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The effect of repetitive transcranial magnetic stimulation on the negative symptoms of chronic schizophrenia and serum brain-derived neurotrophic factor

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Summary

Aim. This study aims to investigate the therapeutic effect of repetitive transcranial magnetic stimulation (rTMS) on the negative symptoms of chronic schizophrenia and serum brain-derived neurotrophic factor (BDNF).

Methods. A total of 86 patients with chronic schizophrenia hospitalised from March to October 2019 were randomly assigned to the active rTMS group or the sham rTMS group, with 43 patients in each group. All patients were administered paliperidone orally at a dose of 3–6 mg/d, and rTMS treatment was given to the active rTMS group. The Positive and Negative Syndrome Scale (PANSS) score and the serum BDNF concentration were calculated in both groups at baseline and after two and four weeks of treatment.

Results. There were no statistically significant differences in the PANSS scores and serum BDNF concentrations between the two groups before treatment ($p > 0.05$). However, after four weeks of treatment, the change in the score on the negative symptom scale in the active rTMS group was greater than in the sham rTMS group ($p < 0.05$), and the serum BDNF levels in the active rTMS group were higher than in the sham rTMS group ($p < 0.05$).

Conclusions. Four weeks of continuous rTMS treatment can effectively improve the negative symptoms of schizophrenia, and the serum concentration of BDNF increases as the duration of rTMS treatment increases.

Key words: schizophrenia, repetitive transcranial magnetic stimulation, serum brain-derived neurotrophic factor, PANSS scale

Introduction

Schizophrenia is a heterogeneous psychiatric disorder that tends to relapse and migrates into chronicity, showing negative symptoms such as emotional indifference and reduced volition, which seriously affect the quality of life of patients [1, 2]. Repetitive transcranial magnetic stimulation (rTMS) involves the use of electromagnetic induction to stimulate the cerebral cortex with magnetic fields of varying frequencies, which depolarises the membrane potential of the cortical nerve cells to generate an induction current, affecting brain cell metabolism and neural electric wave transmission and thus achieving a therapeutic effect on the central nervous system. rTMS is used to modulate specific brain regions, and a previous study suggested that it is beneficial in a variety of neuropsychiatric disorders [3]. Previous studies have shown positive results concerning the use of rTMS in the treatment of schizophrenia, with milder adverse reactions and better clinical tolerance than other forms of treatment [4, 5], but the results reported in the literature are inconsistent. Two previous meta-analyses showed that the rTMS is an effective treatment option for negative symptoms [6, 7]. In addition, a recent double-blind, sham-controlled trial showed that active rTMS treatment is more effective at improving negative symptoms [8]. Conversely, a large multicentre trial indicated that rTMS was not superior when compared with sham rTMS in improving negative symptoms [9]. Thus, this therapy approach is still controversial due to poor evaluation, and it is essential to have reliable biomarkers to explore its effect on schizophrenia [10].

Serum brain-derived neurotrophic factor (BDNF) is a neural growth factor involved in the growth and differentiation of nerve cells and the survival and repair of neurons. Serum BDNF levels are lower in people with schizophrenia than in those without [7]. Therefore, BDNF has become a possible candidate for the diagnostic and therapeutic evaluation of serious mental illnesses, including schizophrenia and depression [11]. Previous studies have shown that BDNF levels can increase after treatment with antidepressant therapies [12]. Additionally, meta-analyses have shown that the level of serum BDNF is strongly associated with the course of schizophrenia and major depressive disorder [13, 14].

Aim of study

This study explores the therapeutic effect of rTMS on the negative symptoms and serum BDNF levels of patients with chronic schizophrenia.

Material

This study was a single-centre, sham-controlled and double-blinded clinical trial. A total of 86 consecutive patients with chronic schizophrenia hospitalised from March to October 2019 were divided into the active rTMS group and the sham rTMS group using randomised numbers, with 43 patients in each group. Only patients who met the following criteria were recruited: (1) satisfied the International Classification of Diseases, Tenth Edition (ICD-10) diagnostic criteria for schizophrenia, (2) course of the disease ≥2 y and (3) aged 18–60 y. The following exclusion criteria were used: (1) brain disease, such as epilepsy and cerebral infarction; (2) underwent interventional surgery, such as heart bypass grafting or (3) alcohol abuse within 30 days prior to the study, alcohol/drug dependence within six months or a history of smoking.

The study was approved by the ethics committee of our hospital, and all selected subjects signed informed consent.

Methods

Treatment methods

Both groups were given paliperidone slow-release tablets (Xian Janssen Pharmaceutical Ltd., batch H20110514) at a starting dose of 3 mg/d and a maintenance dose of 6 mg/d. No other antipsychotics, antidepressants or antimanic drugs were administered, except for benzodiazepines and benzhexol hydrochloride. The rTMS instrument was produced by the Wuhan Yide Materials Supply Co., Ltd. (model YRDCCY-I), and the stimulus coil used was the ∞-shaped coil. For the active rTMS group, the stimulus sites were selected at the left dorsolateral prefrontal cortex, and the stimulus was given at a frequency of 10 Hz in 40 stimulus sequences of 2 s each with a 17 s interval. The rTMS was presented at 110% of the motor threshold, and stimulation lasted for 4 s with 26 s intervals, with a total of 1,600 pulses per session. The treatment was administered for 20 min five times a week for four weeks.

The plane of the stimulation coil is tangential to the scalp, with the central plane aligned to the treatment site at 45° to the patient's sagittal line (see Figure 1). In the sham rTMS group, the coils were placed on the scalp at a 180º angle, and other parameters were consistent with the active rTMS group.

Efficacy assessment

The Positive and Negative Syndrome Scale (PANSS) was scored by two attending psychiatrists who were not involved in the experimental design. The two physicians received scale training and consistency testing before the experiment and later evalu-

ated the trial results simultaneously and independently. A difference of <10 between their scores was regarded as valid, and the final PANSS score was the average of the two scores. The evaluation was performed the day before the rTMS treatment, after two weeks of treatment and after four weeks of treatment. The change in the PANSS score was the actual measured value minus the baseline value and was used for the post-treatment analysis.

Serum brain-derived neurotropic factor measurement

Mature serum BDNF levels were measured in the two groups using an enzyme-linked immunosorbent assay (ELISA) kit on a fasting sample of 4 ml of venous blood extracted between 6:00 and 7:00 a.m. The ELISA kit has a minimum detection concentration of <1.0 pg/ml and does not cross-react with other soluble structural analogues. The measurement was performed the day before rTMS treatment, after two weeks of treatment and after four weeks of treatment.

Safety measurement

The side effects after rTMS intervention were evaluated by using the *Udvalg for Kliniske Undersogelser* side effect rating scale. It comprises 48 items measuring psychic, neurologic, autonomic and other adverse effects. All scales exhibited test–retest correlations of up to 0.8 in repeated assessments [15].

Statistical methods

The statistical analysis was performed using the SPSS 24.0 software. Continuous data were described using the mean ± standard deviation ($\bar{X}$+S). Count data were expressed as frequencies and percentages, and the χ^2 test was used. The mean test was performed using two independent sample *t*-tests, and repeated measures of analysis of variance (ANOVA) were used to compare the variability in measurements at different time points. A p-value of < 0.05 was considered statistically significant.

Results

Characteristics of the study subjects

The subjects in the sham rTMS group were aged 23–56 y (42.1 ± 5.2 y), had a body mass index (BMI) of 22.4–25.6 kg/m2 (23.7 ± 2.2 kg/m2) and had a disease duration of 2.1–5.2 y (3.1 ± 2.3 y). The subjects in the active rTMS group were aged 27–60 y (43.7 ± 4.8 y), had a BMI of 23.1–25.3 kg/m2 (24.4 ± 1.8 kg/m2) and had a disease duration of 2.7–6.0 y (3.4 ± 3.0 y). There were no significant differences

between the two groups in terms of age, sex, BMI or disease duration ($p > 0.05$; see Table 1).

Table 1. **Characteristics of study subjects**

Variables	Active rTIM (n=43)	Sham rTIM (n=43)	*P* Value
Age (y)	43.7 ± 4.8	42.1 ± 5.2	>0.05
Sex (M (%))	20(46.5)	21 (48.8)	>0.05
Education years (y)	10.7 ± 2.6	10.2 ± 2.3	>0.05
BMI (kg/m2)	24.4 ± 1.8	23.7 ± 2.2	>0.05
Disease duration (y)	3.4 ± 3.0	3.1 ± 2.3	>0.05

The comparison of the baseline Positive and Negative Syndrome Scale scores

Before treatment, the patients in the active rTMS group and the sham rTMS group were evaluated using the PANSS. The results showed no statistically significant difference in the negative symptoms, positive symptoms or general psychopathological symptoms, and the difference in the total PANSS scores was not significant ($p > 0.05$; see Table 2).

Table 2. **Comparison of various items of PANSS scale between the two groups before treatment**

Group	n	Negative symptoms	Positive symptoms	General psychopathological symptoms	Total score
Active rTIM	43	23.1 ± 4.5	16.6 ± 3.6	35.9 ± 4.6	75.7 ± 7.0
Sham rTIM	43	22.8 ± 3.3	15.9 ± 2.9	34.9 ± 4.4	73.6 ± 6.2
t		0.412	1.198	0.994	1.621
p		0.683	0.238	0.326	0.113

Comparison of the change in the Positive and Negative Syndrome Scale score before and after treatment

Repeated measures of ANOVA of the PANSS total scores showed that there were no statistically significant effects of time or intervention (see Table 3). Changes in the PANSS scores were evaluated two and four weeks after treatment. When compared with the sham rTMS group, the changes in the PANSS negative symptoms in the active rTMS group were greater after four weeks of treatment ($p = 0.008$). However, there were no significant differences in the change in scores for the positive or the general psychopathological symptoms between the two groups after two and four weeks of treatment ($p > 0.05$; see Table 4).

Table 3. **Repeated measures ANOVA results for PANSS total scores between two groups**

Group	Cases	Baseline	2 weeks	4 weeks
Active rTIM	43	75.7 ± 7.0	81.1 ± 6.7	86.3±4.8
Sham rTIM	43	73.6 ± 6.2	79.5 ± 5.5	82.6±6.2
t		1.621	-0.603	1.281
p		0.113	0.550	0.207

Note: After analysis by using repeated measures ANOVA, F_{time} = 132.011, P_{time} = 0.077; $F_{interaction}$ = 54.922, $P_{interaction}$ = 0.052; $F_{intergroup}$ = 46.113, $P_{intergroup}$ = 0.059.

Table 4. **Comparison of various subtraction values in the PANSS scale between the two groups before and after treatment**

Group	n	Negative		Positive		General psychopathological symptoms		Total score	
		2 weeks	4 weeks	2 weeks	4 weeks	2 weeks	4 weeks	2 weeks	4 weeks
Active rTIM	43	3.2 ± 2.2	5.5 ± 3.4	1.3 ± 0.7	2.6 ± 1.6	2.0 ± 1.8	3.4 ± 2.8	5.4 ± 3.4	10.6 ± 5.7
Sham rTIM	43	2.8 ± 1.7	3.7 ± 2.4	1.2 ± 0.7	2.0 ± 1.3	2.5 ± 1.5	4.0 ± 3.7	5.9 2.9	9.0 ± 6.2
t		1.112	2.793	0.856	1.630	-1.082	-0.828	-0.603	1.281
p		0.273	0.008	0.397	0.111	0.285	0.412	0.550	0.207

The comparison of serum brain-derived neurotrophic factor concentrations before and after treatment

There was no statistically significant difference between the serum BDNF levels in the two groups before treatment (baseline) or after two weeks of treatment ($p > 0.05$). However, when compared with the sham rTMS group, the serum BDNF was significantly higher in the active rTMS group four weeks after treatment ($p = 0.030$). In addition, as the duration of rTMS treatment increased, BDNF levels also increased ($p < 0.05$; see Table 5).

Table 5. **Comparison of serum BDNF level between the two groups before and after treatment (ng/L)**

Group	Cases	Baseline period	2 weeks	4 weeks
Active rTIM	43	6.14 ± 1.11	7.08 ± 1.35	8.02 ± 1.46
Sham rTIM	43	6.17 ± 1.28	6.86 ± 1.39	7.32 ± 1.29
t		1.20	0.709	2.241
p		0.905	0.482	0.030

Note: After analysis by using repeated measures ANOVA, F_{time} = 123.331, P_{time} <0.001; $F_{interaction}$ = 4.100, $P_{interaction}$ = 0.003; $F_{intergroup}$ = 14.840, $P_{intergroup}$ = 0.002.

Safety assessment

After four weeks of intervention, three patients in the active rTMS group reported side effects (one reported tension headaches and two reported a reduced duration of sleep), and four subjects in the sham rTMS group reported side effects (two reported tension headaches, one reported a reduced duration of sleep and one reported emotional indifference). There was no statistically significant difference in the incidence of side effects between the two groups ($p > 0.05$).

Figure 1. **A representative image of rTMS treatment. The plane of the stimulation coil is tangential to the scalp, with the central plane aligned to the treatment site at 45° to the patient's sagittal line**

Discussion

Previous studies have shown abnormal changes in the brains of patients suffering from schizophrenia, including reduced volume of the prefrontal cortex, a reduced number of neurons and lack of regulation in their distribution, and reduced blood flow in the lateral prefrontal cortex [16]. rTMS can inhibit or facilitate networks associated with cognitive function by suppressing or exciting local neural loops [17]. Ueyama et al. [18] found that the long-term use of high-frequency rTMS significantly improves the regeneration of the hippocampal dentate gyrus and that 10 Hz of rTMS stimulation acting on the left prefrontal lobe significantly improves negative symptoms in patients with schizophrenia [19]. Therefore, the stimulation frequency of 10 Hz was chosen for this study.

This study examined the therapeutic effects of rTMS on negative symptoms and BDNF in patients with chronic schizophrenia and found that rTMS can effectively improve the negative symptoms of schizophrenia and increase the level of serum BDNF. The improvement in the negative symptoms was consistent with the rise in the BDNF concentration, which is consistent with the results of other studies [20–24]. In addition, the incidence of side effects was not statistically significant, suggesting that the tolerability of rTMS treatment is acceptable.

Patients with schizophrenia exhibit abnormal brain changes [20, 21], and it is known that rTMS can effectively regulate local blood flow in the brain, control metabolism and secretion in vivo, affect neurotransmitter release, change protein gene expression, increase dentate gyrus regeneration in the hippocampus and increase excitability and blood flow in the local cortex. In this study, after treatment with rTMS combined with paliperidone, the total score and sub-scores of the PANSS evaluated after two weeks and four weeks of treatment were lower than before the treatment. In addition, the negative symptoms score was lowest after four weeks of treatment ($t = 2.793$, $p = 0.008$), which is consistent with the results of previous studies [22, 25, 26]. Repeated series of stimuli and repetition of stimulation sessions could activate pyramidal neurons, which would strengthen existing connections and facilitate the formation of new synaptic connections [27]. It is suggested that combination treatment could promote recovery from chronic schizophrenia and, in particular, improve the negative symptoms of patients.

BDNF, a member of the neural growth factor family, promotes neural cell proliferation, participates in neuronal development and regulates the normal physiological functioning of neural cells. In schizophrenia, proinflammatory cytokines may activate protein kinase signalling through mitogen, causing a nutritional support disorder in the nerve cells and leading to low serum BDNF levels [22–24]. The results of this study showed that during treatment with rTMS combined with paliperidone, serum BDNF concentrations increased after two and four weeks of treatment, with the most prominent increase after four weeks of treatment ($t = 2.241$, $p = 0.030$). This suggests that the induction current generated in the cortex by rTMS stimulation in patients with chronic schizophrenia promotes growth factor production, boosts neurotransmitter biological activity, enhances neurological blood flow and cell-to-cell interaction, increases neurological BDNF expression and serum BDNF concentration and improves negative symptoms.

Although rTMS has achieved significant results in clinical application, as the occurrence and development of schizophrenia-positive symptoms are not yet clear, the mechanism and efficacy of rTMS in the treatment of schizophrenia are also still unclear. Based on the results of previous studies, a 10 Hz stimulation frequency was used in this study, but some studies have shown that different stimulation frequencies also have

certain positive effects on negative symptoms [28–30]. In addition, no consensus has been reached on the most effective parameters and sites for rTMS in treating negative symptoms. Unfortunately, based on the results of a previous randomised controlled study, the effectiveness of rTMS in treating schizophrenia with negative symptoms has not been demonstrated [9]. At present, the Polish Psychiatric Association consensus statement recommends that rTMS could be considered as an option in the treatment of negative symptoms of schizophrenia (level of evidence B, IIb class of recommendation) [31]. Therefore, the efficacy of rTMS in improving the negative symptoms of schizophrenia needs to be confirmed by larger studies over a longer period. Despite the improvement in negative symptoms and BDNF after four weeks in this study, longer observation periods, even up to six months, would result in the accumulation of more data, which could provide a more solid basis for the use of rTMS in the treatment of chronic schizophrenia. Based on the results of this study, we cannot further explore whether the effect was mediated by BDNF, and the relationship between rTMS and BDNF may be epiphenomenal. Another limitation of this study is the observation of potentially statistically significant differences that could be attributable to chance despite conducting many tests of the hypotheses.

Conclusion

Continuous rTMS treatment can effectively improve the negative symptoms of schizophrenia after four weeks of treatment, and the increase in serum concentration of BDNF is related to the duration of rTMS treatment. This method can be used for the treatment of the negative symptoms of schizophrenia. Due to the limitations of our study, additional multicentre studies with large sample sizes are needed in the future to confirm the results of our study.

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