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Case Control Study

Delayed improvements in visual memory task performance among chronic schizophrenia patients after high-frequency repetitive transcranial magnetic stimulation

Xiang-Dong Du, Zhe Li, Nian Yuan, Ming Yin, Xue-Li Zhao, Xiao-Li Lv, Si-Yun Zou, Jun Zhang, Guang-Ya Zhang, Chuan-Wei Li, Hui Pan, Li Yang, Si-Qi Wu, Yan Yue, Yu-Xuan Wu, Xiang-Yang Zhang

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Abstract

BACKGROUND

Cognitive impairments are core characteristics of schizophrenia, but are largely resistant to current treatments. Several recent studies have shown that high-frequency repetitive transcranial magnetic stimulation (rTMS) of the left dorsolateral prefrontal cortex (DLPFC) can reduce negative symptoms and improve certain cognitive deficits in schizophrenia patients. However, results are inconsistent across studies.

AIM

To examine if high-frequency rTMS of the DLPFC can improve visual memory deficits in patients with schizophrenia.

METHODS

Forty-seven chronic schizophrenia patients with severe negative symptoms on

stable treatment regimens were randomly assigned to receive active rTMS to the DLPFC ($n = 25$) or sham stimulation ($n = 22$) on weekdays for four consecutive weeks. Patients performed the pattern recognition memory (PRM) task from the Cambridge Neuropsychological Test Automated Battery at baseline, at the end of rTMS treatment (week 4), and 4 wk after rTMS treatment (week 8). Clinical symptoms were also measured at these same time points using the Scale for the Assessment of Negative Symptoms (SANS) and the Positive and Negative Syndrome Scale (PANSS).

RESULTS

There were no significant differences in PRM performance metrics, SANS total score, SANS subscores, PANSS total score, and PANSS subscores between active and sham rTMS groups at the end of the 4-wk treatment period, but PRM performance metrics (percent correct and number correct) and changes in these metrics from baseline were significantly greater in the active rTMS group at week 8 compared to the sham group (all $P < 0.05$). Active rTMS treatment also significantly reduced SANS score at week 8 compared to sham treatment. Moreover, the improvement in visual memory was correlated with the reduction in negative symptoms at week 8. In contrast, there were no between-group differences in PANSS total score and subscale scores at either week 4 or week 8 (all $P > 0.05$).

CONCLUSION

High-frequency transcranial magnetic stimulation improves visual memory and reduces negative symptoms in schizophrenia, but these effects are delayed, potentially due to the requirement for extensive neuroplastic changes within DLPFC networks.

Key Words: Cognition; High-frequency repetitive transcranial magnetic stimulation; Non-invasive brain stimulation; Randomized controlled study; Schizophrenia; Visual memory deficits

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Core Tip: The main objective of this study was to evaluate the efficacy of high-frequency repetitive transcranial magnetic stimulation (rTMS) in the treatment of visual memory disorders in schizophrenia. Forty-seven patients with chronic schizophrenia who had significant negative symptoms during stabilization therapy were randomly assigned to two groups: Active rTMS over dorsolateral prefrontal cortex ($n = 25$) or false stimulation ($n = 22$) for 4 wk, followed by 4 wk of follow-up. Our results suggest that high-frequency transcranial magnetic stimulation improves visual memory function and relieves negative symptoms in patients with schizophrenia, but with a delay.

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INTRODUCTION

Schizophrenia is a chronic psychiatric disorder characterized by distorted thinking and perception[1]. A comprehensive epidemiological survey reported a median prevalence of 15.2/100000 persons, but individual prevalence estimates in various regions have varied from 7.7-43.0/100000[2], potentially due to genetic factors, diagnostic standards, and the heterogeneity of symptom presentation. The clinical symptoms of schizophrenia are divided into three groups or domains: Positive symptoms such as hallucinations, negative symptoms such as flat affect and anhedonia, and cognitive symptoms, and the predominance of different symptom clusters in individual patients determines the treatment strategy and influences long-term outcome[1,3]. At present, the main treatments for schizophrenia are antipsychotics, but these agents are effective only against positive symptoms[3], while it remains more difficult to improve the negative and cognitive symptoms of chronic schizophrenia even during long-term hospitalization.

Cognitive impairments in schizophrenia include deficits in attention, executive functions such as response inhibition and working memory, verbal learning and memory, and social memory[4] that vary

markedly in severity among individual patients. These symptoms may be detectable prior to clinical disease onset and remain relatively stable over time despite improvements in other symptoms[4,5]. Further, these cognitive deficits contribute to functional disability and predict poor life outcome[4,6,7]. Visual memory is a critical faculty for various forms of learning and for daily activities such as employment. Although prior research has indicated that visual memory impairments are minor in comparison to other cognitive impairments[8], a recent study found that patients with a family history of schizophrenia have considerably worse visual memory scores[9]. Furthermore, several earlier studies reported that patients with schizophrenia have poor visual memory[10,11] and that improvement is associated with better job retention and successful recovery[8]. Thus, any improvement in visual memory that occurs during treatment could be broadly beneficial, especially to patients with a family history of schizophrenia[9].

The prefrontal cortex (PFC) is critical for executive functions such as working memory, cognitive flexibility, and behavioral inhibition; some or all of which may be disrupted in psychiatric disorders including depression, anxiety and schizophrenia. A recent study of patients with bilateral lesions in the ventromedial (vm)PFC[12,13] revealed deficits in the acquisition of Pavlovian threat conditioning (*i.e.*, emotional learning). A recent theoretical review[14,15] on the neurobiology of emotional conditioning concluded that the vmPFC is fundamental for the representation and evaluation of safety- and threat-related information and thus for the relative influence of this information on sustained physiological responses. Imaging studies of patients with depression exhibiting executive dysfunction also revealed damage to dorsolateral prefrontal circuits[16,17]. Therefore, the PFC is a promising target for therapeutic interventions aimed at treating the cognitive and emotional symptoms of schizophrenia. In addition, some scholars proposed that the anatomical-functional interplay between the PFC and heart-related dynamics in human emotional conditioning (learning) and proposes a theoretical model to conceptualize these psychophysiological processes, the neurovisceral integration model of fear, that can be impaired in the context of psychiatric disorders (as schizophrenia)[18-20].

While antipsychotic drugs clearly benefit positive symptoms, they may also disrupt attention and memory in unimpaired subjects. In this regard, atypical antipsychotics are less deleterious than conventional antipsychotics. Nonetheless, cognitive dysfunction is still a major predictor of poor clinical and life outcome among patients with schizophrenia, necessitating the continued development of interventions for improving cognitive function[21]. Among potential treatments, nonpharmaceutical and noninvasive treatments may be particularly effective as patient noncompliance to drug treatment is a major obstacle to effective long-term patient management. Repetitive transcranial magnetic stimulation (rTMS) is one such alternative as it is noninvasive, well-tolerated, and has demonstrated efficacy for the treatment of various psychiatric and neurological diseases, in particular in treatment-resistant depression (TRD), for which it has received United States Food and Drug Administration approval[22,23]. However, studies of clinical efficacy for schizophrenia treatment have thus far reported inconsistent results, possibly to heterogeneity in illness factors (such as duration of illness and baseline psychopathology), assessment methods (such as the assessment tool used and evaluation of bias), and stimulation parameters (such as stimulus location, frequency, intensity and duration)[24,25]. Due to these discrepancies, several meta-analyses have been conducted to investigate the impact of rTMS on the clinical symptoms of schizophrenia[5,26], and a recent report concluded that rTMS of the dorsolateral PFC (DLPFC) is an effective method for the treatment of negative symptoms[24]. A more recent meta-analysis concluded that 1-Hz rTMS had a significant therapeutic effect on auditory hallucinations[27]. In contrast, the same study found no significant effect of 10-Hz rTMS on negative symptoms compared to sham treatment. However, there has been no examination on the efficacy of rTMS targeting the DLPFC on cognitive symptoms such as visual memory. Here, we examined this question and presented possible reasons for the differential efficacy of previous protocols[8-11].

Given the major influence of cognitive dysfunction on long-term outcome, cognitive improvement should be a primary treatment goal[27,28]. Second-generation antipsychotic drugs have been shown to improve positive symptoms, but have little effect on negative symptoms and cognitive deficits[7,28,29]. Alternatively, nonpharmacological interventions such as cognitive remedial training and aerobic exercise have shown promising results for the treatment of cognitive impairment[30]. As well, a previous open label study reported that 1-Hz rTMS of the left temporal parietal cortex and 10-Hz rTMS of the DLPFC improved short-term auditory verbal memory[31]. Wölwer *et al*[21] also reported improved facial affect recognition, a critical component of social cognition, in schizophrenia patients following 10 Hz rTMS to the left DLPFC[21]. A double-blind sham-controlled randomized treatment trial found that 20-Hz rTMS of the bilateral DLPFC improved working memory as measured by the three-back task[32]. However, Mittrach *et al*[33] did not find any beneficial effect of 10-Hz rTMS of the DLPFC on long-term verbal memory, attention, or frontal executive functioning. Similarly, a recent randomized sham-controlled trial including schizophrenia patients with prominent negative symptoms found that active 10-Hz rTMS of the left DLPFC was no more effective than sham treatment for improving cognitive performance[34]. In contrast, we found that rTMS of the left DLPFC can improve the negative symptoms of schizophrenia[35].

Therefore, the primary objective of the current randomized, double-blind sham-controlled study was to examine if a similar rTMS protocol improved visual memory performance. Accordingly, chronic schizophrenia patients with marked negative symptoms among the Chinese Han population were

randomized to receive five sessions *per* week of high-frequency rTMS to the left DLPFC or sham stimulation and were examined periodically for visual memory performance. We hypothesized that visual memory performance would be improved to a greater degree by real rTMS than sham treatment. The secondary objective was to analyze the association between improvement in visual memory and negative symptoms during and following rTMS treatment. This study highlighted the therapeutic potential of rTMS targeting the DLPFC for schizophrenia patients with predominant negative and cognitive symptoms. More broadly, rTMS may be an effective component of more precise and individualized treatment regimens for neurologic and psychiatric disorders.

MATERIALS AND METHODS

Subjects

The subjects of this study also participated in our previous clinical trial published in 2016[35]. Forty-seven schizophrenia inpatients were recruited from Suzhou Guangji Hospital, a city-owned psychiatric hospital in Suzhou City, from June 2013 to May 2015. The inclusion criteria were: (1) Meeting ICD-10 diagnostic criteria for schizophrenia according to two senior psychiatrists; (2) Eight-handed; (3) Aged 20–60 years and Han Chinese ancestry; (4) ≥ 5 -years' duration of illness; (5) Antipsychotic medication fixed for at least 12 mo before enrollment; and (6) Marked negative symptoms as evidenced by a score ≥ 20 on the Scale for the Assessment of Negative Symptoms (SANS). Baseline demographic and clinical characteristics of the study population are summarized in Table 1.

All subjects received a complete medical history review and detailed physical examinations. We excluded candidates with physical diseases such as aneurysm, seizure, stroke, and cardiovascular disorders as well as patients with illegal drug or alcohol abuse/dependence.

This study was approved by the Institutional Review Board of Suzhou Guangji Psychiatric Hospital and each subject provided written informed consent prior to participation following a full explanation of project goals, methods, and risks by a research staff member. All study procedures were performed in accordance with the Declaration of Helsinki. This clinical trial was registered with <https://www.clinicaltrials.gov/> on September 5, 2017 as NCT03273439 (5/9/2017).

Design

This was a single-center, randomized, sham-controlled, double-blinded study conducted as described in our previous report[35]. Briefly, participants received active or sham rTMS on all weekdays for 4 wk (20 sessions in total). Antipsychotic medications and all other medications remained unchanged during treatment. Clinical assessments and cognitive tests were performed at baseline, after the 4-wk treatment (week 4) and 4 wk post-treatment (week 8).

Active and sham rTMS

Repetitive TMS was delivered through a figure-of-eight coil connected to a MAGPRO-R30 magnetic stimulator (Medtronic DantecNeuroMuscular, Skovlunde, Denmark). Prior to each TMS or sham administration, motor threshold (MT) at the left primary motor cortex (M1) was determined as the lowest possible energy required to produce at least five potentials ≥ 0.05 mV in 10 trials from the X. During each active rTMS session, thirty 5-s trains of 10 Hz stimulation were delivered in 30-s intervals at 110% of MT over the left DLPFC (defined as the F3 position of the 10–20 electroencephalogram system). These trains were administered once each weekday for four consecutive weeks (for a total of 30000 individual stimuli). The left DLPFC was chosen as the rTMS target because the majority of previous studies performed rTMS on DLPFC[5,24]. For sham rTMS, all procedures were identical except that the figure-of-eight coil was rotated 180° during stimulator activation. Since rTMS machine was used in a blinded fashion in this study, the coil was thick enough and had a magnetic shielding function (Figure 1).

Psychopathological measures

General psychopathology was assessed using the Positive and Negative Syndrome Scale (PANSS). Negative symptoms were also assessed with the SANS, which consists of 19 items assessing five symptoms of the negative dimension: Affect flattening, avolition-apaty, anhedonia-asociality, and poor attention. Two clinical psychiatrists blinded to treatment condition (real *vs* sham rTMS) assessed PANSS and SANS scores at baseline, at weeks 4 and 8. Inter-rater reliability was satisfactory for both tests ($\kappa = 0.88$ for PANSS and $\kappa = 0.86$ for SANS).

Cognitive performance

The Cambridge Neuropsychological Test Automated Battery (CANTAB) is a widely used computerized assessment tool for cognition in schizophrenia. Since the patients in this study had relatively long disease histories (> 20 years) and most had not received any higher education (Table 1), only the pattern recognition memory (PRM) component of the CANTAB, a relatively straightforward two-choice forced

Table 1 Demographic and baseline clinical characteristics of active and sham repetitive transcranial magnetic stimulation groups

	Active rTMS (n = 25)	Sham rTMS (n = 22)	χ^2 or F	P value
Sex (male/female)	12/13	11/11	0.02	0.89
Age (yr)	45.9 ± 10.0	45.1 ± 10.4	0.05	0.83
Education (yr)	13.0 ± 4.7	12.5 ± 5.7	0.11	0.74
Age of onset (yr)	22.3 ± 6.3	25.2 ± 7.5	2.48	0.13
Antipsychotics			0.42	0.94
Clozapine	14	12		
Quetiapine	3	4		
Aripiprazole	3	2		
Risperidone	3	1		
Olanzapine	1	2		
Chlorpromazine	1	1		
Daily antipsychotic dose (mg) (chlorpromazine equivalent)	323.5 ± 193.1	341.7 ± 168.7	0.08	0.78
PANSS total score	72.1 ± 15.3	69.3 ± 11.5	0.45	0.51
P-subscore	12.6 ± 4.0	10.0 ± 3.3	3.52	0.07
N-subscore	26.7 ± 7.5	25.9 ± 6.9	0.25	0.62
G-subscore	33.8 ± 6.0	33.4 ± 5.4	0.01	0.91
SANS total score	88.1 ± 17.9	88.1 ± 15.2	0.18	0.68
Affect flattening	23.5 ± 5.8	24.1 ± 5.8	0.09	0.76
Alogia	16.0 ± 4.6	16.3 ± 3.4	0.12	0.73
Avolition-apathy	14.0 ± 3.1	14.6 ± 3.1	0.05	0.83
Anhedonia-Asociality	21.4 ± 3.3	21.7 ± 3.2	0.27	0.61
Attention	11.6 ± 2.3	11.4 ± 3.0	0.2	0.66
PRM-number correct	14.7 ± 4.0	15.5 ± 3.7	0.47	0.5
PRM-percent correct (%)	61.3 ± 16.9	64.6 ± 15.6	0.47	0.5

rTMS: Repetitive transcranial magnetic stimulation; P: Positive symptom; N: Negative symptom; G: General psychopathology; SANS: Scale for the Assessment of Negative Symptoms; PRM: Pattern recognition memory; PANSS: Positive and Negative Symptom Scale.

discrimination task, was administered. Subjects were presented with a series of 12 visual geometric patterns, one at a time, at the center of the screen (first presentation phase) and then were required to choose between an already seen pattern and a novel pattern (first recall phase). In the recall phase, previously viewed patterns were presented in reverse order from original presentation. Then, a new series of patterns was presented, followed by a second recognition test given either immediately or after a delay (20 min) to test delayed recognition memory. Performance on the PRM is measured as the number and proportion (%) of correct responses, with a maximum score of 100 (best pattern recognition memory).

Statistical analysis

Continuous variables were first tested for normality using the Kolmogorov-Smirnov one-sample test ($P < 0.05$). All continuous datasets met this criteria, so they were presented as mean ± SD. Continuous baseline variables were compared between active and sham rTMS groups by independent samples *t*-test. Categorical variables were presented as frequency and compared by χ^2 test. Data were analyzed using the intention-to-treat principle so missing data points were replaced with the last observation.

The primary objective of this study was to evaluate the effect of rTMS on visual recognition memory in patients with schizophrenia. Since all variables were normally distributed according to the Kolmogorov-Smirnov one-sample test, the principal outcome (visual memory performance as measured by % correct) was analyzed by repeated-measures analyses of variance with measurement time (baseline and weeks 4 and 8) as the within-group factor and active *versus* sham rTMS as the

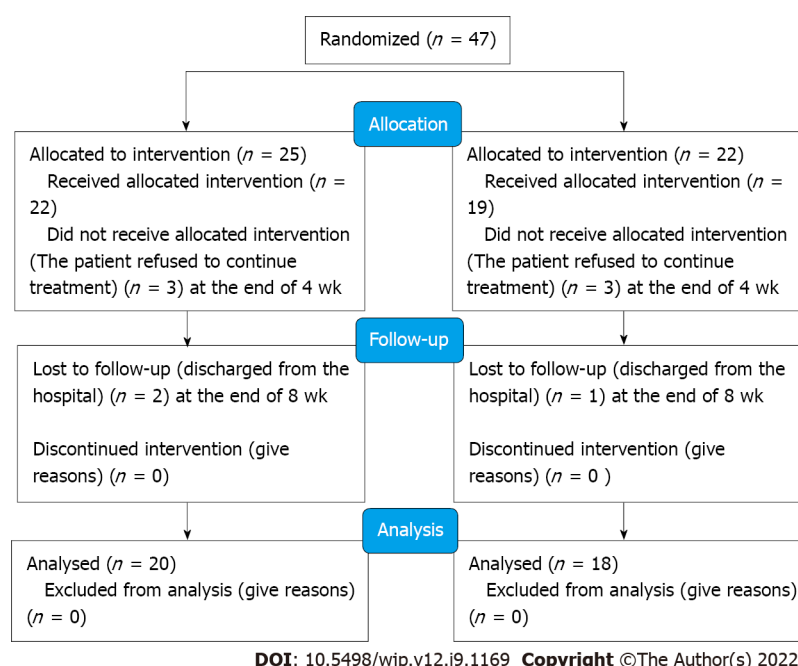


Figure 1 Flow diagram.

between-group factor. If the time \times group interaction was significant, analysis of covariance (ANCOVA) was used to test for differences between groups at the end of weeks 4 and 8, with baseline score as the covariate. If the interaction was not significant, no further statistical tests were performed. The same method was used to analyze changes in PANSS and SANS scores.

The second objective was to determine whether negative symptoms (SANS scores) were correlated with PRM performance (number and proportion correct) in the active and sham rTMS groups before and after treatment. Correlations between changes in SANS scores and visual memory performance were examined by Pearson correlation coefficients, and when significant, the Bonferroni correction was used. Finally, multiple linear regression was used to investigate potential response predictors associated with changes in visual memory scores.

All statistical analyses were conducted using SPSS version 18.0. $P \leq 0.05$ (two-tailed) was considered significant for all tests. In cases with multiple comparisons, P values were adjusted by Bonferroni correction.

RESULTS

Demographic and basic descriptive data

The full details of this clinical trial examining the effects of DLPFC-targeted rTMS on schizophrenia symptoms were reported previously[35]. In total, 47 patients were randomly divided into an active rTMS group ($n = 25$) and sham rTMS group ($n = 22$). However, six subjects withdrew their consent before starting treatment (three in the active and three in the sham rTMS groups). Therefore, 41 participants completed the full set of clinical trial, including 22 in the active rTMS group and 19 in the sham rTMS group.

At baseline, there were no significant differences in demographic variables, PANSS total and subscale scores, SANS total and subscale scores, PRM-number correct, and PRM-percent correct between active and sham rTMS treatment groups (Table 1). Consistent with a potential association between negative symptoms and poor visual memory, PRM performance metrics (number correct and percent correct) at baseline were negatively correlated with SANS total score and all subscale scores ($P < 0.05$ – 0.001) except for the affect flattening subscale ($P > 0.05$).

Efficacy of rTMS treatment for improving cognitive performance

Three participants were lost to follow-up due to premature discharge before week 8 (2 in the active group and 1 in the sham rTMS group), so treatment efficacy analysis included 20 patients in the active group and 18 in the sham group. Repeated measures ANCOVA revealed a significant test time (baseline *vs* week 4 *vs* week 8) \times group interaction ($F = 22.1$, $df = 274$, $P < 0.001$) and a significant main effect of test time ($F = 13.2$, $df = 274$, $P < 0.001$) on PRM performance, but no significant effect of group ($F = 1.37$, $df = 137$, $P = 0.25$). However, the PRM-number correct was significantly higher in the active rTMS group

than the sham group at week 8 ($F = 16.8$, $df = 137$, $P < 0.001$; effect size = 1.35) but not immediately after the 4-week treatment period ($F = 0.49$, $df = 136$, $P = 0.48$). The difference at week 8 was still significant after controlling for the effects of sex, age, disease duration, and drug dose (chlorpromazine equivalent) ($F = 19.2$, $df = 133$, $P < 0.001$), while the difference at week 4 did not reach significance ($F = 0.63$, $P = 0.43$).

In the active rTMS group, the mean number of correct answers on the PRM test increased by 4.54 ± 2.98 from baseline to week 8, while the correct number in the sham group decreased slightly (-0.92 ± 2.72) and the difference between these changes was highly significant (mean 5.46 ± 0.92 , 95%CI: 3.43–7.14, $F = 33.3$, $df = 137$, $P < 0.0001$, effect size = 0.474) (Table 2). However, from baseline to week 4, there was no significant difference in the correct response change between groups (0.41 ± 4.1 vs -0.62 ± 2.8 , $F = 0.75$, $P = 0.39$). rTMS treatment also significantly shortened select time (Figure 2A) and interval time (Figure 2B) in PRM from baseline to week 8 compared to the sham group. We can see that the treatment group decreased with the selection time and interval time in PRM compared with the control group at week 8.

rTMS treatment for psychopathological symptoms

Changes in PANSS and SANS total scores as well as subscale scores (secondary outcomes) are also summarized in Table 2. These SANS results are included from our previous study[35] for comparison and to assess the relationship between effects on negative symptoms and visual recognition memory following rTMS. By the end of 4 wk of treatment, there were no significant differences in SANS total score, all five SANS subscale scores, PANSS total score, and PANSS subscale scores between active and sham rTMS groups (all $P > 0.05$). At 8 wk, however, SANS total score as well as avolition/apathy, anhedonia/asociality, and attention subscores were significantly lower (improved) in the active rTMS group compared to the sham group (all $P < 0.05$) (Table 2). Alternatively, there were no between-group differences in PANSS total and subscale scores at week 4 and week 8 compared to baseline (all $P > 0.05$).

Relationship between improvement in cognitive ability and changes in psychopathological symptoms

The increase in PRM-number correct from baseline to week 8 was significantly correlated with the changes in SANS total score ($r = 0.34$, $df = 38$, $P = 0.034$; Figure 3), SANS alogia subscale score ($r = 0.37$, $df = 38$, $P = 0.024$), and SANS avolition/apathy subscale score ($r = 0.34$, $df = 38$, $P = 0.037$). However, none of these univariable correlations were significant after Bonferroni correction (all $P > 0.05$). Multiple regression analysis revealed a significant association between the increase in PRM-number correct and the change in SANS total score from baseline to week 8 ($\beta = 0.42$, $t = 2.53$, $P = 0.017$).

DISCUSSION

The key results of this study were as follows. (1) DLPFC-targeted 10-Hz rTMS (20 single weekday sessions over 4 wk) had a significant therapeutic effect on the visual recognition memory deficit exhibited by schizophrenia patients with strong negative symptoms, but this response was delayed until several weeks after the end of treatment; and (2) This improvement in visual recognition memory was associated with a reduction in negative symptoms. The delay between treatment and response may help explain previous inconsistencies among studies on the therapeutic efficacy of rTMS.

There is growing acceptance of noninvasive brain stimulation (NIBS) techniques for the treatment of cognitive deficits[7], but only a few studies have examined the efficacy of rTMS for cognitive impairments in schizophrenia. Here, we showed that this specific NIBS regimen can mitigate multiple core symptoms of schizophrenia. Furthermore, this regimen may be a promising therapeutic option for other disorders presenting with emotional dysregulation and cognitive dysfunction. Recent studies have reported that NIBS stably mitigates psychiatric symptoms by noninvasively modulating the abnormal activity of neural circuits (*i.e.*, amygdala–PFC–hippocampus pathways) involved in the regulation of mood and cognition[36]. For instance, a recent review suggested that NIBS can improve mood by modulating emotional memories, while others[37,38] have reported that NIBS can suppress abnormally persistent fear memories in anxiety disorder patients that do not respond to psychotherapy and/or anxiolytic drugs. Multiple studies have also demonstrated the value of NIBS as a research tool for examining the neurological mechanisms underlying depression and anxiety in schizophrenia and other psychiatric disorders[39,40]. For instance, NIBS to the DLPFC after memory reactivation was reported to reduce the subsequent response to learned fear, suggesting that stimulation alters the synaptoplastic processes re-engaged during memory retrieval (term reconsolidation)[41–43]. In accordance with the current study, Barr and colleagues reported that daily 20-Hz rTMS of the DLPFC for 4 wk significantly improved working memory compared to sham stimulation in schizophrenia patients as measured by a three-back task[32]. More impressively, three-back accuracy was similar to that of healthy subjects after treatment[32]. Taken together, these findings suggest that high-frequency rTMS may be an effective treatment for visual and working memory deficits in patients with schizophrenia. In contrast, however, Prikryl and colleagues reported that 15-Hz rTMS over the left DLPFC for 4 wk had no significant effect

Table 2 Cognitive performance measures and clinical symptoms at baseline, week 4, and week 8 in active repetitive transcranial magnetic stimulation and sham multichannel transcranial magnetic stimulation groups

	Baseline (<i>n</i> = 47)	Week 4 (<i>n</i> = 41)	Week 8 (<i>n</i> = 38)	Group F (<i>P</i> value)	Time F (<i>P</i> value)	Group × Time F (<i>P</i> value)
PRM-number correct				1.37 (0.25)	13.2 (< 0.001)	22.1 (< 0.001)
rTMS (<i>n</i> = 25)	14.7 ± 4.0	15.1 ± 3.8	19.2 ± 2.7 ^c			
Sham (<i>n</i> = 22)	15.5 ± 3.7	14.9 ± 4.4	14.6 ± 4.1			
SANS total score				0.89 (0.35)	38.11 (< 0.001)	11.36 (0.002)
rTMS	88.1 ± 17.9	79.0 ± 21.5	72.5 ± 16.8 ^a			
Sham	88.1 ± 15.2	83.6 ± 19.2	83.5 ± 20.5			
Affect flattening				0.39 (0.54)	43.56 (< 0.001)	6.83 (0.013)
rTMS	23.5 ± 5.8	20.1 ± 6.7	18.8 ± 4.8			
Sham	24.1 ± 5.8	22.5 ± 5.9	21.9 ± 6.7			
Alogia				0.23 (0.64)	8.27 (0.007)	5.30 (0.027)
rTMS	16.0 ± 4.6	15.0 ± 4.7	13.6 ± 3.6			
Sham	16.3 ± 3.4	15.9 ± 4.1	16.1 ± 5.1			
Avolition-apathy				1.56 (0.22)	29.56 (< 0.001)	10.00 (0.003)
rTMS	14.0 ± 3.1	12.4 ± 3.5	11.4 ± 2.6 ^a			
Sham	14.6 ± 3.1	14.1 ± 3.9	14.0 ± 3.9			
Anhedonia-Asociality				1.48 (0.23)	1.48 (0.23)	3.84 (0.058)
rTMS	21.4 ± 3.3	20.0 ± 3.9	29.9 ± 6.5 ^a			
Sham	21.7 ± 3.2	20.8 ± 3.8	31.9 ± 6.0			
Attention				0.70 (0.41)	37.00 (< 0.001)	11.61 (0.002)
rTMS	11.6 ± 2.3	9.9 ± 2.9	8.7 ± 2.2 ^a			
Sham	11.4 ± 3.0	10.4 ± 3.7	10.6 ± 3.5			
PANSS total score				0.03 (0.86)	60.02 (< 0.001)	8.42 (0.006)
rTMS	72.1 ± 15.3	65.3 ± 15.9	64.6 ± 16.8			
Sham	69.3 ± 11.5	61.9 ± 16.6	63.1 ± 14.3			
P-subscore				2.99 (0.09)	1.05 (0.313)	0.50 (0.49)
rTMS	12.6 ± 4.0	12.4 ± 4.0	12.5 ± 4.0			
Sham	10.0 ± 3.3	10.5 ± 3.9	10.3 ± 3.6			
N-subscore				0.01 (0.93)	77.76 (< 0.001)	10.12 (0.003)
rTMS	26.7 ± 7.5	22.8 ± 8.8	21.0 ± 7.1			
Sham	25.9 ± 6.9	22.6 ± 7.5	23.1 ± 7.6			
G-subscore				0.31 (0.58)	37.90 (< 0.001)	5.38 (0.026)
rTMS	33.8 ± 6.0	30.3 ± 6.6	29.9 ± 6.5			
Sham	33.4 ± 5.4	31.7 ± 6.2	31.9 ± 6.0			

^a*P* < 0.05.^c*P* < 0.001.

rTMS: Repetitive transcranial magnetic stimulation; PANSS: Positive and Negative Symptom Scale; P: Positive symptom; N: Negative symptom; G: General psychopathology; SANS: Scale for the Assessment of Negative Symptoms; PRM: Pattern recognition memory.

on working memory performance in schizophrenia patients[44]. Thus, the efficacy of different rTMS regimens for the cognitive deficits of schizophrenia requires further investigation in larger clinically heterogeneous populations.

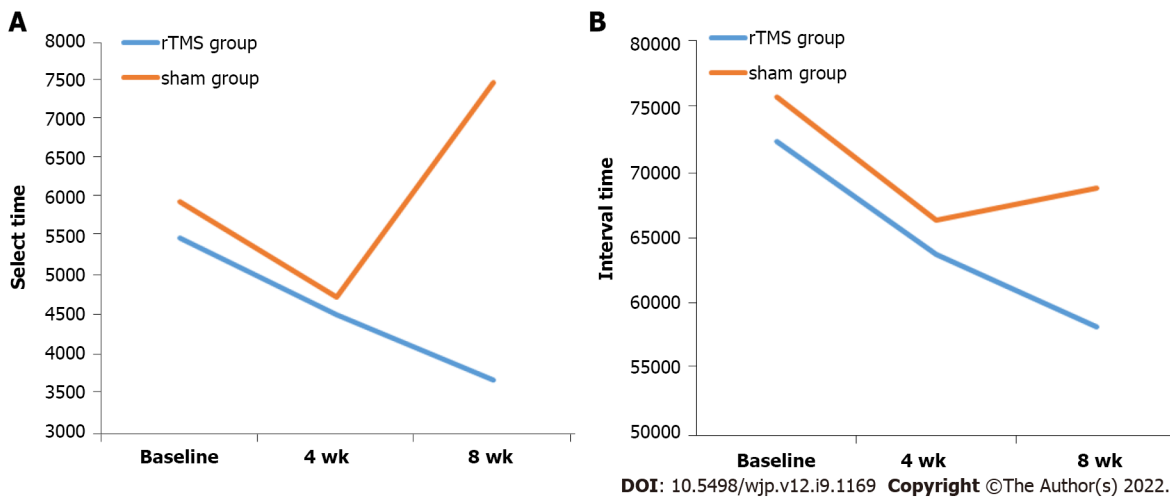


Figure 2 Repetitive transcranial magnetic stimulation treatment also significantly shortened select and interval time in pattern recognition memory from baseline to week 8 compared to the sham group. A: Select time; B: Interval time. rTMS: Repetitive transcranial magnetic stimulation.

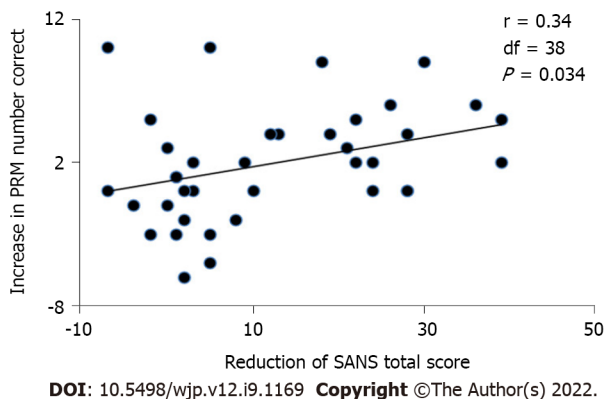


Figure 3 The increase in pattern recognition memory-number correct from baseline to week 8 was significantly correlated with the reduction in Scale for the Assessment of Negative Symptoms total score ($P < 0.05$). This association was confirmed by multiple regression analysis (beta = 0.42, $t = 2.53$, $P = 0.017$). PRM: Pattern recognition memory; SANS: Scale for the Assessment of Negative Symptoms.

In our recently published study[35], we reported that high-frequency rTMS over the left DLPFC for four consecutive weeks reduced the negative symptoms of schizophrenia compared to sham rTMS[42-45], consistent with numerous studies using rTMS to treat the negative symptoms of schizophrenia[42, 43,46-50] but in contrast to many others[34,42,43,51,52]. Further, multiple meta-analyses have also found mixed results[26,53-55]. Our previous and current findings provide a potential explanation for these discrepancies as the effects of multichannel TMS (mTMS) on both SANS scores and PRM task performance were not statistically significant until several weeks post-treatment. The exact reasons for these delayed effects are unclear but are not unusual following NIBS. For example, a recent randomized, sham-controlled two-arm study reported that active intermittent theta burst transcranial stimulation (iTBS) of the left DLPFC significantly reduced negative symptom severity in treatment-resistant schizophrenia patients compared to sham iTBS at 6 mo after the end of treatment[56]. Similarly, a randomized, double-blind, sham-controlled crossover study of accelerated iTBS for 2 wk in patients with TRD found a greater response rate (defined as a 50% reduction in Hamilton Depression Rating Scale score) after two additional weeks compared to immediately after treatment[57]. We speculate that this delay is due to the slow nature of the changes underlying reversal of negative symptoms, such as circuit-level plasticity and improvements facilitated by interpersonal relationships and social activities occurring over an extended period after treatment. In addition, plasticity may also take longer in older patients such as those examined in the current study. Further studies are warranted to test these and other potential mechanisms.

The improvement in visual recognition memory performance (increased number of correct responses) correlated significantly with a decrease in SANS total score at week 8 but not week 4. Moreover, PRM-number correct was correlated with SANS total score and all subscale scores except the affect flattening

subscale at baseline, suggesting shared neurological mechanisms. It is known that both cognitive deficits and negative symptoms of schizophrenia are associated with generalized dopamine (DA) signaling deficits in cortical and extrastriatal regions[58], and recent studies have shown that prefrontal hypodopaminergia can cause striatal DA disorders that in turn can lead to cognitive impairments[59,60]. Conversely, increasing DA release by administering low or moderate doses of psychostimulants improved negative symptoms and cognitive deficits in schizophrenia[60]. High-frequency rTMS applied over the left PFC also increased the release of DA in mesostriatal brain pathways[46] possibly accounting for improved negative symptoms and cognitive deficits. However, a host of other therapeutic mechanism may contribute, warranting further clinical and preclinical investigations.

This study had several limitations. First, the sample size was small, limiting statistical power and precluding exploratory subgroup analyses. Second, due to the homogeneity of the study population, these findings may not be applicable to other ethnic groups, patients in earlier phases of the disease including untreated first-episode patients, and those with distinct symptom clusters. Third, 180° rotation of the figure-of-eight coil did not completely prevent brain stimulation, so a real sham coil should be used in subsequent studies. Fourth, carrying forward the last observation is less suitable for small samples, although this was necessary in only a small portion of individual datasets. Fifth, the 4-wk follow-up period may not be sufficient to measure the full extent (or stability) or symptom improvement. Indeed, previous studies have monitored patients for 3 to 12 mo following treatment. Sixth, it is possible that visual recognition memory is particularly responsive to rTMS, so more comprehensive evaluations are required to establish clinical efficacy, including effects on executive functions, which are markedly impaired in many patients with schizophrenia. Seventh, it is uncertain if some patients recognized the specific treatment (active or sham) as we did not compensate for possible somatosensory effects. Eighth, we chose the left DLPFC based on past studies but other sites may be more effective. In addition, we did not use neuronavigation to determine the location of the DLPFC, which may introduce response heterogeneity. Finally, although antipsychotic drugs were included as covariates in statistical analysis, the different antipsychotic regimens may have distinct effects on the efficacy of rTMS.

CONCLUSION

High-frequency rTMS targeting the DLPFC can improve visual recognition memory in patients with schizophrenia. This high-frequency rTMS protocol may be of substantial clinical value because cognitive deficits are a major barrier to recovery and predict adverse clinical outcomes in patients with schizophrenia and other psychiatric disorders. Although the results of our study are encouraging, larger-scale studies with longer follow-up are needed to confirm the effectiveness of DLPFC-targeted rTMS for the treatment of cognitive deficits in first-episode schizophrenia patients and patients of different ethnicities. Moreover, therapeutic effects on other cognitive domains and the underlying mechanisms warrant further investigation.

ARTICLE HIGHLIGHTS

Research background

At present, antipsychotic drug therapy has little effect on the improvement of some psychiatric symptoms in schizophrenia patients, and drug therapy is not acceptable due to the unbearable adverse drug reactions. There is growing evidence that repetitive transcranial magnetic stimulation (rTMS) is effective for both positive and negative symptoms of schizophrenia.

Research motivation

Schizophrenia has brought great burden to the whole society with high morbidity and disability rate. The United Kingdom and the United States spend around 2% of GDP each year on the treatment, care and rehabilitation of people with schizophrenia. In particular, long-term hospitalization of patients wastes a large number of medical resources, and the existence of negative symptoms is one of the important reasons for long-term hospitalization of patients. Therefore, the use of rTMS adjuvant therapy to explore the possibility of improving the negative symptoms of patients, to promote the remission of patients, improve the social function and quality of life of patients, has good social and economic benefits.

Research objectives

In this study, we assessed the therapeutic effects and safety of left dorsolateral prefrontal cortex (DLPFC) high-frequency rTMS on negative symptoms of schizophrenia. We evaluated the efficacy of rTMS on recognition in patients with chronic schizophrenia.

Research methods

This was a randomized, sham-controlled, double-blinded trial. Patients diagnosed with schizophrenia on stable antipsychotic treatment were randomly assigned to active rTMS treatment group ($n = 25$) or a sham rTMS treatment group ($n = 22$). 25 patients in the active rTMS group received 10-Hz 110% motor threshold rTMS, while 22 patients were subjected to sham rTMS, both being given 4-wk treatment (5 d/wk). Efficacy of negative symptom was assessed with the Scale for the Assessment of Negative Symptoms (SANS), the Positive and Negative symptom scale (PANSS) at baseline, the end of 4 and 8 wk. The cognitive function was assessed with Cambridge Neuropsychological Test Automated Battery at baseline, the end of 4 and 8 wk. The side effects were assessed with TESS at baseline and the end of 4 wk.

Research results

There were no significant differences in pattern recognition memory (PRM) performance metrics, SANS total score, SANS subscores, PANSS total score, and PANSS subscores between active and sham rTMS groups at the end of the 4-wk treatment period, but PRM performance metrics (percent correct and number correct) and changes in these metrics from baseline were significantly greater in the active rTMS group at week 8 compared to the sham group (all $P < 0.05$). Active rTMS treatment also significantly reduced SANS score at week 8 compared to sham treatment. Moreover, the improvement in visual memory was correlated with the reduction in negative symptoms at week 8. In contrast, there were no between-group differences in PANSS total score and subscale scores at either week 4 or 8 (all $P > 0.05$).

Research conclusions

High-frequency TMS can improve visual memory and reduce negative symptoms in patients with schizophrenia, but these effects are delayed, potentially due to the requirement for extensive neuroplastic changes within DLPFC networks.

Research perspectives

In the future, it is necessary to further explore more scientific treatment parameters and more sensitive assessment tools (such as SANS and neuropsychological assessment kits) for rTMS in the treatment of negative symptoms of schizophrenia, and carry out multicenter, large-sample studies.

FOOTNOTES

Author contributions: Du XD contributed to the project administration, funding acquisition, supervision, wrote the review and editing; Li Z contributed to clinical data collection, wrote review and editing; Yuan N contributed to the data curation, investigation; Yin M, Zhao XL, Lv XL, Zou SY, Zhang J, Li CW, Pan H, Yang L, Wu SQ, Yue Y and Wu YX contributed to the conceptualization, data curation and investigation; Zhang XY contributed to the formal analysis, wrote the original draft; Du XD, Li Z and Yuan N have contributed equally to this work.

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Informed consent statement: Each subject provided written informed consent to participate in the study after a researcher staff explained the whole study to each of them.

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Data sharing statement: The data will be available on request from the readers.

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