

Original Article

Beneficial effects of repetitive transcranial magnetic stimulation on cognitive function and self-care ability in patients with non-dementia vascular cognitive impairment

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Abstract: The present study investigated the effects of repetitive transcranial magnetic stimulation (rTMS) on cognitive function and self-care ability in patients with non-dementia vascular cognitive impairment (NVCI). A total of 106 patients with NVCI were randomly classified into the control group (n=53) and study group (n=53). Based on routine treatment, the control group received pseudo rTMS treatment, while the study group received rTMS treatment. After treatment, visual space, executive function, attention, delayed recall, and directional scores of the study group were higher than those of the control group ($P<0.05$). Total effective rates, CDT scores, and MBI scores of the study group were higher than those of the control group ($P<0.05$). Both groups demonstrated a sharp reduction in the P300 latent period ($P<0.05$), though levels were more significant in the study group ($P<0.05$). Levels of serum leptin, VEGF, and NGT of the study group were higher than those of the control group ($P<0.05$). After treatment, the relative α -rhythm relative power spectrum of the frontal F3, Fp1, Fp2, Fz, and T4 of the right sac was remarkably increased, compared to those of the control group ($P<0.05$). Repeated transcranial magnetic stimulation can ameliorate the cognitive function of patients with non-dementia vascular cognitive impairment, improving self-care ability. Thus, it has high clinical application value.

Keywords: Non-dementia type, vascular cognitive impairment, repetitive transcranial magnetic stimulation, cognitive function, self-care ability

Introduction

Non-dementia vascular cognitive impairment (NVCI) is a common complication after strokes. Chronic cerebral insufficiency has been considered to be the pathological process of NVCI pathogenesis [1]. Early onset of the disease is mainly characterized by cognitive impairment. This can cause persistent cognitive and neurological dysfunction as the disease progresses. A survey in Italy showed that the incidence of NVCI is 9.60%, with the risk of conversion to dementia three times that of the normal population [2]. A subtype of vascular dementia, NVCI has a certain chance to convert into vascular dementia. It has been reported that about 46% of NVCI patients converted to vascular demen-

tia within 5 years [3]. Therefore, active intervention in NVCI can help prevent the formation of vascular dementia, improving the prognosis of patients. Clinically, drug treatments based on the control of hypertension, blood glucose, and blood lipids, aiming to improve brain metabolism and brain tissue microcirculation, have been adopted. However, the curative effects are not ideal. Therefore, it is necessary to discover more effective treatment options. Repetitive transcranial magnetic stimulation (rTMS) is a new technology in the field of brain science research. It has many advantages, such as non-invasive and painless progression, simple operation, and high safety levels. Recently, in the therapy of schizophrenia, anxiety and depression comorbidity, Parkinson's dis-

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ease, senile depression, acute cerebral infarction, and other diseases, rTMS has shown significant effects on improving cognitive function [4-6]. Application of rTMS in patients with NVCI has also been studied [7, 8], demonstrating positive effects on improvement of cognition in patients with NVCI. Based on previous studies, the present study further examines the effects of rTMS on cognitive function and self-care ability in NVCI patients, exploring its effects on serum cytokine levels and EEG distribution.

Material and methods

Clinical information

A total of 106 patients with non-dementia vascular cognitive impairment, from January 2017 to January 2018, were selected as subjects for the current study. Inclusion criteria: (1) Patients complying with VCIDN diagnostic criteria; (2) Patients that graduated from primary school or above; (3) Patients that did not participate in similar experiments in the near future; (4) Aged 18-80 years; and (5) Patients and families providing informed consent. The current study was approved by Hebei Yanda Hospital.

Exclusion criteria: (1) Patients with cognitive impairment caused by non-vascular diseases; (2) Patients with insufficiencies in organs, such as the heart, liver and kidneys; (3) Patients with epilepsy and mental illness; (4) Patients clouded in the mind or with dizziness; (5) Patients with communication impairment; and (6) Patients that had taken medication for cognitive impairment within 1 month.

Using the randomized principle, 106 patients were randomly classified into the control group (n=53) and study group (n=53). The control group included 26 males and 27 females. They were aged 55-79 years, with a mean age of (63.87±3.16) years. Ten cases had primary school cultures, 23 had middle school cultures, and 20 cases were college graduates and above. The study group included 28 males and 25 females. They were aged 56-77 years old, with an average age of (63.41±3.28) years. Twelve cases had primary school cultures, 20 cases had middle school cultures, and 21 were college graduates and above. No significant differences were observed in the general informa-

tion between the two groups ($P>0.05$). Thus, the two groups were comparable.

Methods

Both groups were routinely treated and properly exercised. Research group participants were treated with true rTMS. The instrument was a CCY-I transcranial magnetic stimulator purchased from Wuhan Yiruide Medical Equipment New Technology Co., Ltd. Using a circular coil, the stimulation range was the lateral area of the left frontal lobe. The stimulation frequency was 10 Hz and the stimulation intensity was 100% of the exercise threshold level. The stimulation diameter was 1.25 cm, at 3000 pulses/d. Continuous treatment was 5 days for one treatment cycle, with a cycle interval of 2 days. There were 4 treatment cycles. The control group was given pseudo rTMS treatment, using the same instrumentation. Treatment times and locations were also the same. However, the machine was not turned on.

Evaluation criteria

Changes in the following indicators were evaluated before and after treatment, respectively: (1) Montreal Cognitive Assessment Scale (MoCA) was adopted to assess changes in cognitive function, before and after treatment. Assessment items in the scale included language, attention, orientation, visual space and execution, abstract generalization, and delayed memory. It investigated 7 dimensions, with a score of 30 points. If the patient had less than 12 years of education time, 1 point was added. The critical score was 26 points. Higher scores indicated better recognition; (2) Efficacy: Markedly effective: MoCA scores increased by ≥ 4 points after treatment; Effective: MoCA scores increased by 1-3 points after treatment; Ineffective: MoCA scores increased by <1 after treatment. Total efficiency = 1 - Inefficiency; (3) Clock Drawing test (CDT): This test included spatial organization, digital arrangement, pointer, and time. A total score was 30 points. Higher scores indicated better cognitive function and better execution ability. The improved Barthel index (MBI) was used to evaluate the self-care ability of patients before and after treatment. Evaluation items included control of bowel movements, up and down stairs, walking on the ground, and eating. Results ranged from 0 to

100. Scores were positively associated with the recovery of self-recovery capacity; (4) Latency period and amplitude of the event-induced potential P300 was inspected by NTS-2000 electromyography and induced potentiometer. Values were compared between the 2 groups. Two-dimensional images, such as green triangle (target stimulus), red triangle, red @ graph (target stimulus), red square, red trapezoid, and red oval, were used as stimulus signals, with a target stimulus probability of 20%, stimulus time of 400 ms, and interval of 1000 ms. Patient eyes were 1 m away from the pictures. When target stimulation occurred, the patient pressed the button. A total of 450 single stimuli were performed. Ninety of these were target stimuli objects; (5) Determination of serum leptin, vascular endothelial growth factor (VEGF), and serum nerve growth factor (NGT) levels, before and after treatment, was conducted. A total of 3 mL of venous blood was collected and centrifugated at 3000 r/min for 10 minutes. Leptin level were determined by radioimmunoassay. The kit was purchased from LINCO company, USA. VEGF levels were determined by ELISA. NGT levels were determined by double antibody sandwich enzyme-linked immunosorbent assays. The kit was purchased from R&G, USA; (6) EEG distribution, before and after treatment, was compared in the two groups. Amps 300 amplifier and high-density 128-channel EGI acquisition systems were used for inspection and the sampling frequency was 1000 Hz. The patient was in a quiet and relaxed state, while the bilateral mastoid process was used as a reference. Off-line analysis sampling frequency was set as 500 Hz. Relative α -rhythm relative power spectrum of frontal region of F3, Fp1, Fp2, and Fz and high α rhythm of right temporal region T4 (10-13 Hz) were collected; (7) The two groups were compared regarding incidence of adverse reactions, including nausea, transient headaches, and facial muscle numbness.

Statistical analysis

SPSS 23.0 statistical software was used to analyze all data obtained in this study. Measurement data are expressed by $\bar{x} \pm s$. Independent samples-t tests were adopted. The adoption rate of numerical data was compared and χ^2 tests were used. $P < 0.05$ indicates statistical significance.

Results

rTMS improves the cognitive ability of patients with NVCI

Compared with before treatment, visual space and executive function, attention, delayed recall, and directional scores in both groups were increased after treatment. After treatment, the study group demonstrated significantly higher space and executive function, attention, delayed recall, and directional scores than the control group ($P < 0.05$). Changes in language, abstract generalization, and naming dimension were not obvious ($P > 0.05$). Results suggest that rTMS can significantly improve the cognitive ability of patients with NVCI, demonstrating that the curative effects were better than those of the conventional therapy group (**Figure 1**).

rTMS improves clinical symptoms of patients with NVCI

The study group had a higher total effective rate than the control group ($P < 0.05$), suggesting that rTMS can significantly ameliorate clinical symptoms of NVCI patients. Curative effects were shown to be better than those of the conventional therapy group (**Table 1**).

rTMS promotes CDT scores and MBI scores of patients with NVCI

Compared to before treatment, CDT scores and MBI scores of the two groups were increased after treatment. Increases in the study group were more significant ($P < 0.05$). Results showed that rTMS significantly ameliorated the self-living ability of NVCI patients, demonstrating that the curative effects were better than those of the conventional therapy group (**Figure 2**).

rTMS improves event-related evoked potential P300 of patients with NVCI

Compared to before treatment, the latency of P300 was shortened and the amplitude of the two groups was increased after treatment. After treatment, the study group reported a shorter latency period of P300 and higher amplitude than the control group ($P < 0.05$). Results showed that rTMS significantly improved neurophysiological parameters of NVCI

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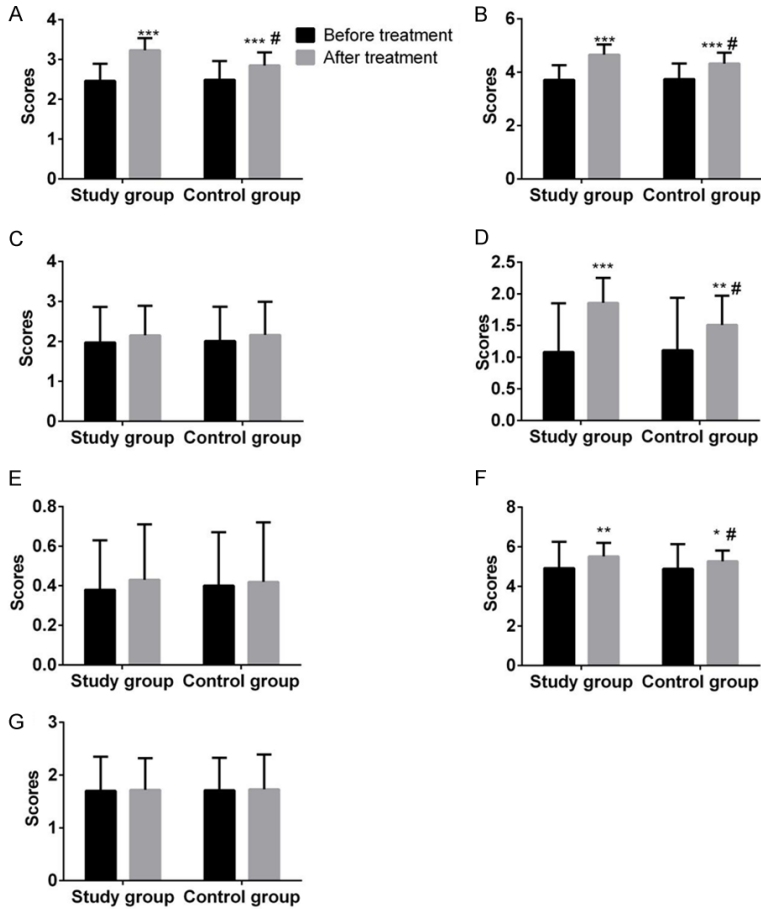


Figure 1. Cognitive function comparison between the two groups. Notes: Compared with before treatment, ** $P < 0.01$, *** $P < 0.001$, compared with the control group, # $P < 0.05$. A. Visual space and executive function; B. Attention; C. Language; D. Delayed memory; E. Abstract generalization; F. Orientation; G. Naming. Notes: Compared with the control group, # $P < 0.05$.

patients and promoted the brain's recognition, processing, and processing speed of external information. Thus, it can significantly promote the recovery of cognitive function of patients. Moreover, the curative effects were better than those of the conventional therapy group (Figure 3).

rTMS improves serum leptin, VEGF, and NGT levels in NVCI patients

Compared to before treatment, serum leptin, VEGF, and NGT levels increased after treatment. Indicators of the study group were higher than those of the control group ($P < 0.05$). Results suggest that rTMS can significantly improve serum leptin, VEGF, and NGT levels in NVCI patients. Therefore, it can promote the repair of brain nerve cells, improving the cognitive function of patients. The curative effects

were better than those of the conventional therapy group (Figure 4).

rTMS improves the high alpha rhythm relative power spectra of patients with NVCI

Compared to before treatment, the relative α -rhythm relative power spectrum of F3, Fp1, Fp2, Fz, and T4 in the right iliac area of the study group was significantly increased after treatment. Levels were significantly higher than those of the control group ($P < 0.05$). The relative α -rhythm relative power spectra of F3, Fp1, Fp2, and Fz in the control group were significantly increased ($P < 0.05$), suggesting that rTMS improved the distribution of EEG in NVCI patients, promoted the recovery of damaged brain waves, and improved cognitive function in patients. The effects were better than those of the conventional therapy group (Figure 5).

rTMS has a low incidence of adverse reactions in NVCI patients

Incidence of adverse reactions was 9.43% in the study group and 1.89% in the control group ($P > 0.05$), suggesting that rTMS, as a physical therapy, might cause nausea, transient headaches, facial muscle numbness, and scalp numbness during application. However, incidence rates of adverse reactions were quite low and the patients could tolerate them well (Table 2).

Discussion

NVCI is more common in the middle-aged and elderly population. It has been reported that incidence of NVCI in the elderly over 65 years of age is 8.70% [9]. The pathogenesis of current NVCI is not fully understood. Cerebral hemorrhaging, subcortical white matter ischemia, and ischemic strokes may cause NVCI [10]. According to reports, 75% of stroke patients

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Table 1. Comparison of curative effects between the two groups

Group	n	Markedly effective	Effective	Ineffective	Total Efficacy
Study group	53	32 (60.38)	18 (33.96)	3 (5.66)	50 (94.34)
Control group	53	23 (43.40)	19 (35.85)	11 (20.75)	42 (79.25)
χ^2		-	-	-	5.267
P		-	-	-	0.022

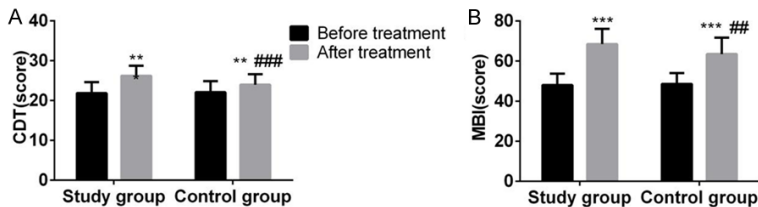


Figure 2. Comparison of CDT scores and MBI scores between the two groups. Notes: Compared with before treatment, ** $P < 0.01$, *** $P < 0.001$, compared with the control group, ### $P < 0.001$. A. CDT; B. MBI.

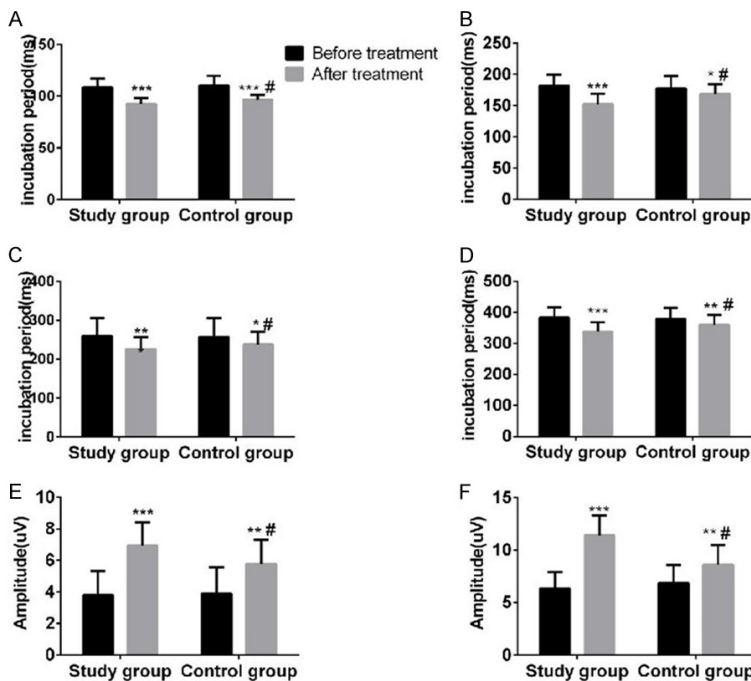


Figure 3. Comparison of the latency of event-related evoked potential P300 between the two groups. Note: Compared with before treatment, * $P < 0.05$, ** $P < 0.01$, *** $P < 0.001$, compared with the control group, # $P < 0.05$. A. N1; B. P2; C. N2; D. P3; E. P2; F. P3.

have varying degrees of cognitive dysfunction, with NVCI the most common. In addition, high blood pressure, diabetes, cognitive levels, age, drugs, and hypotension are important risk factors for NVCI [11, 12]. NVCI is an early stage of dementia, with cognitive impairment as the

main manifestation. Early intervention can effectively prevent its transformation into dementia. At the same time, the heterogeneity of risk factors and clinical features of NVCI makes it possible to reverse the situation. After effective treatment, cognitive impairment of patients can be prevented and reversed. Thus, the prognosis of patients can be effectively improved [13]. In this study, rTMS was used to treat patients with NVCI. Results showed that rTMS significantly improved the cognitive ability and self-living ability of patients after treatment. Combined with rTMS treatment was shown to be more conducive to the recovery of cognitive ability and improvement of self-living ability, along with better efficacy, than the conventional treatment group. Thus, it has high clinical application value.

Moreover, rTMS uses a transcranial magnetic stimulator to stimulate specific parts of the brain. The transcranial magnetic stimulator can generate a changing current. This, in turn, forms a magnetic field that can pass through the scalp tissue and the skull to the cerebral cortex without attenuation. It produces a small amount of induced current that can alter the activity of nerve cells, affecting mental activity [14]. Of these, low frequency rTMS below 1 Hz acts as an inhibitor and can reduce the excitability of nerves. High frequency rTMS

above 1 Hz acts as an excitatory. It increases excitability of the cerebral cortex, increases local cerebral perfusion, and improves local microcirculation. In addition to directly stimulating the cerebral cortex, stimulation of cortical neurons by rTMS can also be transmitted to the

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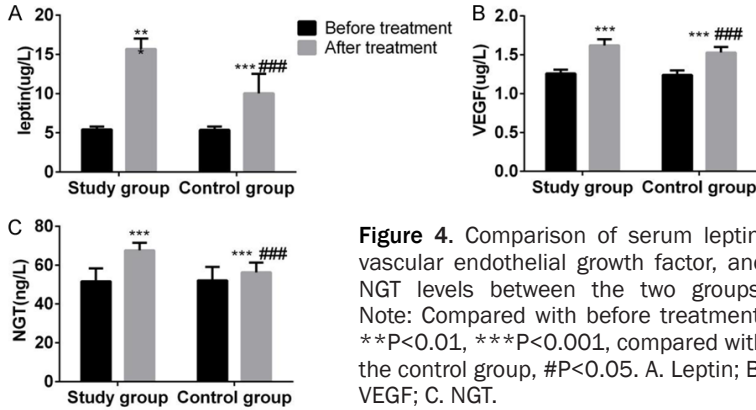


Figure 4. Comparison of serum leptin, vascular endothelial growth factor, and NGT levels between the two groups. Note: Compared with before treatment, ** $P < 0.01$, *** $P < 0.001$, compared with the control group, # $P < 0.05$. A. Leptin; B. VEGF; C. NGT.

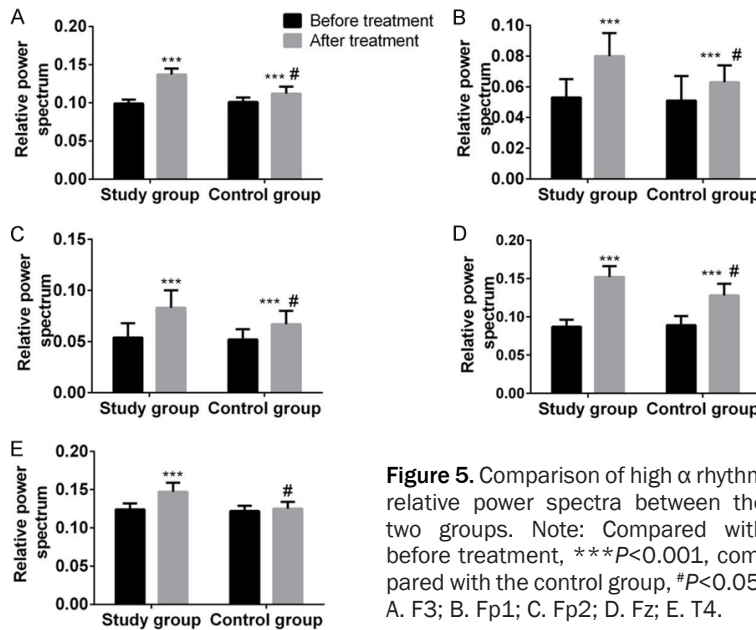


Figure 5. Comparison of high α rhythm relative power spectra between the two groups. Note: Compared with before treatment, *** $P < 0.001$, compared with the control group, # $P < 0.05$. A. F3; B. Fp1; C. Fp2; D. Fz; E. T4.

distant cortex via neural networks, promoting regional reconstruction of cortical function. After the end of rTMS treatment, the biological effects continue for a span of time. This plays a role in promoting the reconstruction of the cerebral cortex network. The purpose of treating peripheral and central nervous system damage is achieved [15]. This is one of the core mechanisms by which rTMS improves cognitive function [16]. Results showed that cognitive function scores, total effective rates, CDT scores, and MBI scores of the study group were better than those of the control group after rTMS treatment. Results suggest that rTMS can improve the efficacy of NVCI and significantly improve cognitive function and self-care abilities of patients. Present results are in accord with previous studies [17].

P300 is a brain neurophysiological indicator that reflects brain activity. It can directly reflect cognitive function. The length of the P300 incubation period can directly reflect the brain's recognition and processing speed. The amplitude of the wave directly reflects the brain's ability to perceive information and information processing [18]. Present results showed that the P300 latency and amplitude increased in the study group after treatment. The change was more obvious than in the control group. Results suggest that, after treatment with rTMS, brain activity and cognitive function impairment levels of the study group were improved. The effects were better than those of conventional therapy alone.

Leptin, also known as cellulite, is a single-chain protein found to be involved in a variety of neuroendocrine metabolic systems in the body. Related studies [19] have shown a positive correlation between serum leptin and MoCA scores in patients with vascular cognitive impairment ($r = 0.402$,

$P < 0.01$). VEGF is a highly biologically active functional glycoprotein involved in physiological processes, such as angiogenesis, neuroprotection, and nerve regeneration [20]. Related studies have found that VEGF declines, to a certain extent, can cause cognitive impairment [21]. NGT is a biologically active protein that promotes the growth and differentiation of nerve cells, showing positive effects on the repair of damaged nerves [22]. Related studies [23] have shown that mouse nerve growth factor can improve cognitive function in patients with acute vascular disease. Results of this study showed that serum leptin, VEGF, and NGT levels in the study group increased after treatment. Changes were larger than those recorded in the control group. Results showed that rTMS treatment can improve serum cytokine levels in patients with NVCI.

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Table 2. Comparison of adverse reactions between the two groups [n (%)]

Group	n	Nausea	Transient headache	Facial muscle numbness	Scalp numbness	Total efficiency
Research group	53	1 (1.89)	2 (3.77)	1 (1.89)	1 (1.89)	5 (9.43)
Control group	53	1 (1.89)	0 (0.00)	0 (0.00)	0 (0.00)	1 (1.89)
χ^2		-	-	-	-	1.590
P		-	-	-	-	0.093

There is synchronous discharge activity in the brain, called EEG in clinical practice. It is a combination of curves that use electronic biotechnology to record the process of brain bioelectricity, reflecting brain activity [24]. The relative power spectrum of the α -rhythm of the frontal and temporal lobe of NVCI patients was significantly lower than that of normal people [25]. Results obtained from this study showed that the relative α -rhythm relative power spectrum of the frontal F3, Fp1, Fp2, Fz, and T4 of the right sac was significantly increased in the study group. Levels were significantly higher than those of the control group after treatment. Results suggest that rTMS treatment can improve the EEG distribution of NVCI patients.

In summary, rTMS is a safe and non-invasive green treatment technology. It can improve cognitive function, self-care ability, serum cytokines, event-related evoked potential, and EEG distribution in patients with non-dementia-type vascular cognitive impairment. Thus, it provides high clinical value.

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Disclosure of conflict of interest

None.

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