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Cognitive Enhancing Effect of High-Frequency Neuronavigated rTMS in Chronic Schizophrenia Patients With Predominant Negative Symptoms: A Double-Blind Controlled 32-Week Follow-up Study

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Accumulating studies have shown that high-frequency (HF) repetitive transcranial magnetic stimulation (rTMS) may improve cognitive dysfunction of the patients with schizophrenia (SCZ), but with inconsistent results. The present study aims to assess the efficacy of different frequencies of neuronavigated rTMS in ameliorating cognitive impairments and alleviating the psychotic symptoms. A total of 120 patients were randomly assigned to 3 groups: 20 Hz rTMS (n = 40), 10 Hz rTMS (n = 40), or sham stimulation (n = 40) for 8 weeks, and then followed up at week 32. The Repeatable Battery for the Assessment of Neuropsychological Status (RBANS) was performed to assess the cognitive functions of the patients at baseline, at the end of week 8, and week 32 follow-up. Psychotic symptoms were assessed with the Positive and Negative Syndrome Scale (PANSS) at baseline and at the end of week 2, week 4, week 6, week 8, and week 32 follow-up. Our results demonstrated that 20 Hz rTMS treatment produced an effective therapeutic benefit on immediate memory of patients with chronic SCZ at week 8, but not in the 10 Hz group. Interestingly, both 10 Hz and 20 Hz rTMS treatments produced delayed effects on cognitive functions at the 6-month follow-up. Moreover, in both 10 Hz rTMS and 20 Hz rTMS, the improvements in RBANS total score were positively correlated with the reduction of PANSS positive subscore at the 6-month follow-up. Stepwise regression analysis identified that the visuospatial/constructional index, immediate memory index, and prolactin at baseline were predictors for the improvement of cognitive impairments in the patients. Our results suggest that add-on HF rTMS could be an effective treatment for cognitive impairments in patients with chronic SCZ, with a delayed effect. Trial registration: clinicaltrials.gov identifier—NCT03774927.

Key words: schizophrenia/cognition/rTMS/randomized controlled trial/immediate memory

Introduction

Schizophrenia (SCZ) is a recurrent and severe mental illness.[1] Prior studies have consistently shown that patients with SCZ display several domains of cognitive impairments, such as working memory, attention, executive function, and cognitive speed[2–4] (reviewed in [5]). Cognitive impairment of SCZ may be related to changes in prefrontal cortex (PFC) maturation,[6] which is a potential treatment target for cognitive remediation in patients.[7] Currently, most antipsychotics effectively improve the positive symptoms at any stage of illness but do not show any improvement in cognitive impairments.[8,9]

Repetitive transcranial magnetic stimulation (rTMS) is an add-on treatment for SCZ who failed in multiple pharmacologic interventions.[10] In schizophrenia, high-frequency (HF, 10–20 Hz) stimulation has been known to cause excitatory effects in reducing the negative symptoms.[11] rTMS is currently being evaluated as a new additional treatment option for cognitive impairments in patients with SCZ who are not responding to multiple drug interventions and works by altering the neuronal

activity in the applied area and its related network.[12–14] Studies about the effects of active rTMS on cognitive dysfunction in SCZ were relatively rare.[15] For example, a pilot randomized controlled trial (RCT) showed that 20 Hz bilateral PFC rTMS significantly improved verbal fluency score of cognitive functions.[13] In another RCT study, Wölwer et al[16] indicated that 10 Hz rTMS stimulation to the left dorsolateral prefrontal cortex (DLPFC) significantly improved facial emotion recognition in SCZ. However, the results were inconsistent[14,17] (reviewed in [18]). Specifically, the most recent meta-analysis demonstrated that prefrontal rTMS exerted pro-cognitive effects in certain patients with depression but not in the patients with SCZ.[12] Collectively, this area is still nascent, and more research is required to explore the duration of benefits and the optimal stimulation parameters for certain domains of cognitive impairments.[19] Inconsistencies in the rTMS treatment regimens may explain significant differences in the results obtained in previous studies reported in the meta-analyses.[20] The localization of treatment (left vs right vs bilateral), duration of treatment, frequencies of stimulation, accuracy of targeting, and patient characteristics should be noted as important varying parameters amongst trials.[21,22] It is still an ongoing issue as to whether more repetitions as in more sessions or more pulses may yield better results.[23] It has been found that the DLPFC is associated with cognitive functions and lower activation of DLPFC is related to cognitive impairment of SCZ.[24,25] However, DLPFC is a relatively large cortical area and the majority of previous studies may not have accurately targeted the DLPFC.[26–28] The neuronavigation system is used for precise targeting and monitoring in rTMS studies by co-registering the subject's head to a standardized brain.[29] Under the guidance of the navigation system, the entire stimulation position becomes accurate.[30]

This study was the first time to compare the efficacy of treatment with 10 Hz and 20 Hz rTMS combined with neuronavigation system and a longer duration of treatment (8 consecutive weeks) in psychotic symptoms and cognitive dysfunction in patients with chronic SCZ, with a follow-up of 6 months. The main purpose of this study was intended to investigate whether the combination of both neuronavigation and HF (10 Hz or 20 Hz) stimulation may be an optimal strategy for improving cognitive function and reducing symptoms in patients with SCZ. We hypothesized that HF-rTMS at both 10 HZ and 20 Hz would significantly improve cognitive impairment and clinical symptoms in SCZ patients, with a significant difference in efficacy between them favoring 20 Hz rTMS. Moreover, rTMS-induced cognitive improvement would be associated with the change in certain clinical symptoms. In addition, we hypothesized that the routine biochemical markers and clinical variables at baseline would predict the improvement of cognitive deficits or clinical symptoms.

Methods

Participants

All participants were enrolled in HeBei Province Veteran Psychiatric Hospital in BaoDing city. The study protocol was approved by the Institutional Review Board of HeBei Province Veteran Psychiatric Hospital. After fully debriefed on the protocol of the study, each participant signed a written informed consent form prior to initiation of the study. One hundred and twenty patients were enrolled and diagnosed with SCZ as determined by the Structured Clinical Interview for DSM-IV (SCID). All patients also met the following inclusion criteria: (1) male; (2) aged 20–60; (3) without abuse or substance dependence except tobacco; (4) patients who had never received rTMS or modified electroconvulsive therapy (MECT) in the past; and (5) received stable doses of antipsychotic drugs for at least 12 months before entry into the study with unresolved negative symptoms (the Positive and Negative Syndrome Scale [PANSS] positive score <24 and PANSS negative score ≥20].

At baseline, a complete medical history and physical examination were obtained from all patients. All recruited participants also met the following exclusion criteria: (1) with recent life stresses, and clinically significant affective disorders for at least 1 month prior to recruitment in the current study, which was assessed based on SCID by the research psychiatrist; (2) with physical diseases such as cerebral pathologies and those receiving electroconvulsive therapy in the past 3 months; (3) with family history of epilepsy; (4) pregnant or breastfeeding; (5) education years less than 5 years by subject report; (6) receiving or planning to start psychotherapy during rTMS treatment or received psychotherapy in the past 6 months before the current study, as we considered that psychotherapy might have an impact on cognitive performance.

Out of a total of 120 patients, 40 patients were randomly assigned in the 20 Hz rTMS group, 40 in the 10 Hz, and 40 in the sham group. Adjustments of dose and type of antipsychotic drugs were not allowed during the study. Thirteen subjects were dropped out due to withdrawal of their consent (6 in 20 Hz rTMS, 4 in 10 Hz rTMS, and 3 in sham rTMS groups), and the magnetic resonance imaging (MRI) images of 10 patients failed to fully recover (4 in 20 Hz rTMS, 4 in 10 Hz rTMS, and 2 in sham rTMS groups). Finally, 97 patients completed the clinical trial, including 20 Hz rTMS (n = 30), 10 Hz rTMS group (n = 32), and sham rTMS group (n = 35). In addition, 8 patients were lost by the end of 6-month follow-up due to unanticipated discharge (4 in 20 Hz rTMS, 2 in 10 Hz rTMS, and 2 in sham rTMS groups) (figure 1). All patients were taking a stable dose of antipsychotics, showing in table 1. Also, 10 patients were on antidepressant medications (escitalopram oxalate, sertraline, and paroxetine). Adjustments of the antidepressants were

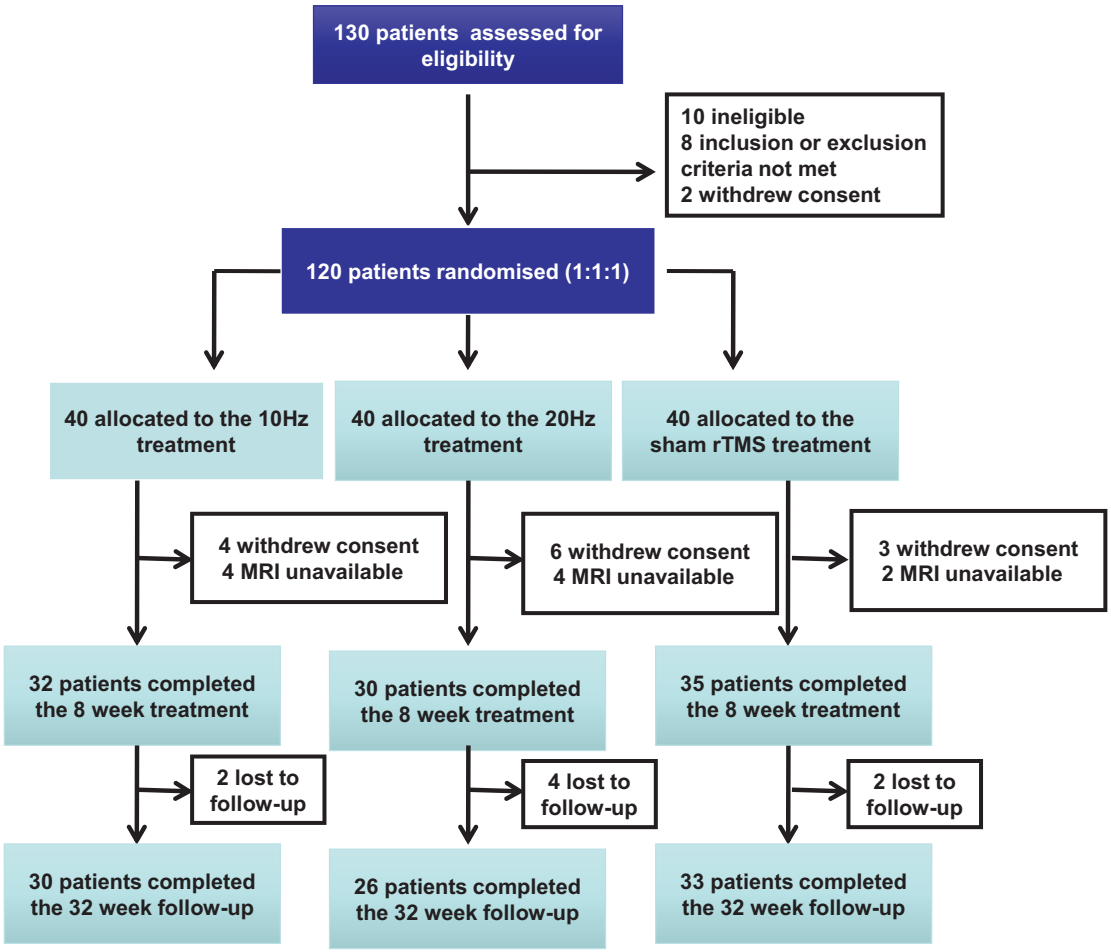

Fig. 1. The study flow chart. *Note*: rTMS, repetitive transcranial magnetic stimulation; MRI, magnetic resonance imaging.

allowed during the study participation. There were no significant differences in demographic and clinical variables as well as Repeatable Battery for the Assessment of Neuropsychological Status (RBANS) scores between patients on antidepressants and the rest of the study sample (all $P > .05$).

Randomization and rTMS Treatment

This study was a single-institution, randomized controlled, double-blinded pilot trial. First, the computer-generated randomization list was complied by simple randomization. After enlistment, an independent third party randomly assigned the patients to 20 Hz, 10 Hz, or sham groups with the proportion of 1:1:1, based on the computer-generated random identification number they received. The researchers including the scale raters and patients were blind to the assignment. Only 1 rTMS operator in the Department of Physical Therapy who conducted the active rTMS or sham treatment knew the assignment; however, he did not participate in this study. 20 Hz and sham administrations were identical in appearance and sound, with similar scalp pain. Patients were, therefore, unable to distinguish between active and sham rTMS.

The patients received rTMS treatment once a day for a total of 40 times using a MagStim Rapid stimulator (Rapid2, MagStim Company Ltd.). The definition of motor threshold (MT) was the same as previous studies.[31] In the 20 Hz group, stimulations over left DLPFC occurred at a power of 110% of MT for 1.6-s intervals with 28-s inter-train interval. In the 10 Hz group, rTMS stimulations over left DLPFC occurred at a power of 110% of MT for 3-s intervals with a 27-s inter-train interval. Forty trains were administered each day (Monday to Friday) for 8 consecutive weeks (total stimuli = 64 000 for 20 Hz and 48 000 for 10 Hz). In sham rTMS, all procedures were identical to the 20 Hz group except for a false coil (P/N: 3950-00, Magstim Co.).[32] The sham treatment produced the same vibration as the true stimulus but no magnetic field and thus no therapeutic effect. Both 20 Hz and sham administrations were identical in appearance and in sound.

After 8 weeks of treatment, rTMS treatments were discontinued. All patients were followed up for another 6 months to examine the improvement of psychotic

Table 1. Demographic Data of 10 Hz, 20 Hz, and Sham rTMS Groups at Baseline

	10 Hz (n = 40)	20 Hz (n = 40)	Sham rTMS (n = 40)	X^2 or F(P-value)	Dropouts (n = 23)	Completers (n = 97)	X^2 or F(P-value)
Age (yrs)	50.7 ± 9.0	52.0 ± 10.1	54.7 ± 6.4	2.5(.10)	57.0 ± 6.8	51.4 ± 9.1	7.1(.01)
Education (yrs)	7.9 ± 2.4	7.9 ± 2.5	7.8 ± 1.9	0.01(.96)	7.1 ± 2.1	7.9 ± 2.1	2.7(.11)
Smokers (%)	78.6	75.6	69.7	0.88(.71)	69.6	75.4	0.3(.59)
Age of onset (yrs)	21.0 ± 2.3	20.2 ± 2.4	21.3 ± 1.5	0.15(.86)	21.5 ± 1.9	20.9 ± 2.2	1.2(.28)
Duration of illness	29.5 ± 9.6	31.0 ± 9.5	34.1 ± 6.3	2.5(.97)	34.7 ± 6.4	30.9 ± 9.1	3.3(.07)
Hospital time	5.5 ± 2.5	6.3 ± 3.5	5.5 ± 3.0	0.36(.70)	7.0 ± 3.4	5.5 ± 2.7	4.6(.03)
Antipsychotics type							
Clozapine	18	22	26		10	53	
Risperidone	8	7	7		5	17	
Olanzapine	4	4	3		3	10	
Chlorpromazine	4	3	1		2	7	
Sulpiride	3	2	1		2	5	
Ziprasidone	3	2	2		1	5	
Dose	416.9 ± 257.6	422.3 ± 231.7	410.5 ± 218.5	0.07(.93)	422.4 ± 221.3	410.5 ± 221.6	1.6(.23)
PANSS total score	74.2 ± 14.5	72.5 ± 12.3	79.8 ± 16.3	2.4(.10)	78.3 ± 16.4	72.6 ± 14.0	2.5(.12)
P subscore	11.9 ± 5.1	11.4 ± 4.8	11.6 ± 3.1	0.3(.71)	11.9 ± 4.1	11.5 ± 4.5	0.1(.74)
N subscore	28.8 ± 6.8	28.2 ± 6.2	31.3 ± 8.1	2.4(.10)	32.3 ± 8.4	28.1 ± 6.8	5.4(.02)
G subscore	32.1 ± 7.4	32.2 ± 7.8	36.3 ± 8.5	2.3(.11)	34.2 ± 9.5	33.0 ± 7.8	0.39(.53)
RBANS total score	59.2 ± 10.1	61.2 ± 12.3	58.6 ± 12.2	0.4(.65)	54.2 ± 7.7	61.3 ± 12.1	5.2(.03)
Immediate memory	49.2 ± 9.9	52.4 ± 12.2	50.5 ± 10.1	0.19(.83)	47.6 ± 6.9	51.8 ± 11.6	2.1(.15)
Attention	70.1 ± 16.6	70.2 ± 16.1	66.5 ± 13.2	0.51(.61)	63.9 ± 14.2	70.9 ± 15.5	2.8(.1)
Visuospatial/ constructional	70.9 ± 10.7	72.8 ± 17.3	69.3 ± 15.2	0.18(.81)	64.4 ± 11.8	72.9 ± 14.6	4.8(.03)
Delayed memory	65.3 ± 16.3	65.1 ± 20.6	64.7 ± 20.1	0.05(.91)	55.5 ± 16.7	66.9 ± 18.6	5.2(.03)
Language	78.3 ± 15.3	79.1 ± 15.0	74.1 ± 15.4	0.72(.49)	75.3 ± 15.4	78.2 ± 15.4	0.5(.5)

Note: PANSS, Positive and Negative Syndrome Scale; P, positive symptom; N, negative symptom; *G*, general psychopathology; RBANS, repeatable battery for the assessment of neuropsychological status; Dose daily antipsychotic dose (mg) chlorpromazine equivalent.

symptoms or cognition at week 32. This 6-month follow-up study was not blinded.

Assessments

The primary outcome measure was cognitive function assessed by RBANS and the secondary outcome measure was clinical symptoms assessed by PANSS. Cognitive function was assessed at baseline, at week 8, and 6-month follow-up using RBANS. Psychotic symptom assessments were conducted at baseline, at the end of week 2, week 4, week 6, week 8, and 6-month follow-up using the PANSS. All outcome measures were assessed by raters who were not permitted access to the treatment sessions.

Neuronavigated Left DLPFC

The anatomic MRI scan of the subjects and the head of the subjects were registered together by frameless stereotactic methods. Using the Polaris infrared tracking system, the head position of the subjects was evaluated to measure the position of scalp marks (nose tip, nasion, and invagination of the left and right ears) seen on the MRI. We placed the transcranial magnetic stimulation (TMS) coil on the target brain area. Neuronavigation software was used to estimate the root mean square of the difference between co-registered anatomical markers which was limited to less than 2 mm for each subject to improve accuracy. After anatomical co-registration, an 8-shaped coil was placed in a direction tangent to the scalp, resulting in a posterior forward current perpendicular to the central sulcus trunk. Based on recent meta-analyses of functional neuroimaging studies on cognitive function, superior region Brodmann area (BA) 46 and posterior region BA9 were used as targets that the rTMS worked on. The positioning parameters of a single coil were kept in the neuronavigation software.

Routine Biochemical Analysis

Blood samples were collected at 7 AM after overnight fasting. The serum levels of blood sugar, hormones, including prolactin, testosterone, thyroid-stimulating hormone (TSH), triiodothyronine (T3), thyroxine (T4), free triiodothyronine (FT3), and free thyroxine (FT4), and lipid profiles, including triglycerides (TG) and total cholesterol (TC), were measured in the hospital laboratory center using commercially available kits from Leadman and an automatic biochemistry analyzer AU2700.

Data Analysis

The demographic characteristics, baseline psychotic symptoms, and baseline neuropsychological test scores

of the 3 groups were compared using analysis of variance (ANOVA) or chi-square. Intent-to-treat (ITT) analysis was carried out and missing data were imputed following the principle of last-observation-carrying-forward (LOCF).

In the longitudinal study, the first aim was to examine the effects of 10 Hz and 20 Hz rTMS on cognitive function and symptoms in 97 patients as the ITT analysis. The main strategy involved repeated-measures (RM) multivariate analyses of variance (MANOVAs). After an RM MANOVA, significant multivariate omnibus test was followed-up with an examination of individual univariate effects. The primary outcome was cognitive function measured by RBANS and the secondary outcome was clinical symptoms measured by PANSS. For the dependent variables, 6 time points (baseline, week 2, week 4, week 6, week 8, and 6-month follow-up) were used as the RM within-effect, and group (10 Hz, 20 Hz vs sham) was used as the between-effect. If the group × time interaction was significant, then the group difference at week 2, week 4, at week 8, and 6-month follow-up was respectively analyzed by analysis of covariance (ANCOVA) with the baseline score as a covariate. If the above interaction effect was not significant, further statistical testing was not required. To adjust for multiple testing, a Bonferroni correction was applied. The Bonferroni procedure refers to all applied independent statistical tests. All statistical analyses were conducted in Predictive Analytics SoftWare (PASW) Statistics, version 22.0 (SPSS, Inc.).

Results

Demographic and Basic Descriptive Data

At baseline, as shown in tables 1 and 2, there was no statistical differences between the 3 groups in demographic characteristics, clinical variables including the PANSS total and subscale scores, and the RBANS total and subscores (all $P > .05$). Moreover, no significant difference between the 3 groups was found in the biochemical analysis (all $P > .05$).

Interestingly, RBANS total score had significant negative correlations with positive subscale score ($r = -.27$, $df = 97$, $P = .04$; Bonferroni corrected $P > .05$), and negative subscale score ($r = -.58$, $df = 97$, $P < .001$; Bonferroni corrected $P < .01$). After controlling for confounders, only a significant association between negative subscale and RBANS total score was found. No significant association between prolactin and cognitive function measured by RBANS was found in the patients at baseline ($P > .05$).

rTMS Treatment for Cognitive Performance

We investigated whether rTMS treatment for 8 weeks and follow-up for another 6 months improved the cognitive functions among 10 Hz, 20 Hz, and sham groups. We conducted a RM MANOVA with RBANS total score and index scores serving as outcome measures, showing that there was a group × time interaction (Wilks' lambda $F_{(2,97)} = 3.1$; $P < .001$), as well as main effects for both time (Wilks' lambda $F_{(2,97)} = 12.4$; $P < .001$) and group (Wilks' lambda $F_{(1,99)} = 0.46$; $P = .5$). Univariate analyses with RM ANCOVA on RBANS total score revealed a significant group-by-time effect ($F_{(4,97)} = 7.4$, $P < .001$; Bonferroni corrected $P < .01$), a significant group effect ($F_{(4,97)} = 5.4$, $P = .008$; Bonferroni corrected $P < .05$), and a significant time effect ($F_{(4,97)} = 29.7$, $P < .001$; Bonferroni corrected $P < .01$) (table 3 and figure 2). Further, RM ANCOVA on 5 domains of RBANS showed that there was only a significant group effect on immediate memory index ($F_{(4,97)} = 5.7$, $P = .006$), together with a significant interaction of group-by-time effect ($F_{(4,97)} = 10.9$,

Table 2. PANSS Total Score and Subscores at Baseline, Week 2, Week 4, Week 6, Week 8, and 6 Months Follow-up in 10 Hz (n= 3 2), 20 Hz (n = 35), and sham (n = 30) rTMS groups

	Baseline (n = 97)	Week 2 (n = 97)	Week 4 (n = 97)	Week 6 (n = 97)	Week 8 (n = 97)	Follow-up (n = 97)	Group × Time F(P-value)
PANSS total score							1.0(.39)
Sham	79.1 ± 16.2	71.3±17.1	68.2 ± 20.9	66.9 ± 21.1	67.2 ± 21.5	61.8 ± 17.2	
20 Hz	72.9 ± 12.1	66.8 ± 12.1	62.5 ± 12.1	60.1 ± 13.9	58.8 ± 13.8	59.9 ± 16.3	
10 Hz	72.5 ± 14.1	71.4 ± 14.0	70.7 ± 13.8	69.7 ± 14.7	68.7 ± 13.4	60.4 ± 20.6	
Positive subscore							0.06(.94)
Sham	11.8 ± 3.2	10.5 ± 2.5	10.7 ± 2.2	10.6 ± 2.3	10.4 ± 2.2	9.3 ± 2.1	
20 Hz	11.2 ± 3.7	10.9 ± 4.1	11.7 ± 4.0	11.0 ± 3.9	10.1 ± 4.1	10.1 ± 3.2	
10 Hz	12.2±5.4	12.2±5.6	11.6±5.6	11.1±5.7	11.0±5.7	10.3±2.6	
Negative subscore							0.68(.58)
Sham	30.3 ± 7.9	27.7 ± 8.1	25.8 ± 8.9	24.9 ± 9.1	22.9 ± 10.5	22.2 ± 7.9	
20 Hz	27.9 ± 6.1	26.3 ± 5.1	22.3 ± 6.1	21.1 ± 5.1	20.1 ± 5.1	21.0 ± 8.4	
10 Hz	27.6 ± 6.5	26.6 ± 6.9	24.5 ± 7.2	23.6 ± 6.8	21.8 ± 5.8	20.5 ± 8.7	
General subscore							1.3(.28)
Sham	35.9±8.2	33.9±8.1	32.1±9.1	33.1±10.1	33.7±10.0	30.1±7.9	
20 Hz	33.2±7.1	31.9±7.0	28.1±7.0	27.9±7.0	26.7±7.1	28.8±8.6	
10 Hz	32.6±7.8	31.4±7.7	30.6±8.2	29.6±8.3	28.6±8.0	29.7±10.2	

Table 3. Cognitive Score and Comparison at Baseline, Week 8, and 6 months follow-up in 10 Hz, 20 Hz, and Sham rTMS groups

	Baseline (n = 97)	Week 8 (n = 97)	6 months (n = 97)	Group F (P value)	Time F (P value)	Group × Time F(P value)
Immediate memory				3.6(.035)	0.75(.48)	15.2(.00)
Sham	50.6 ± 10.0	61.7 ± 14.4	56.3 ± 13.9			
20 Hz	51.9 ± 12.9	72.8 ± 17.3	75.5 ± 18.2			
10 Hz	50.0 ± 9.4	63.5 ± 16.6	83.6 ± 14.2			
	Attention			1.4(.25)	1.4(.25)	1.5(.22)
Sham	63.6 ± 15.0	66.8 ± 13.5	59.6 ± 13.8			
20 Hz	69.6 ± 13.3	70.8 ± 16.4	66.3 ± 16.4			
10 Hz	70.9 ± 17.2	66.1 ± 14.9	70.2 ± 15.7			
Visuospatial/constructional				1.5(.24)	0.59(.56)	7.2(.002)
Sham	69.3 ± 15.0	78.5 ± 13.3	72.2 ± 14.5			
20 Hz	72.0 ± 16.9	82.1 ± 18.6	84.4 ± 17.2			
10 Hz	70.6 ± 10.3	81.0 ± 12.0	92.8 ± 14.3			
Delayed memory				1.5(.24)	1.9(.15)	10.8(.00)
Sham	63.9 ± 20.0	71.0 ± 18.5	72.4 ± 18.8			
20 Hz	65.6 ± 20.0	83.7 ± 21.1	86.0 ± 18.1			
10 Hz	65.8 ± 16.3	78.4 ± 22.9	94.9 ± 14.2			
Language				0.41(.67)	0.88(.42)	4.1(.023)
Sham	74.9 ± 15.1	85.8 ± 17.0	75.8 ± 14.3			
20 Hz	78.9 ± 15.0	84.6 ± 9.5	81.4 ± 10.5			
10 Hz	78.7 ± 15.4	85.7 ± 12.2	88.0 ± 6.8			
RBANS total score				2.8(.07)	1.8(.17)	20.3(.00)
Sham	58.6 ± 12.0	71.3 ± 14.8	60.7 ± 12.4			
20 Hz	60.9 ± 12.1	78.1 ± 16.2	72.9 ± 15.2			
10 Hz	61.2 ± 12.1	74.0 ± 14.6	81.7 ± 13.0			

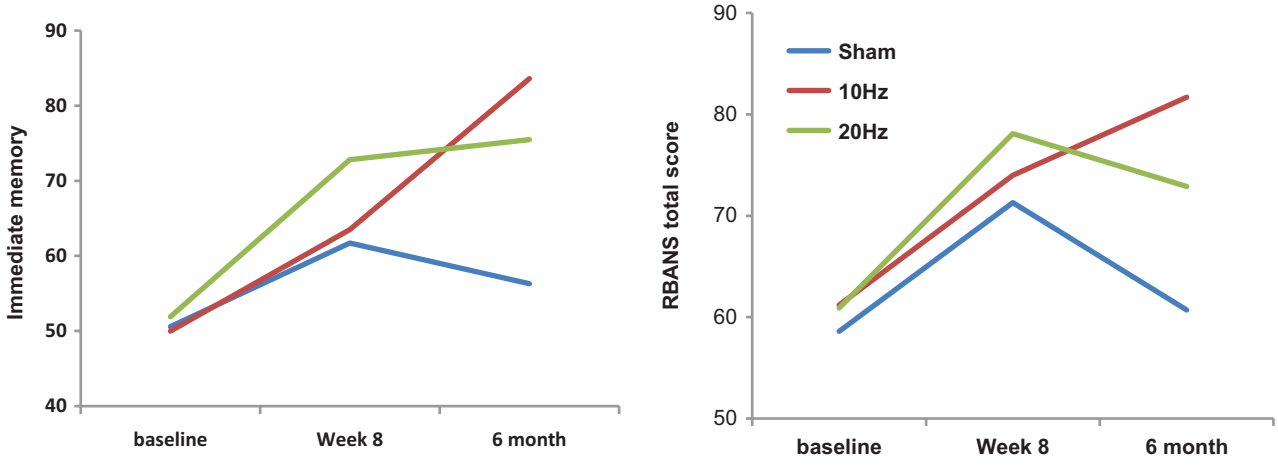

Fig. 2. rTMS treatment significantly increased the immediate memory score and RBANS total score in the patients with schizophrenia both in 10 Hz rTMS and 20 Hz rTMS, as compared with sham stimulation ($P < .05$).

$P < .01$; Bonferroni corrected $P < .01$), and a significant time effect ($F_{(4,97)} = 65.5$, $P < .01$; Bonferroni corrected $P < .01$). The results of RM ANCOVA on other individual domains of RBANS were included in the supplementary Results section. Covariates in the RM MANOVA analysis included age, duration of illness, hospital time, and PANSS negative subscore.

To investigate the effect of 2 stimulation frequencies on cognitive function, the separate repeated-measures ANCOVA were performed between 10 Hz rTMS vs sham, 20 Hz rTMS vs sham, and 10 Hz rTMS vs 20 Hz rTMS. The results showed that there were significant group effects on the RBANS total score between 10 Hz rTMS and sham stimulation ($F_{(1,36)} = 6.4$, $P = .017$; Bonferroni corrected $P > .05$), as well as 20 Hz rTMS and sham stimulation ($F_{(1,36)} = 16.3$, $P < .001$; Bonferroni corrected $P < .01$), while no significant effect between 10 Hz rTMS and 20 Hz rTMS ($F_{(1,36)} = 0.02$, $P = .90$). The 20 Hz rTMS group performed better than the sham group on immediate memory at week 8 ($P = .026$; effect size = 0.70) (table 3).

After covarying for age, duration of illness, hospital time, and PANSS negative subscore, further ANCOVA analysis found that after 6-month follow-up, the RBANS total score and subscores were significantly higher in the

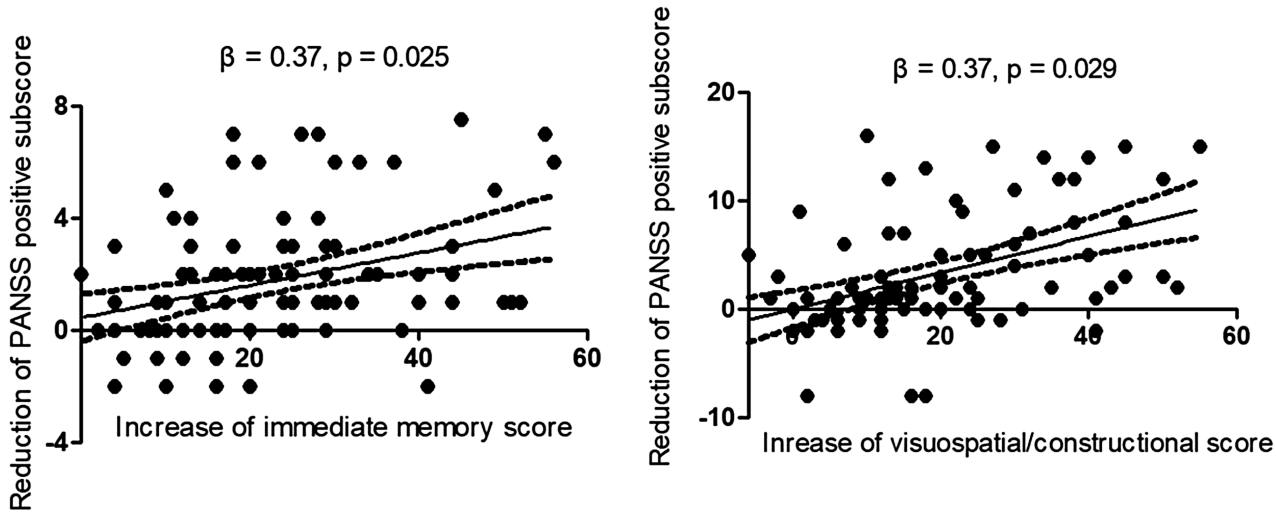

Fig. 3. The increase in immediate memory score was significantly associated with the reduction of the PANSS positive score from baseline to week 8, which was confirmed in further multiple regression (β = .37, *P* = .025). The increase in visuospatial/constructional score was significantly associated with the reduction of the PANSS positive score from baseline to week 32 (β = .37, *P* = .029).

10 Hz group compared with the 20 Hz and sham groups, and higher in the 20 Hz compared with the sham group (table 3). For 10 Hz rTMS treatment vs sham stimulation, further ANCOVA showed that the RBANS total score was significantly higher in the rTMS group than in the sham group at 6-month follow-up ($F_{(1,54)}$ = 31.1, *P* < .001; effect size = 1.65; Bonferroni corrected *P* < .01), as well as its 5 subscores (all *P* < .05). For 20 Hz rTMS vs sham stimulation, ANCOVA showed that the RBANS total score was significantly higher in the 20 Hz rTMS group compared with the sham group at 6-month follow-up ($F_{(1,54)}$ = 57.6, *P* < .001; effect size = 0.88; Bonferroni corrected *P* < .01), as well as its subscores, such as immediate memory index, visuospatial/constructional index, and delayed memory index. For 20 Hz rTMS vs 10 Hz rTMS stimulation, ANCOVA showed that the RBANS total score ($F_{(1,48)}$ = 10.1, *P* = .003; effect size = 0.62; Bonferroni corrected *P* < .05), language index ($F_{(1,48)}$ = 5.5, *P* = .02; effect size = .75; Bonferroni corrected *P* > .05), and visuospatial/constructional index ($F_{(1,48)}$ = 6.1, *P* = .016; effect size = 0.53; Bonferroni corrected *P* > .05) were significantly higher in the 10 Hz rTMS group compared with the 20 Hz rTMS group at 6-month follow-up.

rTMS Treatment for Psychopathological Symptoms

In the secondary outcome, changes in the PANSS and their subscale scores are illustrated in table 2. RM ANCOVA on PANSS and its subscales showed no significant group-by-time effect, group effect, and time effect (all *P* > .05), after covarying for age, duration of illness, hospital time and antipsychotic dosage (chlorpromazine equivalents).

Correlation analysis in active rTMS group showed significant correlations between the increase in immediate memory from baseline to week 8 and the following parameters: the reduction of PANSS positive subscores (*r* = .40, *df* = 63, *P* = .017; Bonferroni corrected *P* > .05). Correlation analysis in active rTMS group showed significant correlations between the increase in visuospatial/constructional index from baseline to 6-month follow-up and the reduction of PANSS positive subscores (*r* = .37, *df* = 60, *P* = .026) (figure 3). However, none of these significant findings survived Bonferroni correction (all *P* > .05). Further analysis showed a significant association between the increase in immediate memory index score and the decrease of PANSS positive subscore (β = .37, *t* = 2.3, *P* = .025), as well as the increase in visuospatial/constructional index score and the decrease of PANSS positive subscore (β = .37, *t* = 2.3, *P* = .029), after covarying for age, duration of illness, hospital time, and antipsychotic dosage.

Potential Predictors of Treatment Response

Multiple linear regression analyses were carried out for 2 stimulation frequencies of rTMS treatment. The treatment effect was represented by the increase in the RBANS scores from baseline to week 8 or 6-month follow-up. Analyses were performed separately both in the 10 Hz rTMS and 20 Hz rTMS treatment groups. Correlation analysis showed that age, education age, onset age, and duration of illness were associated with the change in cognition or PANSS scores (all *P* < .05). Further, since some demographics and clinical data were different between dropouts and completers in the present study, the covariates included age, education, smoke status, onset age, duration of illness, baseline psychopathology, baseline RBANS scores, and baseline laboratory evaluations. Due to the strong positive association between age and duration of illness and to avoid including completely collinear covariates in our multivariate analysis, we chose

the duration of illness as a covariate in the regression analysis. The results showed that immediate memory index (β = −1.4, t = −2.5, P = .034) and visuospatial/constructional index (β = .97, t = 3.3, P = .011) at baseline were significant predictors for immediate memory improvement from baseline to week 8 in the 20 Hz group, while prolactin (β = .23, t = 2.4, P = .025) was a significant predictor for RBANS total score improvement from baseline to 6-month follow-up.

Treatment Side Effects

No serious side effects were reported during or after treatment. Five patients (2 in the 10 Hz rTMS group, 1 in the 20 Hz group, and 2 in the sham group) experienced mild dizziness during the first treatment. Four patients (2 in the 10 Hz rTMS group and 2 in the 20 Hz group) complaint of scalp pain during the first few rTMS treatments, without any specific therapy. No one suffered from a headache. One subject in 10 Hz rTMS group developed insomnia that disappeared after 3 treatments.

Discussion

The major findings of this study are that: (1) 20 Hz rTMS treatment, rather than 10 Hz rTMS, produced an effective therapeutic benefit on immediate memory of patients with chronic SCZ at week 8; (2) both 10 Hz and 20 Hz rTMS treatments produced an delayed effect on cognitive impairments at 6-month follow-up; (3) In the 20 Hz rTMS group, the improvement in immediate memory of patients was associated with the reduction in PANSS positive subscore at the end of week 8. Moreover, in both 10 Hz rTMS and 20 Hz rTMS, the improvement of RBANS total score was positively correlated with a reduction of PANSS positive subscore at 6-month follow-up; and (4) immediate memory index, visuospatial/constructional index, and prolactin at baseline were predictors for the improvements of cognitive impairments in the patients. Our findings showed a clinically meaningful improvement of immediate memory performance only in the 20 Hz rTMS group for short-term treatment compared with 10 Hz rTMS and sham groups, and effective on cognitive impairments both in 10 Hz and 20 Hz for long-term follow-up. Taken together, neuronavigated rTMS appears to be an effective treatment for cognitive impairments in patients with chronic SCZ with a delayed effect.

In this 8-week double-blind sham-controlled randomized clinical trial, patients with 20 Hz rTMS had significantly increased immediate memory score than the sham group when the trial was completed. However, there were no significant differences in RBANS scores between the 10 Hz rTMS and sham groups, and between the 10 Hz rTMS and 20 Hz rTMS groups. Consistent with our results, Barr et al[15] found bilateral 20 Hz rTMS targeted to DLPFC for 4 weeks significantly improved working memory measured by 3-back tasks to be at a level parallel to the normal controls. Additionally, a previous multicenter randomized sham-controlled study in a large sample also found that although stimulation treatment targeted to left DLPFC for 3-week intervention resulted in improvements in multiple domains of cognitive functions, including working memory performance, no statistically significant difference was found between 10 Hz rTMS and sham.[14] The exact mechanisms responsible for the effective treatment of rTMS for cognitive impairments in SCZ are still unknown. Studies have shown that rTMS applied over the left PFC increases the release of dopamine in certain brain pathways,[33] which is consistent with the dopamine hypothesis for cognitive deficits of patients with SCZ.[34] Moreover, animal studies found that HF rTMS increased the concentration of *N*-methyl-D-aspartate (NMDA) receptors, enhanced neurogenesis, and activated the brain-derived neurotrophic factor (BDNF) signaling pathway.[35,36] Thus, a possible explanation for the effect of rTMS on immediate memory is that the above molecular effects may alter the intrinsic and extrinsic properties of neurons and reprogram the expression of neurotransmitters and their receptors, as well as the activation of neurotrophins, leading to long-lasting synaptic plasticity-related changes like long-term potentiation (LTP).[36] However, it should be noted that we found that the 10 Hz treatment showed no significant efficiency at the end of the 8-week treatment period; however, a significant improvement of cognitive functions in the active group compared with the sham group was observed at the 6-month follow-up, indicating a delayed therapeutic effect. Long-term (several months) follow-up after rTMS treatment is rarely investigated. In line with our results, several prior studies found a significant treatment effect up to 4-week follow-up[37] and even up to 6-month follow-up.[38] However, a recent study showed no significant difference between the 10 Hz and sham groups during follow-up.[14] We speculated that the heterogeneity between these 2 studies is likely due to the duration of follow-up. It is worth mentioning that although 20 Hz rTMS treatment significantly improved immediate memory at week 8 compared with sham rTMS, there were no significant differences in any of cognitive domains between the 10 Hz and 20 Hz groups both at week 8 and at 6-month follow-up. These results indicated that both 10 Hz and 20 Hz rTMS treatment may produce similar effects on cognitive deficits in SCZ patients, without a significant dose-dependent manner, suggesting that there may be no mechanistic difference between 10 Hz and 20 Hz stimulation. However, the exact mechanisms underlying the effective treatment of HF rTMS for cognitive deficits in SCZ need to be explored through further investigation.

In the present study, we did not find that HF rTMS over left DLPFC for 8 consecutive weeks displayed a therapeutic effect on clinical symptoms of SCZ, as compared with sham group, but the improvement of cognition was correlated with the reduction of PANSS positive subscore

in patients. Our inability to confirm the improvement of clinical symptoms after treatment with rTMS is in accordance with most of the more recent studies in other groups using rTMS for positive and negative symptoms of SCZ patients,[39–41] as well as recent meta-analyses[42,43] and reviews.[23] However, other studies on rTMS in the treatment of SCZ positive and negative symptoms have found that rTMS has a significant effect on symptoms such as auditory hallucinations.[44–47] Several factors may be responsible for these discrepancies regarding the therapeutic effects of rTMS for symptoms of SCZ, eg, age of patients, different stages of disease progression at baseline (active phase vs remission), adjunctive antipsychotic medication, concomitant medication, duration of rTMS treatment, and techniques of rTMS, such as stimulus frequency, position and intensity of treatment, and the shape and dimension of coils.[48] Thus, further longitudinal studies with a larger sample of SCZ patients are warranted.

Interestingly, although no significant differences in the alleviation of positive symptoms were observed in the active rTMS treatment group vs sham group, we found that the increase in the immediate memory score at week 8 and cognitive function improvement at 6-month follow-up were positively correlated with the reduction in PANSS positive subscore, suggesting a close relationship between the improvements of cognitive deficits and clinical symptoms in patients. In addition, we found a negative relationship between RBANS total score and clinical symptoms at baseline, providing further evidence for this point. Numerous studies supported that cognitive impairments and symptoms share a common pathological mechanism in SCZ.[49] It is known that abnormal levels of neurotransmitters interacted with BDNF are associated with cognitive deficits and positive symptoms of the patients with SCZ.[50,51] Studies have shown that HF rTMS influences the release of dopamine in the mesostriatal brain pathways and regulate BDNF levels,[52–54] which may improve cognitive deficits and positive symptoms simultaneously. In this study, the positive symptoms were improved after treatment with rTMS, however, without significant difference with sham group. But we did find a significant association between the improvement of cognitive deficits and the reduction of positive symptoms. We speculate that the lack of effects of rTMS treatment on positive symptoms was due to the small sample size. Considering that most studies have shown that rTMS was effective for hallucination and negative symptoms of SCH,[42,55] and we did not assess the patients by using the special scales for hallucination or negative symptoms, this may be another reason for the negative results. Therefore, the exact mechanisms underlying how rTMS treatment improved cognitive deficits of SCZ patients warrant further investigation.

Another important finding of the present study was that the patients with lower immediate memory and higher visuospatial/constructional score at baseline were related to the greater improvement of immediate memory. Further, we found that the patients with increased baseline prolactin levels showed greater improvements. Consistent with our study, previous studies have shown that the patients with severe cognitive dysfunction at baseline who received cognitive remediation tended to improve more in cognitive functioning than less impaired participants.[56–58] These findings suggested that those patients with more severe cognitive dysfunctions may need more intensive and longer rTMS treatment to benefit as much or more than those with less cognitive dysfunction. Additional research is needed to better understand how to provide rTMS to address the more severe cognitive impairment often found in longer-term psychiatric inpatients. Moreover, we also found that higher prolactin levels were associated with less improvement in cognitive functions after rTMS treatment. Prolactin plays important roles as a neuropeptide and regulates neurogenesis in the brain.[59] A previous prospective study showed a negative linear relationship between levels of prolactin and executive functions in women during late pregnancy and the early postpartum period, indicating a detrimental role of prolactin on cognition.[60] In recent-onset psychotic patients, studies found that prolactin levels were related to cognitive impairments in processing speed, problem-solving, and poorer general cognition.[61] We speculated that the patients with lower prolactin have severe cognitive impairments and have more improvement with rTMS treatment. However, we did not find any association between prolactin and cognition at baseline. Thus, the exact mechanism warrants further investigation.

Several limitations need attention. First, the sample size is relatively small, which may result in false positive or negative results. Second, our sample consists of elderly patients who have been hospitalized for a long time. Thus, generalizing the results of our study is limited considering the patients had more severe symptoms and a longer duration of illness than first-episode and drug-naïve patients with SCZ. Third, only the left DLPFC was stimulated in our study. Previous studies have shown that bilateral DLPFC stimulation holds promise in improving cognitive outcomes, such as working memory in SCZ.[15] Fourth, although we have speculated several possible mechanisms underlying the therapeutic effects of rTMS for cognitive deficits, our current study did not directly evaluate these possibilities. Further studies should examine the underlying mechanisms through which rTMS improves visual memory or working memory performance in SCZ patients. Fifth, using the PANSS scale to evaluate the negative symptoms is also a weakness of the current study. More recent scales, such as the brief negative symptom scale (BNSS), the Clinical Assessment Interview for Negative Symptoms (CAINS), and the self-evaluation of negative symptoms (SNS), are more relevant. Sixth, since

patients receiving either 10 Hz or 20 Hz stimulation were in the active group, they may guess which active group they were in from the frequency of the stimulation they received. Hence, the blinding procedure was not very effective. In order to maintain the blindness, it would be better to use 2 sham stimulation groups corresponding to 10 Hz and 20 Hz groups, which should be remedied in the future. Seventh, because most of the patients in the hospital are male veterans, only male patients were recruited in this study. Therefore, the results of this study are limited to males and cannot be applied to female SCZ patients. In addition, our results should be validated in female patients.

In summary, the results of the present study demonstrate that HF rTMS treatment is a promising, beneficial tool for cognition in SCZ patients. The potential usefulness of the HF rTMS for cognitive deficits has clinical importance, as cognitive deficits have been reported to be major impediments to social rehabilitation and predict poor clinical outcome in patients with SCZ. Although our findings are encouraging, further studies will be needed to prove its efficacy for cognitive deficits in first-episode and drug-naïve SCZ patients using a larger sample size, different ethnic populations, and multicenter studies.

Supplementary Material

Supplementary material is available at *Schizophrenia Bulletin*. .

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