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RESEARCH ARTICLE

Neuronavigated Repetitive Transcranial Stimulation Improves Neurocognitive Functioning in Veterans with Schizophrenia: A Possible Role of BDNF Polymorphism

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Abstract: It has been reported in the previous literatures that high-frequency (HF) neuronavigated repetitive transcranial magnetic stimulation (rTMS) may improve neurocognitive functioning in patients with schizophrenia. Nonetheless, the heterogeneity of the research findings with regards to the effectiveness of HF-rTMS on the neurocognitive functioning in patients with schizophrenia greatly hinders its clinical application. The current study was designed to determine the predictive role of BDNF variants for neurocognitive improvements after rTMS administration in veterans with schizophrenia. 109 hospitalized veterans with schizophrenia were randomly allocated to active HF-rTMS (n=63) or sham stimulation (n=46) over left DLPFC for 4 consecutive weeks. Neurocognitive functions were assessed by using the Repeatable Battery for the Assessment of Neuropsychological Status (RBANS) at baseline and at the end of week 4. BDNF polymorphism was genotyped by the technicians. Compared with sham stimulation sessions, the immediate memory performance was significantly increased in active sessions after neuronavigated HF-rTMS administration. In addition, patients with the CC homozygotes demonstrated greater improvement of immediate memory after rTMS treatment, while T allele carriers showed no significant improvement in immediate memory domain relative to baseline performance of immediate memory. Our findings suggest that add-on neuronavigated HF-rTMS is beneficial on immediate memory only in patients with CC homozygotes, but not in T allele carriers. This pilot study provides further evidence for BDNF as a promise biomarker in predicting the clinical response to rTMS stimulation.

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1. INTRODUCTION

Neurocognitive deficit is a core symptom of schizophrenia (SZ). Decline in neurocognitive functioning involves a range of domains, including executive functions, working memory and attention [1]. It is reported that relative to the general population, the average reduction in neurocognitive functions is one to two standard deviations (SD) [2]. Improving neurocognitive deficits in SZ is an important treatment goal, which is underscored by the fact of relatively lack of treatment success in most of cognitive domains [3]. There is indeed convincing evidence that antipsychotics, the cornerstone role of treatment in SZ, predominantly aim at positive symptoms and may even have a cumulative effect of worsening cognitive functions [4].

Recently, it has been found that non-pharmacological treatments, such as cognitive behavioral therapy, functional remediation and cognitive remediation are used to improve neurocognitive functioning, and studies also put together great importance to determining whether the brain stimulations can normalize the neurocognitive deficits [5, 6]. Among several types of brain stimulation therapy, repetitive transcranial magnetic stimulation (rTMS) has been proven to be a beneficial treatment option for patients with SZ [7, 8]. rTMS is favorably safe and has no severe adverse effects such as weight gain, tardive dyskinesia, diabetes, *etc*. It has been proposed that HF-rTMS could ameliorate neurocognitive functioning in patients with psychiatric disorder, dementing disorders and normal individuals [9-11]. Specifically, noninvasive brain stimulation can produce "neuroen-

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hancement" when applied to normal individuals and the possibility to "self-enhance" neurocognitive functioning has gained attention outside academic fields [12]. In patients with SZ, Barr *et al.* reported a significant improvement in working memory after bilateral 20Hz rTMS treatment over the dorsolateral prefrontal cortex (DLPFC) [13]. Other recent studies also show significant improvements in verbal working memory, attention, and processing speed over the rTMS stimulation period [14, 15]. On the contrary, several studies have reported that there is no significant improvement in neurocognitive functioning after the administration of rTMS in patients with SZ [16-18], suggesting that the effectiveness of rTMS is inconsistent and controversial among patients.

However, there is no clear evidence of the determinants of a high degree of interindividual variability in the beneficial role of rTMS treatment on cognitive functioning in veterans with SZ. It is known that rTMS is administrated on DLPFC and can induce a magnetic field resulting in the hyperpolarization or depolarization of neurons [19]. rTMS stimulation changes the metabolic activity of brain, cortical excitability, neuronal plasticity and brain functional connectivity between brain regions [20, 21]. Thus, the underlying mechanism for discrepant findings among studies applying rTMS may be partly due to the interindividual variability in the modulatory effects on cortical excitability and/or remote neural network [22, 23]. Identifying factors related to the heritability and stratifying patients accordingly could be important to advance rTMS treatment protocol in cognitive enhancements of SZ more broadly. In fact, a few factors associated with synaptic plasticity, particularly metaplasticity, have been reported to influence the response to rTMS in different neuropsychiatric disorders [24, 25].

Brain-derived neurotrophic factor (BDNF) is a major modulator of synaptic plasticity such as long-term potentiation (LTP) in a variety of regions of the brain and cognitive functioning, including learning, memory and processing speed [26-28]. Rodent studies investigated the influence of rTMS on synaptic plasticity and found that BDNF-TrkB signaling and BDNF-NMDAR interaction were upregulated in the prefrontal cortex and lymphocytes after administration with 5Hz rTMS for 5 days, which induces an upregulation of synaptic excitability because it is known that the BDNF-TrkB signaling enhances glutamatergic neurotransmission and NMDAR-dependent LTP [29-31]. BDNF is encoded by the *BDNF* gene, which is located on chromosome 11 at the boundary of 11p13 and 11p14 in the human [32]. More than one hundred polymorphisms in the *BDNF* gene have been identified and previous evidence has pointed to some specific SNPs and positive associations with the cognitive impairments in SZ [33, 34]. For example, evidence supports that hippocampus-dependent learning and declarative memory is influenced by the *BDNF* Val66Met (rs6265) variant [35]. Declarative memory performance has been shown by numerous studies to be higher in Val/Val homozygotes relative to Met carriers [36-38]. Naturally occurring variants in the *BDNF* gene have also been found to be correlated with the clinical response to rTMS [39-43]. Interestingly, a study from Su *et al.* recently reported that *BDNF* rs12273539 has an impact on visuospatial/construction performance in patients with SZ [44].

Given the great discrepancy in the outcomes of rTMS treatment among patients with SZ, a novel promising biomarker was warranted to predict the response to rTMS in the clinical practice. We hypothesized that *BDNF* rs12273539 polymorphism was a predictive biomarker for the response to the neuronavigated high-frequency (HF) rTMS over DLPFC for 4 consecutive weeks in improving the cognitive performance in veterans with SZ. To test this hypothesis, we designed this study to solve the following research questions. 1) Was neuronavigated HF-rTMS effective on cognitive impairments in veterans with SZ. 2) Was the improvement of neurocognitive performance correlated with *BDNF* rs12273539 variant? 3) Was *BDNF* rs12273539 a predictor for the improvement of neurocognitive performance after administration of active rTMS?

2. MATERIALS AND METHODS

2.1. Participants

A total of 131 patients with SZ were enrolled in HeBei Province Veterans Hospital. All patients met the inclusion criteria: 1) male and Han Chinese; 2) SZ diagnosed by DSM-IV using the Structured Clinical Interview for DSM-IV (SCID); 3) no modified electroconvulsive therapy (MECT) treatment in the past 2 years; and 4) stable type and dose of antipsychotics for at least six months. Exclusion criteria: 1) any other major Axis I disorder using SCID; 2) with risk of self-harm or suicide; 3) other mental disorder diagnosed by an experienced psychiatrist; 4) a family history of epilepsy; 5) pregnant; 6) switching type of antipsychotics or changing the dose; 7) comorbid central nervous system disorder by verbally asking the patients whether they had central nervous system disorders, such as brain pathology, severe headache or severe head injury; 8) with a history of epileptic seizures; 9) inability to communicate; 10) alcohol or drug dependent. Patients without blood samples were removed, and a total of 109 patients were included in this study. Sixty-three patients were located in active HF-rTMS group and forty-six patients were located in sham group.

The protocol was approved by the Institutional Review Board of Hebei Province Veterans Hospital. All patients provided the written, informed consent in this study.

2.2. Treatment Protocol

This study consists of two randomized, blinded, sham-controlled, 4-weeks period and 20-session clinical trials conducted in HeBei Province Veterans Hospital. The first clinical trial consisted of 84 patients and the second was made up of 47 patients. Randomization was conducted by a computer program and sealed envelope. A computer random number generator allocated the SZ patients to the active rTMS group or the sham group. Scale raters were blinded to the trial allocation.

Neuronavigated HF-rTMS was administrated by two experienced operators. During the rTMS treatment sessions, all patients were treated over the left DLPFC for 4 consecutive weeks, once a day, and five times each week with the Mag-Stim Rapid Stimulator [23]. The exact location of the neuronavigated left DLPFC has been reported in our previous study [45]. According to previous studies, superior region Brodmann area (BA) 46 and posterior region BA9 were used as targets that the rTMS worked on [46]. The positioning parameters of a single coil were kept in the neuronavigation software. The definition of motor threshold (MT) was the

same as the latest evidence-based guidelines on the use of rTMS in neuropsychiatric disorders and the stimulations over left DLPFC occurred at a power of 110% of MT [47]. The patients in sham group received the same study procedures as the active rTMS group. The sham coil (P/N:3910-00) looks identical to the active coil, replicates the clicking noise and mimics the sound and feel in active stimulation. The sham stimulation produced the same sensation as the active rTMS, so patients cannot know whether they were allocated to active stimulation group or sham stimulation group.

2.3. Outcomes

The primary outcome measure was the neurocognitive functioning, which was assessed at baseline and at 4-week follow-up using the Repeatable Battery for the Assessment of Neuropsychological Status (RBANS). RBANS contains 5 subtests that consisted of immediate memory index, visuospatial/constructional index, attention index, language index and delayed memory index [48]. In this study, RBANS was assessed by 4 research nurses who were blinded to the randomization number list.

2.4. Genotyping

Patients' blood sample was taken at 7 A.M. after 12 hours of fasting. White blood cells were separated and used to extract germline DNA. DNA was extracted from white blood cells using a standard operating procedure. SNP in the *BDNF* gene was genotyped by using the MALDI-TOF MS platform (Sequenom, CA, USA), following the standard procedure as described in previous studies [49, 50].

2.5. Statistical Analysis

Initial analysis was consisted of all patients. Comparisons of baseline demographic characteristics and neurocognitive functioning were carried out by the independent sample t test between the active and sham stimulation groups. Intent-to-treat (ITT) analyses were performed. Missing outcome data at 4-week follow-up were carried out with the principle of Last Observation Carried Forward (LOCF). The primary hypothesis to determine the efficacy of neuronavigated HF-rTMS on neurocognitive functioning was tested by the repeated-measures (RM) analysis of covariance (ANCOVA) with two within-subject factors: "Time", containing two levels (baseline and week 4) and "Treatment", containing two levels (active rTMS and sham rTMS). The primary hypothesis was tested in the interactive effect between Time and Treatment. If the interaction (Time-by-Treatment) was significant, the difference between active and sham groups at week 4 was compared by ANCOVA with the baseline scores as covariates. If the time-by-group interactive effects were not significant, no further statistical analyses were conducted.

The next analysis was performed in the active rTMS group. The effect of 2 genotypes on the improvement of neurocognitive functioning was tested by the RM-ANCOVA to investigate the interaction between Time and Genotypic group. If the interaction was significant, the differences between two genotypic groups at follow-up were respectively compared by ANCOVA with the performances at baseline as covariates. The improvement of cognitive functions before and after 4 weeks of treatment was compared among *BDNF* genotypes by using the Wilcoxon signed-rank test. Exploratory regression analysis was adopted to examine the predictive factors for the improvement of neurocognitive functioning.

Two-tailed p value was used and the significance level was set at 0.05.

3. RESULTS

3.1. Baseline Demographic and Neurocognitive Functioning

There were no statistical differences in age, education years, age of onset, duration of illness, hospital time and dose of antipsychotics between the active and sham groups (all $p > 0.05$) (Table **1**). The demographic data between the active and sham groups were well matched.

The *BDNF* rs12273539 genotypic frequencies were CC (n=70), CT (n=30) and TT (n=9). The TT homozygotes were combined with CT heterozygote due to an insufficient number of such subjects for analysis. Therefore, the patients were grouped to CC homozygotes (patients with CC genotype) and T alleles (patients with CT genotype and TT homozygotes). We found significant differences in age, duration of illness and onset age between-group comparisons of *BDNF* genotypes (all $p < 0.05$). Patients with CC genotype were younger, young onset age and shorter duration of illness than T allele carriers.

Table **2** summarizes the RBANS total score and its five subscores of SZ patients. There were no significant differences in the baseline RBANS total score and its five subscores between genotypes (all $p > 0.05$).

3.2. Comparison of Cognitive Functions at Different Time Point

All patients well tolerated the rTMS with no severe side effects. A RM-ANCOVA analysis was used to compare the neurocognitive functioning in the active and sham groups at different time points (baseline and endpoint). It was found that there was an interaction effect ($F= 3.9$, $p= 0.05$) and significant main effects of Time ($F= 9.5$, $p= 0.003$) and group ($F= 8.7$, $p= 0.004$) on immediate memory, after controlling for age. However, we found no significant effect of genotypic group or Time or interaction effect on RBANS total score or other index scores (all $p > 0.05$).

Post hoc tests between the treatment groups revealed that there was a significant difference in the increase of immediate memory performance from 4 week to 0 week in the active group ($p < 0.05$). Relative to baseline, patients in the active group exhibited a significant increase in immediate memory. Whereas, compared with baseline, there was no change in immediate memory index in the sham group ($p > 0.05$).

3.3. rTMS Efficacy Among Genotypes

A RM-ANCOVA analysis was further used to compare the cognitive performances between the genotypes in different times. Because of the strong correlations between age and onset age and duration of illness (all $p > 0.6$), and to avoid including completely collinear covariates in the RM-ANCOVA analysis, we chose age as a confounding factor for the following analysis. In addition, education is closely related to cognitive function, which also was controlled in our analysis. The results revealed a significant interaction of Time and genotypic group on immediate memory performance ($F= 6.4$, $p= 0.014$) (Table **3**). At baseline, immediate memory performance in the T allele carriers was significantly higher than that with CC homozygotes ($F= 4.6$, $p= 0.037$).

Table 1. Demographic and clinical data at baseline.

-	Sham rTMS group (n=46)	Active rTMS group (n=63)	X^2 or *F(p)*	CC (n=70)	T carriers (n=39)	X^2 or *F(p)*
Age (yrs)	55.0±8.1	51.8±9.8	3.3(0.07)	51.7±9.4	55.7±8.6	5.0(0.028)
Education (yrs)	7.8±2.3	8.2±2.2	0.6(0.44)	8.3±2.2	7.7±2.2	1.8(0.19)
Age of onset (yrs)	21.2±1.8	20.7±2.1	1.4(0.23)	20.6±2.0	21.4±1.9	4.4(0.04)
Duration of illness(yrs)	33.8±7.9	31.1±9.3	2.5(0.12)	30.9±8.6	34.5±8.8	4.2(0.04)
Hospital time	6.3±2.5	6.2±2.6	0.1(0.73)	6.2±2.5	6.3±2.7	0.07(0.80)
Dose of antipsychotics	427.4±218.6	429.0±220.2	0.01(0.97)	442.6±245.9	403.8±157.8	0.8(0.38)

Table 2. Neurocognitive functioning at baseline.

-	Sham rTMS (n=46)	Active rTMS group (n=63)	X^2 or *F(p)*	CC (n=70)	T carriers (n=39)	X^2 or *F(p)*
Immediate memory	51.7±13.0	57.3±10.9	5.9(0.016)	54.1±11.2	56.4±13.6	0.9(0.35)
Visuospatial/constructional	71.2±15.6	73.7±13.9	0.8(0.38)	72.7±15.7	72.5±12.9	0.01(0.94)
Language	79.4±15.3	77.8±16.6	0.3(0.61)	79.0±16.8	77.5±14.7	0.2(0.64)
Attention	67.8±15.1	70.6±16.0	0.9(0.35)	70.2±16.3	68.1±14.4	0.5(0.49)
Delayed memory	63.6±21.0	63.0±17.4	0.03(0.87)	62.7±20.3	64.0±16.4	0.1(0.76)
Total score	58.8±15.1	60.8±12.7	0.6(0.45)	59.6±13.9	60.6±13.6	0.1(0.73)

Abbreviations: *RBANS* Repeatable Battery for the Assessment of Neuropsychological Status.

Whereas, at endpoint, there was no difference between T allele carriers and patients with CC homozygotes ($p > 0.05$).

In addition, the main effects of Time on attention index and RBANS total scores were significant (all $p < 0.05$). Patients' attention and total scores at 4 weeks at the end of treatment were significantly higher than baseline scores (all $p < 0.05$).

However, the main effects or interaction effects on other RBANS index were not significant (all $p > 0.05$). The above analyses revealed that rTMS treatment may only be effective in improving immediate memory.

3.4. Improvements in Immediate Memory among BDNF Genotype Groups Treated with rTMS

Further analyses between the genotypic groups revealed that there was a significant difference in the increase of immediate memory performance from 0 week to 4 week after treatment in active group between genotypes ($Z = -2.7$, $p = 0.007$). Immediate memory scores showed significantly greater increases in patients with CC homozygotes (12.4 ± 12.0) than T allele carriers (4.9 ± 6.9). When the improvement in immediate memory was added as the dependent variable, and duration of illness, onset age, education, baseline immediate memory and *BDNF* genotype group were added as the independent variables, an exploratory regression analysis was performed and showed that genotype was a significant predictive factor for immediate memory improvement ($beta = -0.28$, $t = -2.12$, $p = 0.038$).

4. DISCUSSION

We found that *BDNF* rs12273539 variant was associated with the response to neuronavigated HF-rTMS treatment for 4 weeks in improving cognitive functioning in SZ. In addition, rs12273539 was a predictor for the efficacy of HF-rTMS in cognitive enhancement, after adjusting for the confounding factors.

BDNF has been demonstrated to modulate NMDAR-dependent LTP and LTD in the adult brain in animal models, which is involved in the cognitive functioning [31, 51]. It has indeed been implicated to be related to treatment response to rTMS [52]. Our findings were consistent with previous studies, indicating that BDNF plays a vital role in clinical response to rTMS. In contrast, the efficacy of rTMS has also been reported to be not regulated by BDNF polymorphism [53, 54]. We propose that the possible explanations for inconsistency of these studies may be related to the methodological differences among researches, such as the difference in the duration of stimulation (2 weeks *vs.* 4 weeks *vs.* 8 weeks), participants recruited (female *vs.* male *vs.* both), polymorphic sites (Val66Met *vs.* rs12273539 *vs.* other polymorphism), stimulation frequency (5Hz *vs.* 10Hz *vs.* 20Hz), clinical characteristics of patients (first-episode *vs.* chronic patients; hospitalization *vs.* outpatients), medication histories. In this study, the male long-termed hospitalized patients with chronic SZ were recruited and applied HF-rTMS for 4 weeks and found that rs12273539 variant was correlated with the response to rTMS.

Rs12273539 variant is the noncoding SNP located in the intron of the *BDNF* gene. T mutant allele can cause a reduction in BDNF production in brain regions such as amygdala and hippocampus. It is also known that T allele is likely to occur together LD with rs6265A (Met66Val) in human [55]. In this study, we found that patients with rs12273539

Table 3. Neurocognitive functioning at baseline and at follow-up between the *BDNF* genotypes.

-	**Baseline (n=63)**	**Week 4 (n=63)**	**Group Effect *F(p)***	**Time Effect *F(p)***	**Group×Time *F(p)***
Immediate Memory Index			1.1(0.31)	0.1(0.92)	6.4(0.014)*
CC	55.0±8.9	65.4±14.9	-	-	-
T carriers	60.8±12.1	64.1±12.8	-	-	-
Visuospatial/Constructional Index			0.2(0.63)	0.7(0.41)	1.4(0.24)
CC	73.9±16.0	80.7±20.3	-	-	-
T carriers	73.3±10.3	75.1±17.6	-	-	-
Language Index			1.5(0.22)	0.7(0.40)	0.5(0.50)
CC	75.5±18.2	78.7±16.7	-	-	-
T carriers	81.4±13.4	82.6±13.9	-	-	-
Attention Index			1.2(0.29)	4.3(0.043)*	0.8(0.38)
CC	69.8±16.8	68.0±17.3	-	-	-
T carriers	71.8±14.8	70.4±12.9	-	-	-
Delayed Memory Index			0.5(0.46)	0.5(0.48)	0.5(0.50)
CC	61.0±18.5	71.5±23.5	-	-	-
T carriers	66.1±15.6	73.6±19.2	-	-	-
RBANS Total Score			1.7(0.20)	5.0(0.029)*	0.5(0.50)
CC	59.5±12.9	66.2±15.9	-	-	-
T carriers	62.8±12.4	69.8±13.7	-	-	-

Note: *controlling for age and education years.

CC homozygotes significantly improved greater after rTMS treatment, whereas T allele carriers cannot improve cognitive functioning after rTMS administration. The potential mechanism might be rTMS-aided cognitive restoration caused by the beneficial effects of synaptic plasticity in patients with CC homozygotes. Evidence from animal studies has shown that the spatial exploration ability was enhanced in the water maze task and NMDA receptor 1 expression in the hippocampus was upregulated after rTMS treatment [29, 56]. In our study, T allele carriers were speculated to have lower ability to activate NMDA receptor channel and enhance NMDA-receptor dependent LTP through the phosphorylation of postsynaptic components and NMDA receptor subunits. Although the exact functions of rs12273539 on BDNF levels remain unknown, literatures have revealed that rs6265 producing a valine (Val) to methionine (Met) substitution at codon 66 (Val66Met) alters the activity-dependent secretion of BDNF and affects hippocampal function and memory performance in humans [36, 37]. It is known that rs12273539 can be constructed *in vivo* with rs6265 as a common haplotype. Indeed, previous studies have shown that haplotype of rs6265(Met)-rs12273539(T)-rs10835210(A) was associated with worse performance in attention index in patients with SZ [57].

Another explanation for the different efficacy between genotypic groups may be due to the differences in rTMS-induced lasting changes in BDNF production-related signaling and strength of LTP/LTD like effects after treatment between CC homozygotes and T allele carriers [29]. Animal studies found that rTMS elicits the secretion of BDNF which enhances its secretion presynaptically and postsynaptically by themselves [58]. The third possible explanation is the interactive effect between BDNF gene and other cognitive-related genes is known to impact the brain plasticity. Candidate genes, including catechol-o-methyltransferase, glutamate Ionotropic receptor NMDA Type subunit 1 and 2B, dopamine receptor D_2 and neurotrophic receptor tyrosine kinase 2 have been proposed as modulators of brain plasticity [41, 59-62]. In addition, the interrelationships between BDNF and candidate genes were reported to be involved in the cognitive impairments in psychiatric disorders and general populations [43], indicating complex functional interaction between BDNF and other neurotrophins or neurotransmitters of synaptic transmission in human. Specifically, previous studies provide evidence that functional polymorphisms in solute carrier family 6 member 4 (SLC6A4) and BDNF genes appear to impact the clinical response to rTMS treatment in patients with mood disorders. For patients with drug resistant depression, 5-HTTLPR and BDNF Val66Met polymorphisms have been reported to be associated with the effectiveness of rTMS treatment. The response was significantly greater in 5-HTTLPR LL homozygotes compared to S

allele carriers and in BDNF Val/Val homozygotes compared to Met carriers [63].

This study included several limitations. The first limitation is the relatively small sample size. Thus, TT homozygotes were combined with CT heterozygote due to an insufficient number of such subjects for analysis (n=9 in both active and sham stimulation groups). A higher number of participants, especially among those bearing the TT homozygotes, would confer strength to the findings. Moreover, further subgroup analyses based on demographic and clinical characteristics among genotypic groups are warranted in a larger sample size. In addition, some negative findings reported here may be due to the low statistical power of the small sample size. Second, only male long-term hospitalized patients with SZ were recruited in this study and our results cannot be generalized to the female patients. With regards to clinical populations, the current findings have limited generalizability in clinical applications as the recruited patients were veterans in hospital. Third, we evaluated only one polymorphism in the BDNF gene. It is more likely that other polymorphisms or genes also can impact the effectiveness of rTMS protocols in SZ. In particular, we did not analyze the interactive effect between BDNF gene and other genes involved in cognitive functions on rTMS-induced plasticity. Fourth, we did not measure the levels of BDNF in CSF or blood and no comparison of BDNF levels was conducted between CC homozygotes and T allele carriers. Fifth, there were significant differences in age, onset age and duration of illness between patients with CC genotype and T allele carriers. In addition, the baseline immediate memory scores were different between the sham and active groups, as such; this might have influenced the impact of rTMS in this subgroup of patients.

CONCLUSION

In summary, this study investigated the impact of BDNF rs12273539 variant on the effectiveness of neuronavigated HF-rTMS stimulation on the cognitive functioning. Our findings provide new insights into a predictive role of 12273539 variant in the clinical response to rTMS stimulation in veterans with SZ. An important clinical significance of our study is to develop BDNF as a potential biomarker for clinical improvement of neurocognitive functioning in response to rTMS treatment in SZ. However, additional researches are warranted considering that rTMS-induced plasticity is complex and not yet fully understood.

AUTHORS' CONTRIBUTION

MX and XS were responsible for study design, statistical analysis, and manuscript preparation. HL, XW, XP, XZ, XL, LZ, YC and YS were responsible for recruiting the patients, performing the clinical rating and collecting the clinical data. FW, XS, MX and YS were involved in evolving the ideas and editing the manuscript. MX was involved in writing the protocol, and co-wrote the paper. All authors have equally contributed and approved the final manuscript.

LIST OF ABBREVIATIONS

HF = High-frequency

rTMS = Repetitive transcranial magnetic stimulation

RBANS = Repeatable Battery for the Assessment of Neuropsychological Status

SD = Standard deviations

BDNF = Brain-derived neurotrophic factor

LTP = Long-term potentiation

ETHICS APPROVAL AND CONSENT TO PARTICIPATE

The study was approved by the Institutional Review Board of HeBei Province Veterans Hospital (Ethic no.: 20070310).

HUMAN AND ANIMAL RIGHTS

No animals were used in this research. All humans research procedures followed were in accordance with the standards set forth in the Declaration of Helsinki principles of 1975, as revised in 2008 (http://www.wma.net/en/20activities/ 10ethics/10helsinki/).

CONSENT FOR PUBLICATION

Written informed consent was obtained from all participants.

AVAILABILITY OF DATA AND MATERIALS

Not applicable.

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CONFLICT OF INTEREST

The authors declare no conflict of interest, financial or otherwise.

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