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Effect of repetitive transcranial magnetic stimulation combined with synchronous working memory training on cognitive function of stroke patients

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Abstract. Objective To investigate the effects of repetitive transcranial magnetic stimulation combined with synchronous working memory training on memory, attention and executive ability in stroke patients. Methods 80 stroke patients were divided into synchronous group, rTMS Group, WM Group and control group by random number table. Aiming at cognitive function, the synchronous group received repetitive transcranial magnetic stimulation combined with synchronous working memory training, the rTMS group received repetitive transcranial magnetic stimulation, the WM Group received working memory training, and the control group received only routine treatment, each group was treated for 20 days. Before and after treatment, Stroop test, Mo-CA test, modified Barthel test were given to the four groups respectively. Results ①Before treatment initiation, there was no significant difference among the four groups ($P>0.05$) ②After treatment, the correct rate of Stroop test at baseline and conflict stage in synchronous group was significantly higher than that in other three groups ($p<0.05$) .It was significantly shorter than WM Group and control group at baseline($p<0.05$), and significantly shorter than control group at conflict stage($p<0.05$). ③In Mo-CA test, modified Barthel test , the performance of synchronous group was significantly higher than that of other three groups ($p<0.05$) .Conclusion Repetitive transcranial magnetic stimulation combined with synchronous working memory training can effectively improve the cognitive function of patients with stroke, and the therapy is worth popularizing.

Keywords: Repetitive transcranial magnetic stimulation, working memory training, synchronous, stroke, cognitive function

1. Introduction

Stroke is the leading cause of mortality and disability in adults in our country. According to the China Stroke High-risk Population Screening and Intervention Program, an estimated 17.8 million [95% confidence interval (CI) 17.6-18.0 million] adults in China had experienced a stroke in 2020 [1]. Post-stroke cognitive impairment (PSCI) cannot be neglected because it drastically impact the daily life of patients and their families [2]. PSCI has been linked to diminished self-care abilities, reduced quality of life, accelerated physical function decline ,as well as heightened risks of disability and mortality [3].

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The overall prevalence of PSCI in our country is 80.97% [4], which brings a heavy burden to the society and families.

With the diversification of research methods, cognitive function training has shifted towards the development of core ability [5], making research and training on working memory a primary focus.

Working memory deficit is a prevalent cognitive impairment observed in stroke patients. Following a stroke, all components of the working memory system are compromised [6]. Previous studies have demonstrated that working memory training can ameliorate abnormal activation patterns and reorganize functional activation networks in stroke patients, leading to enhanced activation of impaired working memory areas and improved neural efficiency in unaffected brain regions associated with working memory [7].

Repetitive transcranial magnetic stimulation (rTMS) represents an innovative non-invasive rehabilitation approach that regulates neuroplasticity, enhances the brain’s capacity to retrain neural circuits, and facilitates recovery as well as acquisition of new compensatory skills [8]. Research has indicated that transcranial magnetic stimulation exerts a significant regulatory effect on working memory [9].

Currently, there is no unified standard for the treatment of PSCI, considering that both repetitive transcranial magnetic stimulation and working memory training can improve the cognitive function of patients with PSCI when used alone, however, there are few reports about repetitive transcranial magnetic stimulation (TMS) combined with synchronous working memory training, so this study used synchronous therapy to provide evidence for exploring new cognitive therapy for PSCI patients.

2. Materials and methods

2.1. General information

2022.01-2023.05, inpatients and outpatients in the Department of Rehabilitation Medicine, Hongqi Hospital, Mudanjiang Medical College.

The selection criteria were as follows: (1) participants aged over 18 years; (2) head CT/MRI confirmed a recent (<1 month) head injury located in the core brain areas (frontal lobe, temporal lobe, basal ganglia, etc.); (3) absence of artificial pacemaker or artery stent; (4) no use of cognitive-enhancing medications; (5) Montreal Cognitive Assessment (MOCA) score below 26 points; (6) stable vital signs of the patients; and (7) informed consent obtained from all participants.

Exclusion criteria: (1) a history of epilepsy; (2) a history of mental disorders; (3) significant visual and hearing impairment; (4) severe unilateral neglect, left and right agnosia; (5) inability to cooperate with related studies. This study was approved by the Ethics Committee of Hongqi Hospital affiliated with Mudanjiang Medical College (No. 2023041).

The study enrolled a total of 80 patients, with 20 in the synchronous group, 20 in the rTMS group, 20 in the WM group, and 20 in the control group. There were no significant differences observed among the four groups regarding age, sex, and years of education ($P > 0.05$), as shown in Table 1.

Table 1. Comparison of general data of enrolled patients

Group	Number	Sex		Age ($\bar{x}\pm s$)	Years of education ($\bar{x}\pm s$)	The cause	
		Male	Female			ICH	CI
Synchronization Group	20	17	3	61.25±8.80	11.20±2.78	4	16
rTMS group	20	17	3	60.95±9.20	10.45±2.68	3	17
WM group	20	16	4	60.40±9.71	9.90±2.40	4	16
Control Group	20	16	4	64.15±10.75	10.05±2.46	2	18
P		0.951		0.613	0.393	0.799	

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2.2. Training method

In the synchronous group, the therapist conducted one-to-one synchronous working memory training during repetitive transcranial magnetic stimulation. Patients assumed a supine position and used a specially designed low pillow to support their head and prevent movement. The repetitive transcranial magnetic device was used to stimulate the dorsolateral area of left frontal lobe, 20 Hz, pulse 820, stimulation 1 second, interval 28 seconds, the stimulus intensity was 80% -120% of resting motor threshold (RMT). Before initiating the initial treatment, it is essential to gather RMT values: instruct the patient to assume a seated position, ensure relaxation of the abductor pollicis brevis muscle, and elicit stimulation of the corresponding primary motor cortex (M1). To establish the minimum M1 stimulation intensity for this particular patient, at least 5 out of 10 consecutive trials should exhibit a peak-to-peak amplitude of evoked EMG greater than 50μV [10]. The working memory training employed the N-back task, wherein the therapist sequentially presented patterned cards to the patient. The patient's task was to compare each card with its preceding card, and the difficulty of the training was manipulated by varying the number of intervening cards between them. Specifically, when n = 1, patients compared each card with its immediate predecessor; for n = 2, they compared each card with the one two positions prior; and so forth, thereby setting different levels of difficulty for training tasks [11]. The aforementioned treatment was administered for a duration of 20 minutes per session, six times per week, over a period of 20 days.

For cognitive impairment, the rTMS group received repetitive transcranial magnetic stimulation exclusively, while the WM group underwent working memory training solely, with each session lasting 20 minutes and conducted six times a week for a duration of 20 days. The control group did not engage in any relevant cognitive function training. Additionally, exercise therapy, physical factor therapy, speech and swallowing therapy, occupational therapy, and other interventions were administered to all groups based on the patients' condition and stroke diagnosis and treatment standards

2.3. Outcome measures

The therapist, who was unaware of the grouping, evaluated the therapeutic outcomes of both patient groups pre- and post-treatment. The specific details are as follows.

(1) Stroop test: utilizing the WeChat mini-program 'MPL' Stroop test, the assessment is divided into two stages. The first stage serves as the baseline phase, where patients are required to determine the number of strings displayed on the screen and respond by pressing the corresponding numerical keys. In contrast, the second stage represents the conflict phase, wherein patients need to discern and indicate the quantity of numbers ('2, 33, 444, 1111') presented in each string on-screen by pressing their respective numerical keys.

(2) MOCA test: The Montreal Cognitive Assessment Scale (MO-CA) was employed to evaluate patients' cognitive function, encompassing 11 items across 8 cognitive domains and yielding a total score of 30 [12].

(3) The Modified Barthel Index (MBI) was employed to evaluate the patients' capacity for independent living and their overall quality of life, with a maximum score of 100. A higher score indicates enhanced proficiency in activities of daily living.

2.4. Statistical analysis

The SPSS 26.0 statistical software package was utilized for data processing. The counting data obtained in this study were analyzed using the chi-square test, while the measurement data, which exhibited a normal distribution, were subjected to one-way analysis of variance. In case of group differences, further analysis was conducted using the LSD method. Statistical significance was considered at $P < 0.05$.

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3. Results

3.1. Stroop test

Before treatment, there were no significant difference between the four groups in terms of time spent and accuracy at baseline and conflict level(P>0.05).

After treatment, the synchronization group exhibited significantly shorter time durations compared to the WM Group and control group at baseline ($p < 0.05$), as well as a shorter duration than the control group during the conflict stage ($p < 0.05$). Moreover, the synchronization group demonstrated higher correct rates than all other three groups both at baseline and during the conflict stage ($p < 0.05$). In comparison to the control group, the rTMS group displayed reduced time usage in the conflict phase ($p < 0.05$) along with higher correct rates at both baseline and conflict phases ($p < 0.05$). No significant differences were observed between the WM Group and synchronous group in terms of duration and accuracy during both baseline and conflict stages ($P > 0.05$). Please refer to Table 2 for detailed information.

Table 2. Comparison of Stroop test scores before and after training in four groups (x ± s)

Project	Before				After			
	Base time(ms)	Base Accuracy	Conflict time(ms)	Conflict Accuracy	Base time (ms)	Base Accuracy	Conflict time(ms)	Conflict Accuracy
Synchronization(n=20)	1981.45±504.06	0.67±0.20	2092.15±570.99	0.55±0.23	981.55±152.85[②③]	0.88±0.15[①②③]	1043.25±190.10[③]	0.83±0.17[①②③]
rTMS(n=20)	2164.25±397.31	0.60±0.21	2127.20±355.06	0.46±0.25	1153.95±240.99	0.74±0.17[③]	1170.50±269.78[③]	0.69±0.20[③]
WM(n=20)	2086.65±302.00	0.55±0.17	2278.20±250.84	0.43±0.13	1175.65±349.39	0.67±0.17	1238.10±369.52	0.55±0.16
control(n=20)	2110.35±470.78	0.55±0.19	2032.40±439.82	0.50±0.26	1289.70±349.65	0.60±0.19	1426.70±493.92	0.54±0.23
P	0.648	0.217	0.128	0.188	0.001	0.000	0.009	0.000

3.2. Mo-ca Test

There were no significant differences in Mo-CA scores among the four groups prior to treatment ($P > 0.05$). After treatment, the synchronous group exhibited significantly higher Mo-CA scores compared to the other three groups ($p < 0.05$). The rTMS group also demonstrated significantly higher Mo-CA scores than the control group ($p < 0.05$). No significant difference was observed between the WM Group and control group ($P > 0.05$). Please refer to Table 3 for detailed information.

Table 3. Comparison of MO-CA scores before and after training in four groups (x ± s)

Group	Before	After
Synchronization(n=20)	14.65±3.79	25.75±2.95[①②③]
rTMS(n=20)	14.70±3.05	21.65±3.44[③]
WM(n=20)	14.70±3.60	19.75±4.47
control(n=20)	14.65±2.64	19.10±3.86
P	1.00	<0.001

3.3. Modified Barthel test (MBI)

Before treatment, there were no significant differences in MBI scores among the four groups ($P > 0.05$). Following treatment, the synchronous group exhibited significantly higher MBI scores compared to the other three groups ($p < 0.05$). The rTMS Group also demonstrated higher scores than the control group

($p < 0.05$). However, there was no significant difference in MBI between the WM Group and control group ($P > 0.05$). Please refer to Table 4 for detailed information.

Table 4. The scores of MBI before and after training in the four groups were compared (x ± s)

Group	Before	After
Synchronization(n=20)	36.40±21.97	77.90±14.94①②③
rTMS(n=25)	35.30±22.48	64.70±17.57③
WM(n=20)	34.30±23.41	59.25±23.60
control(n=20)	36.05±21.08	51.60±19.43
P	0.991	<0.001

4. Discussion

4.1. Research on PSCI

PSCI falls under the category of Vascular Cognitive Impairment (VCI), encompassing executive function, language expression, memory, attention, and visual-spatial ability as its primary cognitive domains that are variably affected [13]. The etiology of PSCI is multifaceted, involving alterations in various gray matter structures [14], Pathological lesions originating along the course of white matter fibers surrounding the infarct [15], Furthermore, the combined effect of medial temporal lobe atrophy (MTLA) and white matter hyperintensities or single lesions in the brain's white matter was observed [16]. Simultaneously, the patient's age [17], education level [18], systemic obesity and other factors [19] are also implicated in the pathogenesis of PSCI.

Currently, PSCI lacks predictive criteria [20]and therapeutic criteria. The conventional approach primarily encompasses pharmacological intervention, psychobehavioral symptom management, and rehabilitation interventions [13], the clinical efficacy, however, remains suboptimal. Given the multifactorial etiology of PSCI, a comprehensive approach encompassing vascular, lifestyle-related, and psychosocial interventions should be concurrently implemented to achieve effective prevention and treatment [21].

4.2. The effect of simultaneous training of rTMS and WM on PSCI.

In recent years, several combined therapies have emerged as promising approaches for ameliorating the dysfunction observed in patients with post-stroke cognitive impairment (PSCI). Notably, the integration of repetitive transcranial magnetic stimulation (rTMS) with cognitive training has demonstrated superior efficacy in restoring cognitive function and enhancing activities of daily living among individuals afflicted by PSCI [22]. The combination of acupuncture and rehabilitation therapy demonstrates a significant improvement in the Mo-CA, MBI, and FMA scores among patients with PSCI, surpassing the efficacy of individual therapies [23]. High-frequency rTMS combined with speech and auditory feedback training can effectively regulate the levels of serum NSE and S100 β protein in patients [24]. Simultaneous cognitive-motor dual-task training (CMDT) in patients with post-stroke cognitive impairment (PSCI) can effectively reduce the reaction time of central neurons, enhance oxygen supply to the frontal lobe, accelerate nerve conduction speed and cognitive processing, thereby improving overall cognitive function [25].

In this study, we proposed a novel approach to rTMS synchronous working memory training. The findings indicated that the synchronous group exhibited superior performance compared to the other three groups. During treatment in the synchronous group, simultaneous stimulation of the DLPFC area was achieved. Consistent with Hebb's theory, repetitive firing of one neuron facilitates firing of another functionally connected neuron, thereby strengthening synaptic connections between neuronal cells and enhancing synaptic efficiency [26]. The top-down early control can promote the enhancement of memory representation. The top-down early control facilitates the enhancement of memory representation. The information from DLPFC is transmitted to the occipital cortex within 0 to 200 ms after the onset of exogenous cues, resulting in amplified lateralized P1AC components and earlier lateralized Adan components [27]. Numerous studies have substantiated that rTMS effectively targets the identical brain networks as the treatment task, and concurrent treatment exhibits a synergistic effect on plasticity enhancement [28].

5. Conclusion

The combination of rTMS and synchronous working memory training has the potential to enhance cognitive function in patients, with observed improvements extending to activities of daily living (ADL) and limb dysfunction. However, it is important to acknowledge certain limitations such as a small sample size and lack of long-term patient follow-up. Additionally, the treatment process necessitates one-to-one therapist training, which may pose challenges for large-scale implementation. Future research should focus on refining the content of this study.

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