high schools/vocational schools	28,6%	71,4%	0,247
Duration of Illness ≥ 1 year	92,9%	78,6%	0,622
Side Effects (headache)	7,1%	0%	-
Antipsychotic Therapy	85,7%	85,7%	-
COBRA Baseline Score, mean±SD	22.64 ± 1.82	22.57 ± 1.83	0,918
YMRS Baseline Score, mean±SD	12.36 ± 2.90	11.86 ± 2.51	0,630
MADRS Baseline Score, mean±SD	17.71 ± 2.43	12.57 ± 2.41	< 0.001

Source: Primary Data, 2026

The baseline characteristics of the two groups were relatively similar ($p > 0.05$) on all variables except the MADRS baseline score ($p < 0.001$, the intervention group was higher), and side effects during the intervention were minimal (only 1 subject reported headache).

Normality Test and Comparison of COBRA Scores Between Groups

The results of the Shapiro-Wilk normality test showed that all COBRA and Δ COBRA scores in the two groups were normally distributed ($p > 0.05$), so parametric analysis could be used. A comparison of COBRA scores and odds ratios of cognitive function improvements at each time of measurement is presented in Table 2 below.

Table 2. Comparison of COBRA Scores and Odds Ratios of Improvement in Cognitive Function Between Groups

Time	Intervention (mean $\pm$ SD)	Control (mean $\pm$ SD)	Average Difference	p	GOLD (95% CI)
T1 (Initial)	22.64 $\pm$ 1.82	22.57 $\pm$ 1.83	0,07	0,918	-
T2 (Middle)	16.71 $\pm$ 2.52	20.43 $\pm$ 2.17	-3,71	< 0.001	2,5 (0,937-4,063)
T3 (End)	12.50 $\pm$ 2.98	19.07 $\pm$ 2.81	-6,57	< 0.001	4,5 (2,906-6,093)

At the baseline (T1), there was no significant difference in COBRA scores between groups ($p = 0.918$). At the middle (T2) and late (T3) measurements, the intervention group showed significantly lower COBRA scores than controls ($p < 0.001$ in both), with the OR of cognitive function improvement increasing from 2.5 (T2) to 4.5 (T3).

Changes in COBRA Scores within and Between Groups

The change in COBRA score from T1 to T3 in each group, as well as the comparison of the difference in change (Δ COBRA) between groups at each time interval, are presented in the following Table 3.

Table 3. Change in COBRA Score in Groups and Comparison of Change Differences (Δ COBRA) Between Groups

Groups	T1 (Initial)	T2 (Middle)	T3 (End)	p (in a group)
Intervention	22.64 $\pm$ 1.82	16.71 $\pm$ 2.52	12.50 $\pm$ 2.98	< 0.001
Controls	22.57 $\pm$ 1.83	20.43 $\pm$ 2.17	19.07 $\pm$ 2.81	< 0.001

Interval	Intervention (mean $\pm$ SD)	Control (mean $\pm$ SD)	Average Difference	p	Cohen's d
Δ T1-T2 (early-mid)	5.93 $\pm$ 1.44	2.14 $\pm$ 1.41	3,79	< 0.001	2,661
Δ T2-T3 (mid-end)	4.21 $\pm$ 0.70	1.36 $\pm$ 1.01	2,86	< 0.001	3,293
Δ T1-T3 (early-end)	10.14 $\pm$ 2.07	3.50 $\pm$ 2.31	6,64	< 0.001	3,027

Both groups experienced significant changes in COBRA scores over time ($p < 0.001$), but the intervention group showed much greater improvement across all ranges, with a mean difference in Δ COBRA T1-T3 of 6.64 points (Cohen's $d = 3.027$, classified as a very large effect size).

Regression Analysis: The Influence of Bilateral rTMS and Mood Symptoms

The results of the analysis of simple linear regression (the effect of the research group on Δ COBRA T1-T3) and multiple linear regression (the effect of Δ MADRS and Δ YMRS on Δ COBRA T1-T3) are presented in Table 4 below.

Table 4. Results of Simple and Multiple Linear Regression

Analysis	Variable	B (95% CI)	p
Simple Regression	Group (rTMS bilateral vs control)	-6,643 (-8,323 to -4,963)	< 0.001
Multiple Regression	Δ MADRS	-0.025 (-0.873 to 0.823)	0,951
	Δ YMRS	-0.284 (-1.368 to 0.800)	0,595

The study group had a significant effect on Δ COBRA T1-T3 ($B = -6.643$; $p < 0.001$), confirming that bilateral rTMS significantly improved improvement in cognitive function compared to controls. In contrast, neither changes in MADRS (depressive symptoms) nor YMRS (mania symptoms) scores had a significant effect on Δ COBRA ($p = 0.951$ and $p = 0.595$), indicating that improvement in cognitive function was relatively independent of changes in affective symptoms.

Demographic and Clinical Characteristics of the Subject

The mean ages of both groups (29.5 and 29.1 years) are in line with the epidemiological characteristics of bipolar disorder which generally appear in late adolescence to young adulthood and occur recurrent with functional burden remaining during productive age (Kalman et al., 2021). The balanced gender distribution is in line with global epidemiological data, although some studies report that women tend to have a slightly higher burden of disease (Lai et al., 2023; Zhong et al., 2024). The majority of subjects are unmarried, consistent with bipolar disorder that is prevalent in young adults and can interfere with interpersonal function and relationship stability (Zhong et al., 2024; Zhan et al., 2025; Solmi et al., 2022). The duration of the illness ≥ 1 year in the majority of subjects reflects the characteristics of bipolar disorder as a chronic-recurrent condition (Esaki et al., 2021; Oliva et al., 2024).

Minimal side effects (only 1 case of headache) demonstrate a good and tolerable safety profile of bilateral rTMS, consistent with the literature that headache is the most frequent rTMS side effect although generally mild-moderate (Hett & Marwaha, 2020), with variations in individual intensity may be explained by peripheral nerve activation and scalp muscle contraction in the coil area, or lower pain sensitivity in certain individuals (Rajain et al., 2023; Overvliet et al., 2021). The pattern of pharmacological therapy (dominant antipsychotic, low antidepressant) reflects the standard clinical practice of inpatient acute phase bipolar management, where antidepressants are administered with caution because they risk triggering mood shifts toward mania when not combined with mood stabilizers/antipsychotics (Singh et al., 2025; Oliva et al., 2024).

Effectiveness of Bilateral rTMS on Improvement of Cognitive Function

The regression coefficient of -6.643 showed that the intervention group experienced a much greater decrease in COBRA scores than the controls; because lower COBRA scores reflect better cognitive function, these findings indicate that bilateral rTMS has a positive effect on improving cognitive function in bipolar disorder patients. These findings are in line with

McIntyre et al. (2021) who reported the potential benefits of rTMS on cognitive function, particularly the verbal learning domain, although it has not shown significant improvement in all cognitive domains.

Cognitive Improvement Independence from Changes in Affective Symptoms

The absence of a meaningful effect of Δ MADRS and Δ YMRS on Δ COBRA indicates that improvements in cognitive function in bipolar disorder patients do not always run in parallel with changes in affective symptoms. These findings are in line with the literature that reports that cognitive deficits in bipolar disorder can persist even in the euthymic phase and are relatively stable, so stabilization of affective symptoms through standard therapies is not necessarily sufficient to result in optimal cognitive recovery (Kesavan et al., 2025; Nicoloso-SantaBarbara et al., 2023). Neurobiologically, this can be explained by the differences in underlying brain tissue between the two domains: affective symptoms are more related to limbic circuits (amygdala, hippocampus), while cognitive function primarily involves DLPFC and the Central Executive Network (CEN); although both systems interact with each other, changes in mood domains are not always commensurate with changes in cognitive domains (Bi et al., 2022; Kishi et al., 2024; Mesbah et al., 2023). The COBRA instrument itself assesses patients' perceptions of daily cognitive abilities including executive function, attention, memory, and information processing speed (Lima et al., 2018; Lin et al., 2019; Nicoloso-SantaBarbara et al., 2023), supporting that cognitive function is a relatively independent clinical domain and needs special attention, not just as a consequence of mood swings.

Advantages and Limitations of Research

The strengths of this study include a specific focus on bilateral rTMS as an adjuvant therapy for the improvement of cognitive function (different from many previous studies that focused more on mood symptoms and a unilateral approach), as well as a pretest-posttest control group design with three measurement points (beginning, middle, end) that allows for gradual observation of cognitive changes. The limitations of the study include: sampling at a single location with a limited number of subjects (affecting the generalization of results), the use of subjective/self-report (COBRA) cognitive assessment instruments that can be influenced by emotional states and other psychological factors, and the relatively short duration of follow-up that does not allow for the evaluation of the sustainability of the effects of rTMS on cognitive function in the long term.

CONCLUSION

Bilateral rTMS as an adjunctive therapy showed potential for reducing subjective cognitive complaints in patients with bipolar disorder. The findings of this study support the importance of considering cognitive symptoms as a therapeutic target in the management of bipolar disorder alongside affective symptoms. However, because evidence regarding the use of rTMS in bipolar disorder remains limited and stimulation protocols have not been fully standardized, the clinical implications of these findings should be interpreted cautiously. Therefore, these results should be regarded as preliminary evidence supporting the potential role of bilateral rTMS as an adjunctive intervention for cognitive complaints rather than as a basis for definitive clinical recommendations.

From a clinical perspective, these findings provide preliminary support for considering rTMS within a comprehensive adjunctive treatment approach, particularly for patients with bipolar disorder who continue to experience cognitive complaints despite standard treatment. From a scientific perspective, this study contributes to the limited literature on bilateral rTMS in bipolar disorder, particularly regarding cognitive outcomes, and provides a basis for further investigation using more rigorous study designs, standardized stimulation protocols, and objective neurocognitive assessments.

Future research should employ randomized controlled, multicenter designs with larger and more representative samples to improve external validity and generalizability. Longer follow-up periods and objective neuropsychological assessments should also be incorporated to determine the durability of cognitive changes and establish whether improvements in subjective cognitive complaints correspond to measurable improvements in cognitive performance.

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CONFLICT OF INTEREST

The author states that this research was conducted without any commercial or financial relationship that can be interpreted as a potential conflict of interest.

AUTHOR CONTRIBUTION

The author fully contributes to the formulation of the main idea, collects library data, analyzes and interprets the primary text of the figure, and prepares the manuscript. All authors have agreed on the final version of the manuscript.

GENERATIVE ARTIFICIAL INTELLIGENCE USAGE STATEMENT

The author states that generative artificial intelligence (AI) was used in the preparation of this manuscript. The author acknowledges the use of generative AI to help improve language clarity and improve the grammatical structure of the manuscript. The use is done in compliance with the applicable ethical guidelines regarding the use and disclosure of generative AI in scientific research. Each author has made substantial intellectual contributions to this work. The entire manuscript content has been carefully reviewed to ensure its accuracy, and the author is solely responsible for the integrity and final content of the manuscript.

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