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# The effect of repeated transcranial magnetic stimulation combined with cognitive rehabilitation training on post-stroke cognitive impairment

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**Abstract. – OBJECTIVE: The aim of this study was to explore the effect of repetitive transcranial magnetic stimulation (rTMS) combined with cognitive rehabilitation training on post-stroke cognitive impairment (PSCI).**

**PATIENTS AND METHODS: We retrospectively reviewed clinical data from 119 patients with PSCI admitted to our hospital from December 2021 to April 2023, of which 58 received pure cognitive rehabilitation training (control group) and 61 received rTMS combined with cognitive rehabilitation training (observation group). We calculated measures of cognitive function rehabilitation, daily living activity abilities, latency and amplitude of P300 wave of evoked potential, and serum biochemical index levels before and after the intervention in the two groups.**

**RESULTS: After the intervention, the scores of the Montreal Cognitive Assessment (MoCA) scale and Rivermead behavioral memory test (RBMT) had improved in the two groups. Also, the Modified Barthel Index (MBI) scores of the two groups increased after the intervention. The P300 wave latencies in both groups decreased and their amplitudes increased after the intervention. The levels of serum neurotrophin-3 (NT-3) and brain-derived neurotrophic factor (BDNF) in the two groups were higher, and the levels of brain glial fibrillary acidic protein (GFAP) were lower after the intervention. All these improvements were more marked in the observation group than in the control group (all $p<0.05$).**

**CONCLUSIONS: Compared with simple cognitive rehabilitation training, the training combined with rTMS was more effective at restoring cognitive function, improving daily living activity abilities, and improving the treatment outcome of patients with PSCI.**

*Key Words:*
Cognitive rehabilitation training, Post-stroke cognitive impairment, Repeated transcranial magnetic stimulation.

## Introduction

Stroke is a multifactorial cerebrovascular disease[1]. The continuous improvement of treatment technologies has led to a significant decrease in the mortality rate of stroke[2]. However, survivors are often left with sequelae such as cognitive impairment, dysphagia, speech communication disorder impairment, and motor dysfunctions[1,3].

Post-stroke cognitive impairment (PSCI) is the most common type of complication after stroke[1,4]. Patients are often left with varying degrees of agnosia, visuospatial, memory, and attention disorders[5]. Moreover, patients with PSCI are unable to cooperate during rehabilitation training effectively and actively and achieve poor overall functional rehabilitation effects, resulting in diminished physical and mental health that pose a burden to their families and society[1,4,5].

Clinical research[6] has confirmed that early cognitive function rehabilitation training helps restore the cognitive function of patients while improving their daily living activity abilities. Traditional clinical cognitive rehabilitation training can improve the cognitive function of patients with PSCI to a certain extent, but the overall effect is less than ideal[7]. Repetitive transcranial magnetic stimulation (rTMS) is an important clinical rehabilitation technique with advantages such as safety, reliability, simple operation, and non-invasiveness[6-8], and it can improve executive and memory functions[7,8].

However, the evidence on the combination of rTMS and cognitive rehabilitation training for the treatment of PSCI is scarce. Our hospital has adopted rTMS combined with cognitive rehabilitation training as an intervention to treat patients with PSCI, and this study aims to review and analyze the effectiveness of the intervention to provide a reference for clinicians.

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## Patients and Methods

We retrospectively reviewed the clinical charts of 119 patients with PSCI treated in our hospital from December 2021 to April 2023 who met the enrolment criteria. Among the patients, 63 were men and 56 women, with an age range from 54 to 83 years (average, 67.7±7.2 years). The course of the disease ranged from 28 to 67 days (average, 48.8±9.5 days), and the body mass index (BMI) from 17.9 to 28.4 kg/m$^2$ (average, 23.5±2.8 kg/m$^2$). We divided the patient data into a control group of 58 patients who received simple cognitive rehabilitation training and an observation group of 61 patients who underwent rTMS combined with cognitive rehabilitation training.

### Inclusion Criteria

- Patients with data conforming to PSCI diagnostic criteria and confirmation by magnetic resonance imaging (MRI), computed tomography (CT), and other techniques[9].
- Patients with records of a first stroke episode.
- Patients with clear consciousness and stable vital signs.
- Patients with complete clinical data.

### Exclusion Criteria

- Patients with cognitive impairment or severe aphasia before a stroke episode.
- Patients with previous craniocerebral surgery.
- Patients with a history of epilepsy, traumatic brain injury, or cerebral hemorrhage.
- Patients with cognitive impairment due to other causes.
- Patients with visual and auditory impairments.

We ensured all procedures involving human participants carried out in this study were in accordance with the ethical standards of our institution, and/or the National Research Council, and the Declaration of Helsinki (revised in 2013). We obtained written informed consent from the patients or legal guardians, and the medical Ethics Committee of our hospital approved the study [No. 2022-085-02 (z), date: 2022-06-02].

Cognitive rehabilitation training included six different steps: (1) Attention training through visual tracking, guessing games, continuous counting, and other methods; (2) memory training through short passage memorization, image sequence recall, and image memorization; (3) visual-spatial structure skill practice through puzzles, chess, building blocks, and other methods; (4) directional exercises through the perception of characters, time, and space; (5) thinking and reasoning training by creating daily life scenarios and conducting judgment and reasoning exercises by looking at pictures to find differences; (6) execution exercises through manual production and other measures. The above sessions were 60 minutes long, 5 times per week, for a total of 4 weeks of intervention.

We selected the rTMS device from the Magpro R30 transcranial magnetic stimulator (MagVenture, Farum, Denmark) and an 8-shaped coil. Patients were guided to take a semi-supine or supine position and to relax their entire body. The plane of the magnetic stimulation coil was tangent to the surface of the skull, and the magnetic stimulation frequency was set to 10 Hz, with the left dorsolateral frontal cortex area as the magnetic stimulation site. The magnetic stimulation intensity was set to 80% of the exercise threshold. After 2 seconds of stimulation, patients rested for 20 seconds before the next one; the total session lasted 20 minutes, and there were 5 sessions per week once a day for a total of 4 weeks of intervention.

### Outcome Measures

1) Cognitive function rehabilitation before and after the intervention: we used the Montreal Cognitive Assessment (MoCA) with a total score of 30 points to evaluate cognitive function, including abstract overview, delayed recall, orientation, language, attention, visual space, and executive function. The higher the score, the better the cognitive function. We applied the Rivermead behavioral memory test (RBMT) to assess daily memory ability, including image recognition, object memorization, and name memorization. The total possible score was 24 points (the higher the score, the better the memory function).
2) Daily living activity abilities before and after the intervention: we performed Modified Barthel Index (MBI) assessments with a maximum possible score of 100 points (the higher the score, the better the daily living activity abilities).
3) Latency and amplitude of P300 wave evoked potential before and after the intervention: we used a Viking Quest 4-channel desk myoelectric evoked potential system (Thermo Scientific Nicolet Corporation, Madison WI, USA), ensuring that the resistance between the elec-

**Table I.** Comparison of two groups of baseline data.

| Group | Gender (male/ female) | Age (years) | BMI (kg/m$^2$) | Course of disease (days) | Education level | |
|---|---|---|---|---|---|---|
| | | | | | Below high school | High school and above |
| Combined group (n = 61) | 34/27 | 68.7 ± 7.2 | 47.8 ± 9.1 | 23.8 ± 2.6 | 39 (63.9) | 22 (36.1) |
| Simple group (n = 58) | 27/31 | 66.7 ± 7.1 | 49.9 ± 9.8 | 23.3 ± 3.0 | 33 (56.9) | 25 (43.1) |
| $\chi^2/t$ 1.004 | 1.525 | -1.186 | 0.981 | 0.616 | | |
| $p$ 0.316 | 0.130 | 0.238 | 0.329 | 0.432 | | |

trode and the skin did not exceed 5 k Ω, the sensitivity was set at 5 μV, and the analysis time at 100 ms; the P300 latency and amplitude were automatically recorded.

4) Serum biochemical indicators before and after the intervention, including levels of NT-3, BDNF, and GFAP: after drawing 4 mL of fasting venous blood from each participant, the supernatants were centrifuged, and used to determine the variable levels using enzyme-linked immunosorbent assays (Shanghai Mbio Biotechnology kits; Shanghai, China).

### Statistical Analysis

We conducted all data analysis using the SPSS 22.0 software (IBM Corp., Armonk, NY, USA). After evaluating the normality of the data using the Shapiro-Wilk test, we expressed normally distributed data as means ± standard deviations. We used the independent sample *t*-test for inter-group comparisons and the paired *t*-test for intra-group comparisons. We expressed non-normally distributed data as medians and interquartile intervals, and we used the Mann-Whitney U test for inter-group comparisons and the Wilcoxon signed rank test for intra-group comparisons. We represented counting data as numbers of cases and used the Chi-squared test to assess associations. We considered all $p$-values <0.05 as indicative of statistical significance.

## Results

We found similar baseline data in the two groups of patients ($p$>0.05) (Table I).

Before the intervention, we found similar MoCA, RBMT, and MBI scores in the two groups ($p$>0.05). After the intervention, the scores of MoCA, RBMT, and MBI in both groups increased compared to the baseline values, but the observation group values rose higher than the control group values ($p$<0.05) (Table II).

Before the intervention, we found similar P300 wave latencies and amplitudes in the two groups ($p$>0.05). After the intervention, the P300 wave latencies decreased, and the amplitudes increased in both groups compared to the baseline values before the intervention. Moreover, the mean P300 wave latency in the observation group was lower than that in the control group, and the mean P300 wave amplitude was higher than that in the control group ($p$<0.05) (Table III).

**Table II.** Comparison of cognitive function rehabilitation and daily living activity abilities between the two groups (points).

| Time | Group | n | MoCA | RBMT | MBI |
|---|---|---|---|---|---|
| Before the intervention | Observation group | 61 | 15.9 ± 2.5 | 9 (8, 12) | 45.4 ± 8.1 |
| | Control group | 58 | 15.2 ± 2.7 | 9 (8, 12) | 44.4 ± 7.7 |
| | $t$/Z | | 1.439 | -0.887 | 0.674 |
| | $p$ | | 0.153 | 0.375 | 0.502 |
| After the intervention | Observation group | 61 | 24.2 ± 2.3[a] | 15 (14, 18)[a] | 66.9 ± 7.3[a] |
| | Control group | 58 | 21.2 ± 2.5[a] | 12 (11, 15)[a] | 61.1 ± 6.9[a] |
| | $t$/Z | | 6.689 | -5.033 | 4.475 |
| | $p$ | | < 0.001 | < 0.001 | < 0.001 |

Compared with values before treatment in this group, [a]$p$ < 0.05. Montreal Cognitive Assessment (MoCA) scale, Rivermead behavioral memory test (RBMT), Modified Barthel Index (MBI).

**Table III.** Comparison of P300 wave amplitude latencies between two groups.

| Time | Group | n | P300 wave latency (ms) | P300 wave amplitude (uV) |
|---|---|---|---|---|
| Before the intervention | Observation group | 61 | 397.5 ± 22.5 | 5.39 ± 0.63 |
| | Control group | 58 | 401.8 ± 21.6 | 5.28 ± 0.60 |
| | *t* | | -1.072 | 0.969 |
| | *p* | | 0.286 | 0.334 |
| After the intervention | Observation group | 61 | 313.1 ± 21.1[a] | 9.77 ± 0.68[a] |
| | Control group | 58 | 347.8 ± 19.8[a] | 8.09 ± 0.60[a] |
| | *t* | | -9.235 | 14.130 |
| | *p* | | < 0.001 | < 0.001 |

Compared with values before treatment in this group, [a]$p < 0.05$.

Before the intervention, the levels of NT-3, BDNF, and GFAP between the two groups were similar ($p>0.05$). After the intervention, the levels of NT-3 and BDNF in both groups increased, while the levels of GFAP decreased compared to the baseline values before the intervention. In addition, after the intervention, the levels of NT-3 and BDNF in the observation group were higher and those of GFAP were lower than those in the control group ($p<0.05$) (Table IV).

## Discussion

The results of this study show that applying rTMS combined with cognitive rehabilitation training provides benefits to patients with PSCI, and the combined approach can lead to effective cognitive function restoration and daily living activity abilities improvements. Transcranial magnetic stimulation is an important treatment for nervous system diseases[7,8] that sends electromagnetic pulses to cortical neurons in the brain and changes their membrane potential, inducing exciting currents along their axons to activate surrounding neurons, thereby generating a therapeutic effect[8,10]. rTMS can provide repeated and continuous stimulation to specific cortical locations, resulting in a cumulative effect that can excite a large number of neurons[7,10]. After the magnetic stimulation, the biological effects continue for some time, maintaining the cerebral cortical network function[10,11]. Meanwhile, TMS serves as a tool for the impact of drugs on cortical plasticity; Patients receive psychotropic drugs while undergoing treatment, which can affect neuronal excitability and plasticity, and may interact to affect rTMS treatment outcomes[12,13]. Yin et al[14] confirmed that patients with PSCI who receive rTMS treatment show more significant improvements in the Victoria Stroop and Rivermead behavioral memory tests and higher scores in the Activities of daily living (ADL) and MoCA. Our results are consistent with those. rTMS can activate local neurons, enhance cortical excitability, and increase local cerebral blood flow, all important features for restoring the function of the ischemic penumbra area by promoting nerve cell growth and regulating glucose metabolism, thereby allevi-

**Table IV.** Comparison of serum biochemical index levels between the two groups.

| Time | Group | n | NT-3 (ng/ml) | BDNF (ng/ml) | GFAP (ug/L) |
|---|---|---|---|---|---|
| Before the intervention | Observation group | 61 | 7.17 ± 1.03 | 10.8 ± 2.3 | 1.55 ± 0.42 |
| | Control group | 58 | 7.26 ± 1.05 | 11.1 ± 2.2 | 1.52 ± 0.54 |
| | *t* | | -0.481 | -0.635 | 0.412 |
| | *p* | | 0.631 | 0.527 | 0.681 |
| After the intervention | Observation group | 61 | 12.7 ± 1.7[a] | 19.3 ±2.3[a] | 0.51 ± 0.24[a] |
| | Control group | 58 | 10.0 ± 1.3[a] | 15.8 ± 2.4[a] | 0.71 ± 0.32[a] |
| | *t* | | 9.550 | 8.184 | -3.793 |
| | *p* | | < 0.001 | < 0.001 | < 0.001 |

Compared with the values before treatment in this group, [a]$p < 0.05$. Serum neurotrophin-3 (NT-3), brain-derived neurotrophic factor (BDNF), glial fibrillary acidic protein (GFAP).

ating any secondary cerebral ischemic injury and strengthening the tolerance of the brain tissues to ischemia and hypoxia[11,14]. Li et al[15] studied the application of an rTMS scheme to patients with PSCI, and their results confirmed that it can improve cognitive function and help regulate the levels of thyroid hormones. rTMS can also regulate the excitabilities of the cerebellum thalamus cortex network and limbic system by downregulating the threshold of synaptic conduction and improving it. The technique can also affect neuronal excitability by regulating the serum levels of synaptophysin, dopamine, acetylcholine, and other neurotransmitters, and by promoting the re-establishment of the brain nerve functions to restore cognitive function[16,17]. Chu et al[18] confirmed that effective transcranial magnetic stimulation therapy based on cognitive rehabilitation training improves the cognitive function of patients with PSCI and their quality of life. Colella et al[19] showed that rTMS can effectively improve individual spatial neglect, memory, execution, and attention. rTMS can also improve the brain metabolism and cerebral blood flow status, restoring ionic balance, accelerating synaptic recovery and remodeling, inhibiting programmed cell apoptosis, and enhancing the transmission of many neurotransmitters necessary for the reconstruction of cortical functional networks. Esposito et al[20] also showed that rTMS can effectively improve memory and learning functions, possibly by enhancing the expressions of synaptophysin (mRNA and protein) and brain-derived nerve growth factor and enhancing the synaptic plasticity in the hippocampal CA1 region, so as to improve the cognitive and neural functions.

NT-3 and BDNF are important neurotrophins. NT-3 can sustain the function of neurons and promote synapsis formation; BDNF has important roles in neural cell repair, differentiation, and proliferation, and can improve cognitive, memory, and learning abilities; GFAP is a cytoskeleton component and an important astrocyte marker, its serum expression is closely associated with the degree of brain injury[20]. We observed that after treatment, the serum levels of NT-3 and BDNF were higher, while those of GFAP were lower in the observation group than in the control group. These results further demonstrate the benefits of rTMS in patients with PSCI, showing it can effectively regulate the expression of relevant neural factors to ensure favorable disease outcomes.

### Limitations

This study was a single-center retrospective analysis with a small sample size and inherent selection bias. We studied a few indicators and failed to conduct long-term follow-ups, and we cannot attest to long-term efficacy and sustained changes in brain function after rTMS treatment cessation. Finally, our hospital applied standard rTMS treatments without prior determination of the optimal stimulation plan.

## Conclusions

For patients with PSCI, simple cognitive rehabilitation training combined with rTMS can more effectively restore cognitive function, improve daily living activity abilities, and improve disease treatment results than cognitive rehabilitation training alone.

### Conflict of Interest

The authors declare that they have no conflict of interests.

### Funding

No funding was received.

### Availability of Data and Materials

The datasets used and/or analyzed during the current study are available from the corresponding author on reasonable request.

### Authors' Contribution

HZ conceived and designed the study. HW, XQ, YM and ZW collected the data and performed the analysis. HZ was involved in the writing of the manuscript. All authors have read and approved the final manuscript.

### Ethics Approval

We ensured all procedures involving human participants carried out in this study were in accordance with the ethical standards of Cangzhou Central Hospital, and/or the National Research Council, and the Declaration of Helsinki (revised in 2013). The Medical Ethics Committee of Cangzhou Central Hospital approved the study [No. 2022-085-02 (z), date: 2022-06-02].

### Informed Consent

We obtained written informed consent from the patients or legal guardians.

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