ORIGINAL ARTICLE

Psychiatry and Clinical Psychopharmacology 2020;30(4):346-353
DOI:10.5455/PCP.20200221124442

Cognitive Improvements from Adjunct Therapy with Transcranial Magnetic Stimulation are Short-Lived In Patients with Remitted Bipolar Disorder

Ying Wang [a*], **Chuanxin Liu** [b*], **Tao Fang** [c*], **Xiaodong Lin** [d], **Deguo Jiang** [d], **Jingjing Zhu** [d], **Chunjun Zhuo** [c], **Jiaen Ye** [d]

[a] *Tianjin Anding Hospital, Department of Psychiatric-Neuroimaging-Genetics and Comorbidity Laboratory;* [b] *School of Mental Health, Jining Medical University Department of Biological Psychiatry;* [c] *The Fourth Center Hospital of Tianjin, Department of Radiology;* [d] *Wenzhou Seventh People's Hospital, Department of Psychiatry and Neuroimaging Centre, Wenzhou, China*

Abstract

Background: Repetitive transcranial magnetic stimulation (rTMS) has been used as an adjunct therapy to improve the cognitive abilities of patients with remitted bipolar disorder (BPD). This is accomplished through functional brain activity alterations. However, there is limited information about the duration and persistence of cognitive improvements. In the current study, we investigated the long-term (four weeks) cognitive effects of adjunct treatment with rTMS in patients with remitted BPD.

Methods: wenty-one patients with remitted BDP were enrolled in the study. rTMS was used in patients for four weeks. Global functional connectivity density (gFCD) was used to assess the alterations in brain activity before and after rTMS. The MATRICS Consensus Cognitive Battery (MCCB) was used to evaluate the cognitive abilities of patients before and after rTMS.

Results: Compared to the baseline, cognitive improvements were detected in patients at the end of two weeks of treatment, as determined through increased MCCB scores. Increases in gFCD were observed in the frontal cortex, inferior temporal lobe, and parietal lobe. However, the MCCB scores remained stable during the third week of treatment and began to decline by four weeks post-treatment. Similarly, the increased gFCD values also declined to nearly baseline values by the fourth week post-treatment.

Conclusions: High frequency rTMS can improve the cognitive abilities of patients with remitted BPD rapidly; however, the beneficial effects are short-lived and begin to disappear by three weeks after treatment. The brain activity alterations induced by rTMS also increased initially, followed by substantial declines, suggesting that desensitization or exhaustion may play a role. Further studies are needed to determine the optimal method for maintaining long-term cognitive improvements in patients with remitted BPD.

ARTICLE HISTORY

Received: Feb 21, 2020
Accepted: Jun 20, 2020

KEYWORDS: bipolar disorder, transcranial magnetic stimulation, global functional connectivity, cognitive function, desensitization, exhaustion

INTRODUCTION

Patients with bipolar disorder (BPD) display a wide array of cognitive impairments, ranging from delayed processing speeds to impeded visual and verbal learning [1]. However, none of the cognitive impairments found in patients with BPD have been associated with the state of the disease. For example, cognitive impairment profiles are similar between symptomatic and non-symptomatic patients with BPD, as well as between patients with different types of BPD, such as type 1 and type 2 BPD [2,3]. The prevalence of cognitive impairment in BP is high, with executive function impairments being the most prevalent at 5-58%, followed by attention/working memory impairments at 10-52%, speed/reaction time impairments at 23-44%, verbal memory impairments at 8-42%, and visual memory impairments at 12-33% [4,5]. Cognitive impairments have also been found to increase the progression of other disease symptoms in patients with BPD [6,7]. Considering the deleterious effects of cognitive impairments, researchers have aimed to improve the cognitive abilities of patients through adjunct therapy with repetitive transcranial magnetic stimulation (rTMS) [8].

Corresponding authors: Jiaen Ye and Chuanjun Zhuo, E-Mail: Jiaeny1999@163.com and chuanjunzhuotjmh@163.com

* These authors contributed equally to this work and are co-first authors.

To cite this article: Wang Y, Liu C, Fang T, Lin X, Jiang D, Zhu J, Zhuo C, Jiaen Ye J. Cognitive Improvements from Adjunct Therapy with Transcranial Magnetic Stimulation are Short-Lived In Patients with Remitted Bipolar Disorder. Psychiatry and Clinical Psychopharmacology 2020;30(4):346-353, DOI: 10.5455/PCP.20200221124442

In previous reports, rTMS has been associated with improvements in the cognitive functioning of patients with BPD [9, 10]. In addition, cognitive improvements have been linked to specific brain activity alterations. For example, bilateral rTMS was previously found to decrease the functional activity of the default mode network (DMN) and sensorimotor network (SMN), leading to the improvement of executive functioning and verbal memory [11]. In another study, rTMS was found to improve the cognitive control processing circuit [12]. Recently, Thomas-Ollivier *et al*. reported that rTMS could improve the verbal fluency and psychomotor retardation of patients with BPD [8]. In another study, Yang *et al*. found that rTMS could improve the Measurement and Treatment Research to Improve Cognition in Schizophrenia (MATRICS) Consensus Cognitive Battery, commonly known as the MCCB, category fluency subtest [13]. In combination, these previous demonstrate that rTMS may improve the cognitive functioning of patients with BPD by stimulating the bilateral or left dorsolateral prefrontal cortex (PFC). In general, high frequency rTMS stimulation of the dorsolateral PFC yielded substantial improvements in the cognitive functioning and psychomotor retardation of patients with BPD, with minimal safety concerns [9]. The cognitive improvements from rTMS may be due to altered brain activity in the cognitive – and memory-related functional networks, such as the DMN and central executive network (e.g., prefrontal lobe, insular lobe, temporal lobe, and hippocampus) [14, 15].

While some reports have demonstrated that rTMS may improve the cognitive functioning of patients of BPD, the majority of these studies observed short-term cognitive effects. To the best of our knowledge, no studies have assessed the persistent or long-term therapeutic effects of rTMS on the cognitive functioning of patients with BPD. In addition, the brain activity alterations associated with cognitive improvements have not been studied in these patients. Hence, in this pilot study, we aim to assess the persistent therapeutic effects of high frequency rTMS in patients with BPD, while also characterizing alterations in brain activity associated with the cognitive improvements. We hypothesize that high frequency rTMS can improve the cognitive functioning of patients with BPD for several weeks, and that cognitive improvements may be associated with specific functional brain alterations.

METHODS

Patients

For this study, 30 patients with BPD (type I) in clinical remission were obtained from Wenzhou Seventh Hospital Outpatient Center between July 2016 and December 2016. The average patient age was 30.8 ± 3.4 years (range: 22-36 years) and consisted of 60% males (n=18) and 40% females (n=12). Patient selection as accomplished using the inclusion and exclusion criteria outlined in Table 1. This study was approved by the Wenzhou Seventh People's Hospital's Ethics Committee (IRB date: 2016-01-20). Prior to the study, written informed consent was obtained from all of the participants. The clinicodemographic data of the patients were recorded.

Table 1. List of inclusion and exclusion criteria for this study.

No.	*Inclusion criteria*	*Exclusion criteria*
1	DSM diagnosis of BPD	Moderate-to-severe physical illnesses, such as respiratory, cardiovascular, endocrine, neurological, liver, or kidney disease
2	Maintain clinical remission during the entire study, with HAMD-17 score below 7 and YMRS score below 5	Received electroconvulsive therapy (ECT) within last three months
3	No contraindications to rTMS (e.g., epilepsy)	Loss of consciousness for more than 5 min due to any cause
4	No previous exposure to rTMS	Left-handedness (determined by the AHPQ)
5	No metal implants in any part of the body, including metal implants in the head or neck region, cardiac pacemakers, fixation elements, or artificial joints	History of ophthalmic diseases
6	No tattoos on any part of the body	High myopia
7	No history of neurologic or psychiatric disease or other health problems	Contraindications to magnetic resonance imaging (MRI), including claustrophobia
8	Right-handedness (based on the EHI)	IQ < 80
9	Normal or corrected-to-normal vision and normal color vision, as assessed by basic vision tests	
10	No major self-reported life events during the study period	
11	No alcohol or other substance abuse throughout the study period	

AHPF, Annett Hand Preference Questionnaire; BPD, bipolar disorder; DSM, Diagnostic and Statistical Manual of Mental Disorders, ECT, electroconvulsive therapy; EHI, Edinburgh Handedness Inventory; HAMD, Hamilton Rating Scale for Depression; IQ, Intelligence Quotient; rTMS, repetitive transcranial magnetic stimulation; YMRS, Young Manic Rating Scale.

rTMS Procedure

Each patient received one daily session of rTMS for four consecutive weeks. At the baseline and after each session, the patients were immediately evaluated for their cognitive abilities using the MCCB. In addition, magnetic resonance imaging (MRI) was performed after the second week of treatment. To ensure consistency between the patients, the dosages of mood stabilizers and other therapeutic agents were fixed during the study. Patients who experienced severe episodes of mania or depression that required immediate intervention were discarded from the study.

The rTMS was carried out in accordance with safety guidelines from previous studies [8-16]. The scalp locations of the abductor pollicis brevis and 5-cm site were found and traced on the swim cap with previously published movement visualization techniques [15,16]. Briefly, rTMS was applied over the left dorsolateral prefrontal cortex (DLPFC) using a figure-eight-shaped coil, which induced a maximum electrical field that peaks beneath the intersection of the two windings. The Magstim high-speed stimulator (Magstim Company Limited, Wales, UK) was used for delivering the treatment. The left DLPFC stimulation site was defined as the region 5-cm anterior from the area of the optimal site for the primary motor cortex of the left hemisphere, also known as the Pascual-Leone method.[16] This method was previously reported to accurately target the DLPFC area. The motor threshold (MT) was determined for each patient prior to treatment. The stimulation intensity was 110% of the motor threshold of the right abductor pollicis brevis muscle, and the stimulation frequency was constant at 10 Hz. The other stimulation parameters were: 45 trains with 3 sec duration and divided into three blocks, with an inter-train interval of 10 sec for each block. The inter-block interval was 20 sec, resulting in 1,350 pulses/session for approximately 10.5 min/day. Each treatment session was performed at the same time each day (9:00 am UTC+8) [16].

MRI Data Acquisition

The 3.0-Tesla MR system (Discovery MR750, General Electric, Milwaukee, WI, USA) was used in this study. Functional magnetic resonance imaging (fMRI) was performed using the GE Healthcare Discovery MR750 3T MRI system (General Electric, Milwaukee, WI, USA), with an eight-channel phased-array head coil. The patients were required to lay in a supine position and asked to restrict thoughts and head movements during the imaging session. The imaging parameters were: 2,000 msec repetition time (TR), 45 msec echo time (TE), 32 slices, 4-mm slice thickness, 0.5-mm gap, field of view (FOV), 64 × 64 acquisition matrix, and 90° flip angle. SENSitivity encoding (SENSE), with a SENSE factor of two and parallel imaging, were used for all of the scans. The high-resolution and 3-dimensional turbo-fast echo T1-weighted sequence was with the following parameters: 8.2/3.2 msec TR/TE, 188 slices, 1-mm thickness, no gap, FOV= 256 × 256, acquisition matrix= 256 × 256, and 12° flip angle [17].

fMRI Data Pre-Processing

Resting-state fMRI scans were processed using Statistical Parametric Mapping 8 (SPM8; http://www.fil.ion.ucl.ac.uk/spm). First, the initial ten scan volumes were removed to account for scanner stabilization and patient acclimation. Next, the remaining volumes were corrected to account for slice timing and motion artifacts, of which translational and rotational motions of less than 2-mm and 2° were allowed. Six motion parameters and average blood oxygen level-dependent (BOLD) signals of the ventricles and white matter were removed from the datasets. Data with specific volume framewise displacement values that were >0.5 were excluded from the analysis. Bandpass frequencies ranging from 0.01 to 0.08 Hz were used to filter the data. Each structural image was co-registered to the average functional image, and the transformed images were co-registered to the Montreal Neurological Institute (MNI) space using linear registration. The motion-corrected functional volumes were spatially normalized to the MNI using parameters estimated during the linear co-registration. Lastly, the functional images were re-sampled into 3-mm cubic voxels for further analyses [18].

Brain Activity Assessment and Global Functional Connectivity Density (gFCD) Calculation

Global functional connectivity density (gFCD) is an ideal index for assessing whole-brain activity as it reflects the entire brain connectivity, along with alterations of the baseline brain metabolism. The gFCD was calculated for each voxel using a customized Linux script. The Pearson's linear correlation was used to explore functional connectivity between the voxels, with a correlation coefficient threshold of $r > 0.6$. Only voxels within the cerebral grey matter mask were used to calculate the gFCD, and the gFCD for any given voxel (x0) was calculated as the total number of functional connections [k(x0)] between x0 and all of the other voxels using a growth algorithm. This procedure was repeated for all of the voxels. To further normalize the distribution, each gFCD value was divided by the average value of all the voxels. A 6 × 6 × 6 mm^3 Gaussian kernel was used to spatially smooth the gFCD maps and minimize the effects of anatomical differences among patients, ages, genders, illness durations, and education levels [19].

HAMD, YRMS, and MCCB Assessments

The total severity of hypomanic/manic or depressive symptoms was assessed using the Hamilton Rating Scale for Depression (HAMD) or Young Manic Rating Scale (YMRS), while anxiety symptoms were assessed with the Hamilton Anxiety Rating Scale (HAMA). All of the scales were used to evaluate patients before and after treatment with rTMS. The cognitive abilities of patients were assessed with the MCCB. Specifically, MCCB was used to characterize the trajectory of cognitive ability alterations before and after treatment with rTMS. Lastly, the Global Assessment of Functioning (GAF) was used to assess the global functioning of patients before and after rTMS.

Statistical Analysis

The paired *t*-test was performed in triplicate to compare the gFCD and MCCB alterations before and after treatment. The alterations at the end of the second week were compared to the baseline (pre-rTMS), while the alterations at the end of the third week were also compared to the baseline. A two-tailed *p*-value < 0.05 was considered to be statistically significant [20-22].

RESULTS

Clinicodemographic Data of Patients in This Study

Initially, 30 patients with BPD in remissions were enrolled in this study. Although the dosage of the therapeutic agents remained constant throughout the study, five patients relapsed. In addition, four patients withdrew from the study due to self-reported adverse effects, including headache and other uncomfortable feelings. Three patients failed to undergo MRI and were excluded from the study. In total, 21 patients were included in the analysis (Figure 1). The clinicodemographic data of the patients are shown in Table 2.

Table 2. The clinical and demographic characteristics of patients (n=21) at baseline in this study.

Variable	Patient data
Age (years)	22.0 (4.2)
Gender ratio (female/male)	9/12
Illness duration (years)	11.5 (0.5)
Educational level (years)	16.4 (3.8)
HAMD	3.0 (1.5)
HAMA	3.0 (1.0)
HMRS	2..0 (0.5)
GAF	88.7 (10.5)
MCCB scores	
MCCB total scores	185.5 (10.2)
Speed processing	33.0 (8.5)
Attention	28.0 (5.0)
Working memory	29.2 (8.7)
Verbal learning	25.2 (8.5)
Visual learning	20.2 (2.4)
Problem reasoning	21.0 (9.5)
Social cognition	28.9 (10.7)

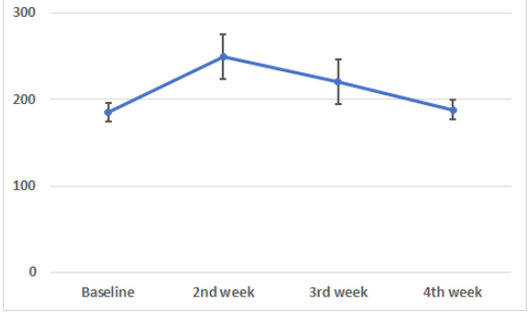

Figure 1. Flowchart of the patients with BPD enrolled in the study.

Age, illness duration, education level, HAMD, HAMA, HMRS, GAF, are MCCB expressed as the mean [standard deviation (SD)]. GAF, Global Assessment of Functioning; HAMA, Hamilton Anxiety Rating Scale, HAMD, Hamilton Rating Scale for Depression, YMRS, Young Manic Rating Scale; MCCB, MATRICS Consensus Cognitive Battery

Alterations in The Cognitive Abilities of Patients with Bpd After Rtms

The 21 patients with BPD symptoms remained in remission during the four-week study term. Despite the disease remaining in remission, the MCCB demonstrated significant improvements in cognitive abilities ($P < 0.05$), with each item score of the MCCB also increasing. At the end of the third week of treatment, the MCCB scores remained higher than those at baseline (i.e., before treatment), but were lower than the MCCB scores at the end of the second week of treatment. More notably, at the end of the fourth week of treatment, the MCCB scores sharply decreased, almost reaching the baseline values. This indicates that the positive effects of rTMS were short-term, as they were only noticeable for up to two weeks after treatment. The trajectory of MCCB alterations induced by adjunct therapy with rTMS is shown in Figure 2. The alterations in cognitive abilities before and after adjunct treatment with rTMS in patients with remitted BPD are shown in Table 3.

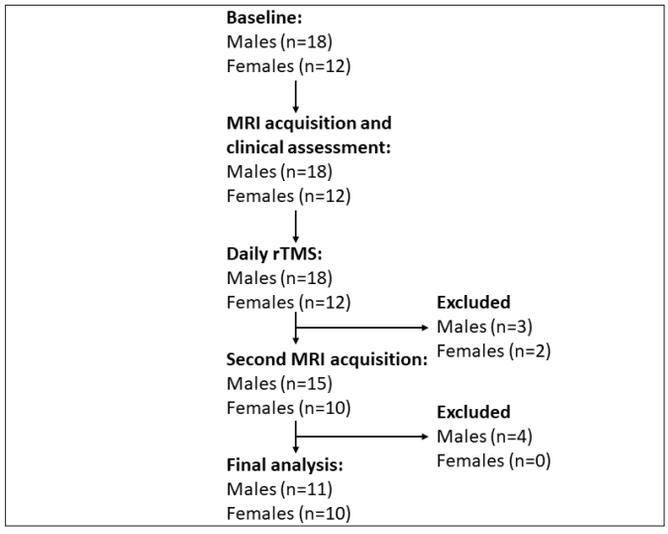

Figure 2. The trajectory of MCCB alterations induced by adjunct treatment with rTMS

gFCD Alterations

Compared to the baseline values, high frequency rTMS induced increased gFCD primarily in the prefrontal frontal, frontal lobes, inferior temporal lobes, and bilateral parietal lobes. (Figure 3). More notably, at the end of the fourth week of treatment, the gFCD increases in the frontal and temporal lobes were small when compared with the baseline value (Figure 4). These findings further suggest that adjunct therapy with rTMS provides short-term benefits that peak at two weeks post-treatment and begin to subside at three weeks post-treatment.

Table 3. The alterations in cognitive abilities before and after four weeks of adjunct treatment with rTMS in patients with remitted BPD.

Variables	Baseline	Two weeks after treatment	Three weeks after treatment	Four weeks after treatment	*F*/*t*	*P*
HAMD	3.0 (1.5)	2.3 (2.20)	2.5 (1.8)	2.0 (1.9)	0.789	0.693
HAMA	3.0 (1.0)	2.6 (1.5)	2.8 (0.9)	2.5 (2.5)	0.511	1.456
HMRS	2..0 (0.5)	2.0 (1.6)	2.3 (1.0)	2.8 (1.9)	0.496	0.398
GAF	88.7 (10.5)	85.0 (15.42)	88.0 (17.5)	92.0 (18.5)	0.283	0.121
MCCB scores						
MCCB total scores	185.5 (10.2)	249.6 (25.7)	220.4 (24.9)	188.5 (11.2)		
Speed processing	33.0 (8.5)	43.5 (10.5)	40.0 (11.0)	34.0 (11.2)		
Attention	28.0 (5.0)	30.5 (4.5)	28.4 (5.0)	29.0 (4.0)		
Working memory	29.2 (8.7)	35.5 (5.0)	30.6 (8.7)	29.4 (7.1)		
Verbal learning	25.2 (8.5)	39.2 (10.5)	31.8 (4.5)	26.0 (7.4)		
Visual learning	20.2 (2.4)	40.5 (1.5)	34.2 (2.0)	21.5 (2.0)		
Problem reasoning	21.0 (9.5)	27.5 (5.0)	26.7 (3.4)	19.6 (10.5)		
Social cognition	28.9 (10.7)	32.9 (9.8)	28.9 (8.0)	29.0 (5.7)		
MCCB alterations after 2, 3, and 4 weeks of adjunct treatment with rTMS in patients with remitted BPD when compared to baseline.						
2 weeks *vs.* baseline		t = - 11.520, *P* < 0.001				
3 weeks *vs.* baseline			t = - 8.745, *P* < 0.001			
4 weeks vs. baseline				t = - 0.478, *P*=0.346		

Values are shown at the mean [standard deviation (SD)]. All abbreviations found in the table should be included here. GAF, Global Assessment of Functioning; HAMA, Hamilton Anxiety Rating Scale, HAMD, Hamilton Rating Scale for Depression, YMRS, Young Manic Rating Scale; MCCB, MATRICS Consensus Cognitive Battery.

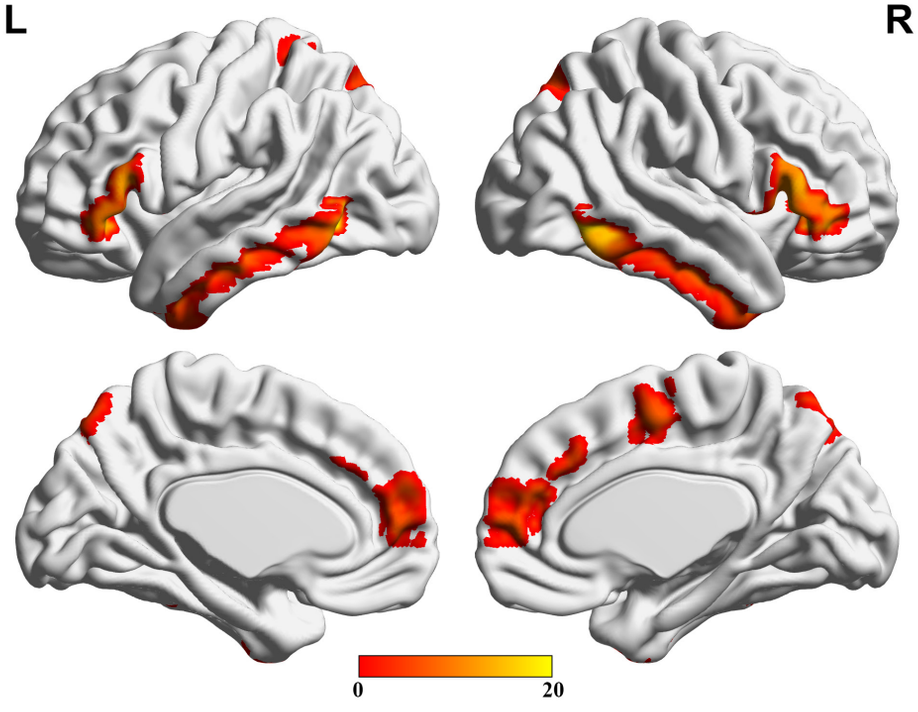

Figure 3. rTMS adjunct treatment-induced gFCD alterations at the end of the second week of treatment, as compared with the baseline values.

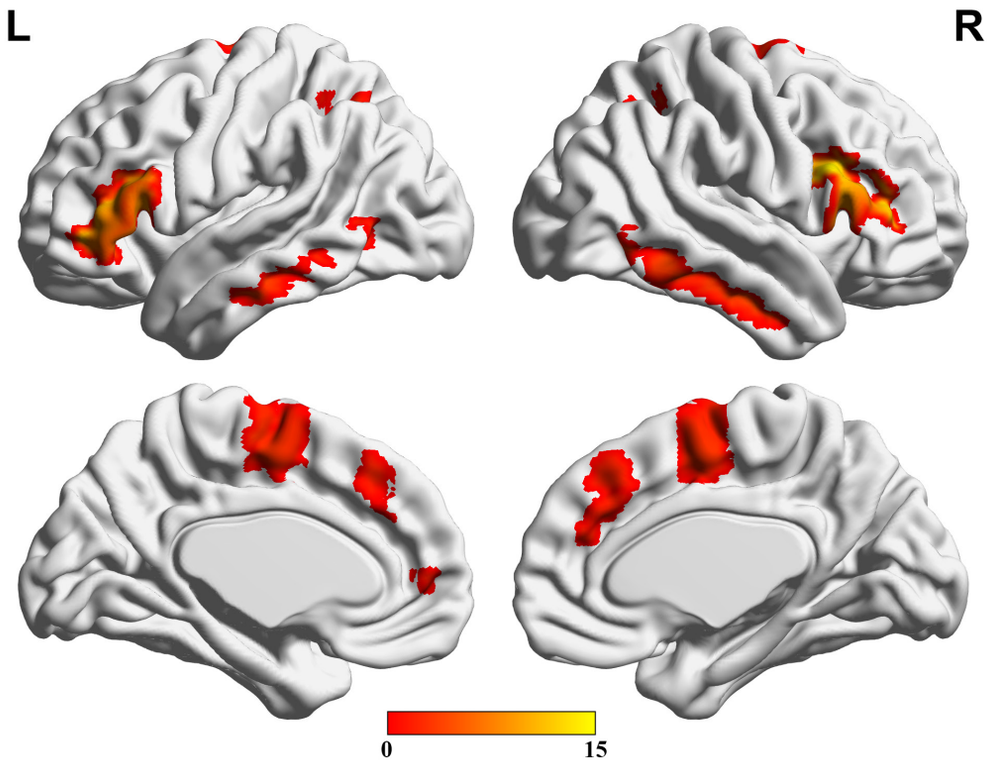

Figure 4. rTMS adjunct treatment-induced gFCD alterations at the end of the fourth week of treatment, as compared with the baseline values.

DISCUSSION

In this pilot study, we have shown that adjuvant treatment with rTMS can improve the cognitive abilities of patients with remitted BPD. The cognitive improvements occured approximately two weeks after treatment, yet the effects began to weaken by three weeks after treatment. Hence, adjunct therapy with rTMS results in short-term increased brain activity, which is quickly followed by decreased brain activity in the fourth week after treatment.

Previous studies have demonstrated that adjunct therapy with rTMS may improve the cognitive abilities in patients with remitted BPD through alterations in functional brain activity. However, the majority of previous studies have focused on the short-term effects of rTMS at 1-2 weeks post-treatment [9, 13, 23]. A few studies have reported on the relatively long-term effect of rTMS on cognition. In the present pilot study, we found that the therapeutic effects of rTMS were limited to 1-2 weeks post-treatment. Previous studies reported that rTMS could increase neural activity significantly within seven days in the frontocentral cortex [24, 25]. In addition, rTMS has been shown to improve the cognitive control function, anterior cingulate cortex activity, and reciprocal interaction of the PFC, leading to improved cognitive abilities within seven days of starting treatment [26-28].

Our pilot study also demonstrates that rTMS can induce the activation of the bilateral prefrontal and parietal lobes in 14 days, which is consistent with previous findings [8-16]. Our findings converge with previous studies to demonstrate that rTMS can regulate the functionally reciprocal interaction of the frontocentral cortex, which plays a pivotal role in cognitive processing, leading to the improved cognitive functioning of patients with BPD within one to two weeks after treatment. Unlike previous studies, we found that the cognitive improvements gradually weakened from the third week of treatment, although the illness was stable and rTMS was maintained. We postulate that this weakening of cognitive improvement may be due to cortex neuron desensitization, which is generated by the continued exposure to the rTMS stimulus. However, it could be related to the exhaustion of brain neural activity caused by continuous exposure to high frequency rTMS stimulation. This is similar to the dopamine exhaustion hypothesis in patients with treatment-refractory schizophrenia and serotonin exhaustion hypothesis in patients with treatment-refractory depression [29, 30]. Our postulation requires further investigation in the future.

Our pilot study indicated that changes in cognitive abilities induced by adjunct treatment with rTMS overlap with the gFCD trajectory. This finding supports our postulation that cortex neural activity desensitization or exhaustion may play a role in the short-lived effects of rTMS. However, the

trajectory was eliminated by the sharp decrease in MCCB scores at the end of the fourth week of treatment. This phenomenon provides an important clue about how to possibly increase the duration of cognitive improvements in the future.

Limitations

There are several limitations to our pilot study. First, we were unable to regress the impact of different mood stabilizers and other pharmacological agents because we could not convert them to a uniform dosage. This is unlike many schizophrenia studies that used a chlorpromazine equivalent. However, we fixed the dosages of each patient and also compared the patients before and after treatment, which would any potential bias to a large extent. Secondly, in this study, we used high frequency rTMS stimulation, yet some studies have reported that bilateral stimulation may be a better method. In future studies, we plan to explore this method to determine the optimal method. Third, this study used a small patient population, and larger studies are needed to verify our findings. In addition, this study could benefit from a drug-naive cohort of patients to better evaluate the therapeutic effects of rTMS. Finally, in this pilot study, we conducted paired t-tests in triplicate to compare gFCD and MCCB alterations before and after treatment. This may inflate type I error and may require correction of the *p*-levels. As an alternative option, a one-way ANOVA for repeated measures may be conducted with appropriate post-hoc tests.

CONCLUSIONS

High frequency rTMS can improve the cognitive abilities of patients with remitted BPD rapidly, yet the benefits are short-lived and begin to weaken by three weeks post-treatment. The functional brain activity alteration induced by rTMS verified the initial improvement in cognitive functioning, followed by a rapid decline, which may be due to desensitization or exhaustion. Hence, we plan to investigate new ways to increase the length of cognitive improvements in patients with remitted BPD in the future.

Funding: This work was supported by grants from the Project of Wenzhou Science and Technology Bureau (2017Y0797 to J.Y.), National Natural Science Foundation of China (81871052 to C.Z.), the Key Projects of the Natural Science Foundation of Tianjin, China (17JCZDJC35700 to C.Z.), the Tianjin Health Bureau Foundation (2014KR02 to C.Z.), the Zhejiang Public Welfare Fund Project (LGF18H090002 to D.J.), Tianjin Anding Hospital Scholar Award (300000 Yuan to C.Z.), and the Key Project of Wenzhou Science and Technology Bureau (ZS2017011 to X.L.).

Data availability statement: The datasets generated and analysed during the present study are available from the corresponding author on reasonable request.

REFERENCES

[1] Sperry SH, O'Connor LK, Ongur D, Cohen BM, Keshavan MS, Lewandowski KE. Measuring cognition in bipolar disorder with psychosis using the MATRICS Consensus Cognitive Battery. J Int Neuropsychol Soc. 2015;21(6):468-472.

[2] Van Rheenen TE, Rossell SL. An empirical evaluation of the MATRICS Consensus Cognitive Battery in bipolar disorder. Bipolar Disord. 2014;16(3):318-325.

[3] Burdick KE, Russo M, Frangou S, Mahon K, Braga RJ, Shanahan M, et al. Empirical evidence for discrete neurocognitive subgroups in bipolar disorder: clinical implications. Psychol Med. 2014;44(14):3083-3096.

[4] Douglas KM, Gallagher P, Robinson LJ, Carter JD, McIntosh VV, Frampton CM, et al. Prevalence of cognitive impairment in major depression and bipolar disorder. Bipolar Disord. 2018;20(3):260-274.

[5] Cullen B, Ward J, Graham NA, Deary IJ, Pell JP, Smith DJ, et al. Prevalence and correlates of cognitive impairment in euthymic adults with bipolar disorder: A systematic review. J Affect Disord. 2016;205165-181.

[6] Green MF. Cognitive impairment and functional outcome in schizophrenia and bipolar disorder. J Clin Psychiatry 2006;67(Suppl 9):3-8.

[7] Sole B, Jimenez E, Torrent C, Del Mar Bonnin C, Torres I, Reinares M, et al. Cognitive variability in bipolar II disorder: who is cognitively impaired and who is preserved. Bipolar Disord. 2016;18(3):288-299.

[8] Thomas-Ollivier V, Foyer E, Bulteau S, Pichot A, Valriviere P, Sauvaget A, et al. Cognitive component of psychomotor retardation in unipolar and bipolar depression: Is verbal fluency a relevant marker? Impact of repetitive transcranial stimulation. Psychiatry Clin Neurosci. 2017;71(9):612-623.

[9] Myczkowski ML, Fernandes A, Moreno M, Valiengo L, Lafer B, Moreno RA, et al. Cognitive outcomes of TMS treatment in bipolar depression: Safety data from a randomized controlled trial. J Affect Disord. 2018;23520-26.

[10] Sole B, Jimenez E, Torrent C, Reinares M, Bonnin CDM, Torres I, et al. Cognitive impairment in bipolar disorder: Treatment and prevention strategies. Int J Neuropsychopharmacol. 2017;20(8):670-680.

[11] Kazemi R, Rostami R, Khomami S, Baghdadi G, Rezaei M, Hata M, et al. Bilateral transcranial magnetic stimulation on DLPFC changes resting state networks and cognitive function in patients with bipolar depression. Front Hum Neurosci. 2018;12356.

[12] Li Y, Wang L, Jia M, Guo J, Wang H, Wang M. The effects of high-frequency rTMS over the left DLPFC on cognitive control in young healthy participants. PLoS One 2017;12(6):e0179430.

[13] Yang LL, Zhao D, Kong LL, Sun YQ, Wang ZY, Gao YY, et al. High-frequency repetitive transcranial magnetic stimulation (rTMS) improves neurocognitive function in bipolar disorder. J Affect Disord. 2019;246851-856.

[14] Momi D, Neri F, Coiro G, Smeralda C, Veniero D, Sprugnoli G, et al. Cognitive enhancement via network-targeted

cortico-cortical associative brain stimulation. Cereb Cortex 2019;30(3):1-12.

[15] Lee MR, Caparelli EC, Leff M, Steele VR, Maxwell AM, McCullough K, et al. Repetitive transcranial magnetic stimulation delivered with an H-Coil to the right insula reduces functional connectivity between insula and medial prefrontal cortex. Neuromodulation 2019;23(3). doi: 10.1111/ner.13033.

[16] Anand S, Hotson J. Transcranial magnetic stimulation: neurophysiological applications and safety. Brain Cogn. 2002;50(3):366-386.

[17] Calderone DJ, Martinez A, Zemon V, Hoptman MJ, Hu G, Watkins JE, et al. Comparison of psychophysical, electrophysiological, and fMRI assessment of visual contrast responses in patients with schizophrenia. Neuroimage 2013;67153-67162.

[18] Zhuo C, Zhou C, Lin X, Tian H, Wang L, Chen C, et al. Common and distinct global functional connectivity density alterations in drug-naive patients with first-episode major depressive disorder with and without auditory verbal hallucination. Prog Neuropsychopharmacol Biol Psychiatry 2020;96109738.

[19] Zhuo C, Zhu J, Qin W, Qu H, Ma X, Tian H, et al. Functional connectivity density alterations in schizophrenia. Front Behav Neurosci. 2014;8404.

[20] Luo N, Tian L, Calhoun VD, Chen J, Lin D, Vergara VM, et al. Brain function, structure and genomic data are linked but show different sensitivity to duration of illness and disease stage in schizophrenia. Neuroimage Clin. 2019;23101887. doi: 10.1016/j.nicl.2019.101887.

[21] Jing R, Li P, Ding Z, Lin X, Zhao R, Shi L, et al. Machine learning identifies unaffected first-degree relatives with functional network patterns and cognitive impairment similar to those of schizophrenia patients. Hum Brain Mapp 2019;40(13):3930-3939.

[22] Shan PW, Liu W, Liu C, Han Y, Wang L, Chen Q, et al. Aberrant functional connectivity density in patients with treatment-refractory obsessive-compulsive disorder: a pilot study. J Int Med Res. 2019;47(6):2434-2445.

[23] Basavaraju R, Mehta UM, Pascual-Leone A, Thirthalli J. Elevated mirror neuron system activity in bipolar mania: Evidence from a transcranial magnetic stimulation study. Bipolar Disord. 2019;21(3):259-269.

[24] Larson MJ, Clayson PE, Clawson A. Making sense of all the conflict: a theoretical review and critique of conflict-related ERPs. Int J Psychophysiol. 2014;93(3):283-297.

[25] West R, Alain C. Effects of task context and fluctuations of attention on neural activity supporting performance of the stroop task. Brain Res. 2000;873(1):102-111.

[26] Chouiter L, Dieguez S, Annoni JM, Spierer L. High and low stimulus-driven conflict engage segregated brain networks, not quantitatively different resources. Brain Topogr 2014;27(2):279-292.

[27] Botvinick MM, Cohen JD, Carter CS. Conflict monitoring and anterior cingulate cortex: an update. Trends Cogn Sci 2004;8(12):539-546.

[28] Vanderhasselt MA, De Raedt R, Baeken C, Leyman L, Clerinx P, D'Haenen H. The influence of rTMS over the right dorsolateral prefrontal cortex on top-down attentional processes. Brain Res 2007;1137(1):111-116.

[29] McIntyre RS, Filteau MJ, Martin L, Patry S, Carvalho A, Cha DS, et al. Treatment-resistant depression: definitions, review of the evidence, and algorithmic approach. J Affect Disord 2014;1561-1567.

[30] Elkis H, Buckley PF. Treatment-Resistant Schizophrenia. Psychiatr Clin North Am 2016;39(2):239-265.