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Effect of transcranial magnetic stimulation on treatment effect and immune function



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ABSTRACT

To explore the effect of transcranial stimulation on the therapeutic effect and immune function of patients with post-stroke depression (PSD). Methods Selection in September 2020–April 2021 on the diagnosis of 70 patients with PSD as the research object, 35 patients were randomly divided into control group and intervention group and control group given conventional treatment, the intervention group in the control group on the basis of the application of transcranial magnetic stimulation treatment, compare the curative effect of two groups of patients after the treatment cycle and the effects on the immune function. Results After treatment, the levels of DA, NE, 5-HT in 2 groups were significantly increased, and those in the observation group were significantly higher than those in the control group ($P < 0.05$). After 8 weeks of treatment, serum Gly content in 2 groups was significantly increased and Glu content was significantly decreased compared with before treatment. Compared with the control group, serum Gly content in observation group was significantly increased and Glu content was significantly decreased after treatment ($P < 0.05$). After 8 weeks of treatment, the contents of IL-1 β , IL-6 and TNF- α in serum of 2 groups were significantly decreased, compared with the control group, the contents of IL-1 β , IL-6 and TNF- α in serum of observation group were significantly decreased ($P < 0.05$); Before treatment, there was no significant difference in PHQ-9 score and MBI score between the two groups ($P > 0.05$). After 8 weeks of treatment, PHQ-9 score and MBI score in the two groups were better than before treatment, and the observation group was better than the control group ($P < 0.05$). Conclusion Transcranial magnetic stimulation therapy can not only effectively promote the synthesis and release of monoamine neurotransmitters in patients with post-stroke depression, regulate the inhibitory/excitatory amino acid neurotransmitters, reduce inflammatory response, improve the clinical treatment effect and enhance the immune function of PSD patients, which has clinical application value.

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1. Introduction

Stroke is a disease of serious morbidity and mortality around the world, if stroke patients are not in the symptoms within 4.5 h, reduce the direct damage of stroke attack to brain cell neurons, reduce the impact of stroke attack disability, stroke patients often appear movement disorders, language disorders, visual impairment and different degrees of functional damage, seriously

affect the prognosis and quality of life of stroke patients (Barthels and Das, 2020). Post-stroke depression (Poststroke depression, PSD) is the most common mental disorder after stroke, and about a third of patients are affected in the first five years after stroke, leading to depression attacks, rehabilitation of limb function and decline of quality of life (Levada and Troyan, 2018). Therefore, the effective treatment of PSD is particularly important. Transcranial magnetic stimulation technology (Transcranial Magnetic Stimulation, TMS) is a painless noninvasive treatment method to stimulate brain nerves through the skull. With the development of technology, transcranial magnetic stimulation (rTMS) with continuous adjustable repeated stimulation appears, and achieves the purpose of treating clinical neurological diseases, mental diseases and promoting cognitive function rehabilitation through different degrees of frequency rTMS, as a research tool and treatment intervention for antidepressant treatment, can play therapeutic effects to reduce depression symptoms and promote

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improved cognitive function in patients (Gold et al., 2019). It has received extensive research support and clinical application from scholars at home and abroad, and is certified by the Food and Drug Administration (FDA) (McClintock et al., 2018), is allowed to be used in the treatment of mental disorders such as depression, obsessive-compulsive disorder. In this study, 70 PSD patients admitted by the hospital were selected as the study objects to explore the clinical treatment effect of transcranial magnetic stimulation on patients with depression after stroke and their impact on immune function, so as to provide more basis for the clinical treatment of PSD patients and promote the clinical application of TMS.

2. Materials and methods

2.1. General information

The 70 PSD patients confirmed from September 2020 to April 2021 were selected as the research subjects, and were randomized into control and observation groups, with 35 cases each. The study was approved by the hospital's ethics committee, and all patients and their families were informed and agreed to the study.

2.2. Inclusion and exclusion criteria

Inclusion criteria: stroke was diagnosed with head CT or MRI; depression, PSD; Health Questionnaire (PHQ-9) ≥ 5 ; age > 18 ; informed consent to join the study.

Elimination criteria: those with a long-term history of depression or antidepressants; those with serious dysfunction in cardiopulmonary and other vital organs; those with metal foreign bodies or other implanted devices (such as cochlear implants, pacemakers, etc.); those with obvious audio-visual, verbal and cognitive disorders unable to complete the examination ⑤ is combined with epilepsy or other neurological disorders.

2.3. Treatment method

Both groups of patients were given routine drug therapy combined with rehabilitation training and cognitive behavioral intervention. Routine treatment: Conduct symptomatic drug treatment for cerebrovascular diseases. Patients were given routine oxygen inhalation, anticoagulant, antiplatelet aggregation, and cerebrovascular expansion and other clinical drug treatment, to control their blood pressure and blood sugar, and to control and prevent the recurrence of stroke. The control group gave the antidepressant Paxil hydrochloride tablet (GlaxoSmithKline (Tianjin) Co., Ltd., national drug registration number H10950043), 20 mg/tablet, guiding patients to take a meal at breakfast, do not chew the tablet swallowed completely, 1 time/d.

Rehabilitation training is evaluated by the rehabilitation therapist on the patient's physical movement function, including upper and lower limb exercise, and a personalized rehabilitation training plan for the patient's physical function rating, 1 time/d, 30–40 min/times, 4–5 d/weeks, with a total of 8 weeks. In rehabilitation training, combined with the content, mode and strength of rehabilitation training, rehabilitation training are appropriately adjusted to promote the recovery of limb exercise ability.

Cognitive behavior intervention: conduct basic assessment of cognitive behavior, master their cognitive function, and develop patient intervention plan, explain the causes and possible clinical manifestations of PSD, such as refusing antidepressant related treatment, social interaction, depression, answer questions about disease treatment, encourage patients to actively cooperate with treatment, establish treatment confidence, actively identify nega-

tive emotions, actively improve negative emotions and thinking, correct wrong cognition of disease treatment and rehabilitation, and guide patients and their families to establish a positive optimism. Cognitive behavioral intervention for 8 weeks, twice a week, 30 min–45 min/. Regularly assess improved cognitive ability and appropriately adjust intervention methods for the outcome.

On the basis of the treatment of the control group, the combined transcranial stimulation treatment used the pulse magnetic field stimulation instrument M-10 Ultimate (Shenzhen Yingzhi Technology Co., Ltd.) to target the H1 coil and the bilateral dorolateral and ventrolateral prefrontal cortex to increase the intensity and penetration of the left brain hemisphere (Kaster et al., 2018). The frequency 0.5 Hz, stimulation intensity 0.70 T, pulse time limit 90 s, to 30 s 1 sequence, 1 sequence stimulation per day and 5d one course A 2d, rest after one session was followed by the second session, with 8 TMS sessions

2.4. Observation indicators

Patient health questionnaire (9 and PHQ-9), modified Barthel (MBI) Patient Health Questionnaire-9 was a measure of depression and >4 diagnosed depression (Levis et al., 2019). MBI is a common scale to measure daily living disability or dependence in stroke patients (Lee et al., 2020), 0–100, the lower the score indicates the poor living ability. At 1d before treatment and 8 weeks after treatment, the 5 ml, blood collection site of the two groups was fasting venous blood before the elbow, 1d, of serum was static placed at room temperature after anticoagulant, and the serum was taken for -80°C freezing in the medical refrigerator. The HPLC method is used (Hirowatari and Yoshida, 2019). Determination of the patient serum monoamines and amino acid neurotransmitters, including dopamine (dopamine, DA), norepinephrine (norepinephrine, NE), 5-serotamine (5-hydroxytryptamine, 5-HT) and amino acid neurotransmitters including glutamate (glutamate, Glu) and glycine (glycine, Gly). Enzymatic-linked immunosorption method was used (Menezes et al., 2020). Patient serum inflammatory factor levels, including interleukin-1 β (interleukin-1 β , IL-1 β), interleukin-6 (interleukin-6, IL-6), and swelling necrosis factor- α (tumor necrosis factor- α , TNF- α)

2.5. Statistical methods

SPSS 20.0 statistical software for data analysis, measurement data is represented by $\bar{x} \pm s$ and t test; count data by n (%) and χ^2 test by $P < 0.05$.

3. Results

3.1. General information

General data comparison between the two groups is not typically significant ($P > 0.05$), see Table 1.

3.2. Serum DA, NE, 5-HT level comparison

Serum DA, NE, 5-HT levels increased significantly after treatment, and the differences were statistically significant ($P < 0.05$). Meanwhile, the serum DA, NE, 5-HT levels were significantly higher than those in the observation group, and the differences were statistically significant ($P < 0.05$) (Table 2, Fig. 1).

3.3. Patients of serum Gly and Glu levels

After 8 weeks of treatment, the serum Gly was significantly increased between the two groups, significantly less Glu

Table 1

A comparison of general data between the two groups.

General information.		Control group (n = 35)	Observation group (n = 35)	The t value.	The P value
Gender (for example)	Male.	23	20	0.571	0.067
	Female	12	15	0.735	0.135
Average age (year of age)		50.20 ± 6.28	55.61 ± 6.84	0.433	0.064

Table 2

Patients Before and after serum DA, NE, 5-HT level treatment (±s)-x.

	Time	Control group (n = 35)	Observation group (n = 35)	The T value	The P value
DA (g/L)	Before the treatment	124.72 ± 17.35	32.53 ± 5.47	0.725	0.561
	After the treatment	156.45 ± 17.66 ^a	48.67 ± 6.72 ^a	10.826	0.031
NE (g/L)	Before the treatment	124.24 ± 16.86	30.32 ± 4.51	0.653	0.077
	After the treatment	197.45 ± 20.46 ^a	63.43 ± 7.88 ^a	12.561	0.023
5-HT (ng/L)	Before the treatment	220.49 ± 24.38	222.47 ± 23.78	0.721	0.062
	After the treatment	272.45 ± 29.16 ^a	324.64 ± 36.51 ^a	11.215	0.326

Note: Compared with the control group after treatment.

^a P < 0.05.

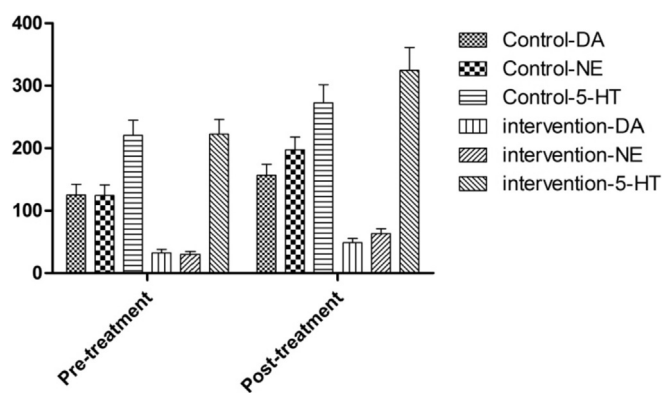


Fig. 1. Compared before and after treating serum DA, NE, 5-HT levels in group patients.

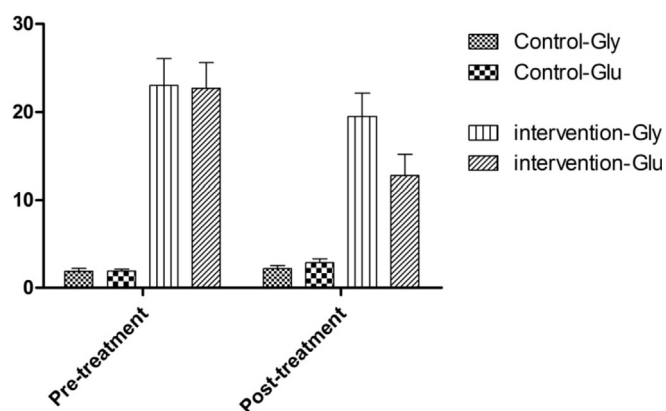


Fig. 2. Compare of serum Gly and Glu levels.

(P < 0.05) and between the observation group from the control group (P < 0.05) (Table 3 and Fig. 2).

3.4. Comparison of serum IL-1β, IL-6, TNF-α content in group patients

After 8 weeks of treatment, the serum IL-1β, IL-6, TNF-α content was significantly reduced and statistically significant (P < 0.05); the observed group was significantly reduced compared with the control group (P < 0.05) (Table 4 and Fig. 3).

3.5. Before and after treatment between PHQ-9 and MBI scores

The first two PHQ-9 scores and MBI scores were not statistically significant (P > 0.05). After 8 weeks of treatment, both PHQ-9 scores and MBI scores were better than before treatment, and

Table 3

Patients of Gly and Glu levels (±s, mmol/L)-x.

	Time	Control group (n = 35)	Observation group (n = 35)	The t value.	The P value
Gly	Before the treatment	1.88 ± 0.32	23.07 ± 3.04	0.453	0.662
	After the treatment	2.19 ± 0.35 ^b	19.52 ± 2.65 ^b	6.358	0.004
Glu	Before the treatment	1.92 ± 0.23	22.74 ± 2.93	0.568	0.634
	After the treatment	2.87 ± 0.45 ^b	12.76 ± 2.43 ^b	10.145	0.033

Note: Compared with the control group after treatment.

^b P < 0.05.

the observation group was significantly better than the control group, and the difference was statistically significant (P < 0.05) (Table 5 and Fig. 4).

4. Discussion

Post-stroke depression (PSD) is the most common psychiatric problem in stroke care, with about a third of patients experiencing depression early or later after stroke, causing poor functional recovery of PSD patients, recurrent vascular problems, decreased quality of life, and high mortality problems (Wu et al., 2019). Therefore, the timely diagnosis and therapeutic intervention of PSD are particularly important. The pathogenesis of PSD is related to many physiological and social and psychological factors, including hypothalamic-pituitary-adrenal axis abnormalities, monoamine

Table 4
Before and after treatment of serum IL-1β, IL-6, TNF-α content in group patients (±s, ng/L)-x.

		Control group (n = 35)	Observation group (n = 35)	The t value.	The P value
IL-1β	Before the treatment	39.67 ± 5.34	38.73 ± 4.93	0.653	0.074
	After the treatment	30.85 ± 4.71 ^c	20.59 ± 3.64 ^c	10.254	0.035
IL-6	Before the treatment	15.29 ± 2.33	14.96 ± 4.12	0.854	0.762
	After the treatment	10.54 ± 2.31 ^c	7.05 ± 1.57 ^c	12.671	0.021
TNF-α	Before the treatment	37.26 ± 5.23	36.53 ± 4.81	0.664	0.725
	After the treatment	30.51 ± 4.05 ^c	23.94 ± 4.21 ^c	11.698	0.025

Note: Compared with the control group after treatment.
^c P < 0.05.

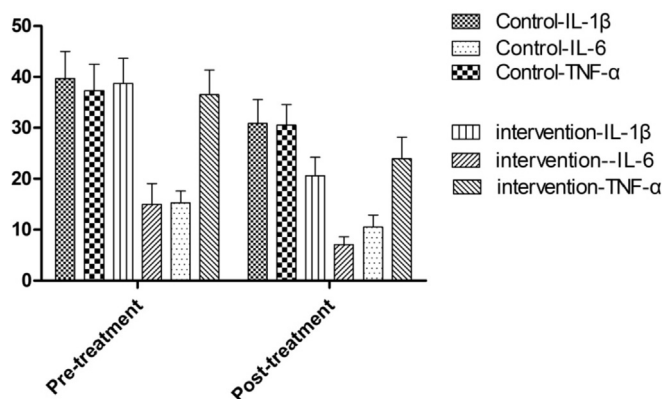


Fig. 3. Before and after comparison of serum IL-1β, IL-6, TNF-α content.

neurotransmitters, immunological changes, inflammatory response, genetic variation, and many other theories (Villa et al., 2018; Wang et al., 2018). PSD has many intervention methods, including clinical drugs such as blood pressure reduction and statin intervention, guiding physical exercise, healthy diet and other lifestyle intervention, and cognitive rehabilitation training. With the progress of TMS technology, more and more PSD patients receive rTMS technology and improve the functional state of regulating cortex circuits (Mijajlović et al., 2017). Transcranial magnetic stimulation (TMS) is a non-invasive EEG stimulation technique that utilizes time-varying magnetic field-induced currents in the cortical region, which specifically activates the target brain region, highly safe, painless and well tolerated (Rawji et al., 2020), Patients are vulnerable to accept and adhere to treatment.

This study showed that after 8 weeks of TMS, the serum levels of DA, NE and 5-HT in observation group were significantly higher than those in CONTROL group, and the synthesis and release of monoamine neurotransmitters such as DA, NE and 5-HT increased, which played an inhibitory role in alleviating anxiety, depression and other adverse emotions. Due to the attack of stroke and the lack of timely treatment and other reasons, neuronal cell damage at the focal site is directly caused, resulting in the reduction of the synthesis and release of monoamine neurotransmitters such as dopamine, norepinephrine and 5-hydroxytryptophan. When

Table 5
Before and after PHQ-9 and MBI scores.

	Time	Control group (n = 35)	Observation group (n = 35)	The t value.	The P value
The PHQ-9 score is given.	Before the treatment	17.34 ± 1.65	18.23 ± 1.21	0.684	0.764
	After the treatment	13.04 ± 1.41 ^d	9.56 ± 0.34 ^d	10.623	0.033
The MBI score is given	Before the treatment	37.54 ± 5.61	38.61 ± 5.81	0.772	0.635
	After the treatment	52.31 ± 5.73 ^d	67.59 ± 6.51 ^d	12.954	0.002

Note: Compared with the control group after treatment.
^d P < 0.05.

the level of monoamine neurotransmitters in serum drops to a certain extent, stroke patients will appear stress, anxiety, depression and other negative emotions. The antidepressant treatment mechanism of TMS may be closely related to the monoamine neurotransmitter system, amino acid transmitter system and cortical circuits with abnormal baseline functional connections in depression. By regulating the excitability of the cerebral cortex, the release of dopamine and striatum is increased, and the release of serotonin is increased, suggesting the antidepressant effect of monoamine neurotransmitters (Jinlong et al., 2020). At the same time, studies have shown that GABA is a major inhibitory neurotransmitter in the brain and plays an important role in the pathophysiology of depression. Magnetic resonance imaging (MRI) of patients with major depression showed low levels of GABA in the limbic system, suggesting that depression may be the result of the imbalance of inhibitory/excitatory amino acid neurotransmitters (Dubin, 2017). This study showed that, compared with the control group, the content of Gly in the observation group was significantly increased and the content of Glu was significantly decreased after treatment. After TMS treatment, inhibitory amino acid neurotransmitters such as Glu were decreased, and excitatory amino acid neurotransmitters such as Gly were increased, and a relative balance of inhibitory/excitatory amino acid neurotransmitters was maintained in serum. The brain tissue function of PSD patients was improved to a certain extent, and the depression was correspondingly reduced, which alleviated the anxiety and depression of patients to a certain extent.

IL-1 β is an inflammatory cytokine in brain tissue, which is produced in microglia cells activated after central nerve inflammation, and plays an important role in brain injury. Studies have shown that increased levels of peripheral inflammatory factors such as IL-1β within 24 h after stroke and lasting for several months are associated with anti-therapeutic bidirectional depression (Yi et al., 2021). Closely related to inflammation and depression, research report pointed out that depression cycle increased pro-inflammatory cytokines, tumor necrosis factor alpha, IL - 6, such as higher levels, prompt in patients with cerebral apoplexy was depression may be associated with low-grade inflammation, inflammation may affect the dopamine system (Wijeratne and Sales, 2021), depressed patients (McCann et al., 2016) the body immune system may be suppressed. The results of this study

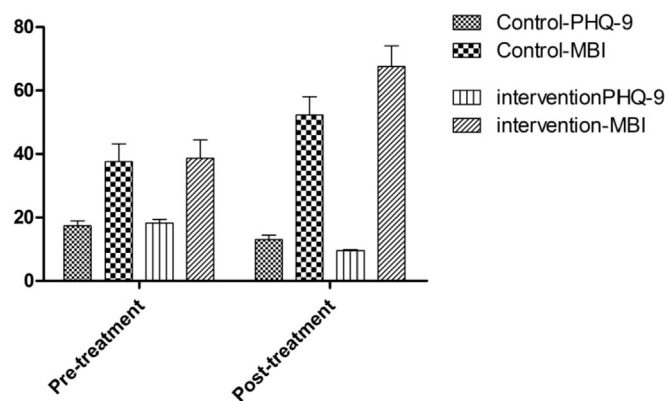


Fig. 4. Before and after comparison of PHQ-9 and MBI scores.

showed that the serum levels of IL-1 β , IL-6 and TNF- α in the observation group after 8 weeks of treatment were significantly reduced compared with the control group, possibly because TMS can promote the activation of the immune state in vivo and improve and maintain the immune function. Due to complex physiological, psychosocial and other factors, stroke patients often have depressive symptoms, which is not conducive to the rehabilitation of limb function after stroke and the inability to improve cognitive and behavioral ability, but also may increase the risk of stroke recurrence and the gradual aggravation of depression and malignant behaviors such as self-injury and suicide. Study found (Dai et al., 2020; Lee and Kim, 2018) most of the patients with depression, especially the elderly to conventional antidepressant treatment effect is not ideal, with medications and behavioral interventions combined TMS technology, help to improve the patients adverse emotions such as anxiety, depression, reduce their risk of suicide, and improve the patients' daily life ability, promote the limb function after stroke in patients with reconstruction.

TMS, in which a large coil is placed close to the patient's scalp, produces rapidly changing magnetic pulses that regulate cortical excitability and lead to depolarization of the underlying brain regions. Although rTMS is a non-invasive eeg stimulation technique with fewer side effects, it is considered an alternative to electroconvulsive therapy. However, studies have found that rTMS can induce seizures, so it is not recommended for patients with epilepsy. During the treatment of rTMS, the existing neurological diseases of patients, the age of patients and the change of medication methods should be taken into account, which may reduce the seizure threshold and induce epilepsy. Therefore, it is necessary to prepare for the treatment of epileptic seizures during the treatment, and stop the eeg stimulation therapy in time and manage the complications in case of any adverse reactions (Mann and Malhi, 2021).

At present, the clinical efficacy of TMS on PSD patients has been proved by extensive clinical research data, which can realize the regulation of neuroplasticity, improve the brain's ability to train neural circuits and neuroprotective effect (León Ruiz et al., 2018). More scholars have proposed that the current research direction is mainly focused on the short-term and immediate effects of TMS in enhancing cognition, and whether it can be effective in the long term needs more research data to support. The optimal frequency, number of pulses, and interval of rTMS, as well as its application in other diseases, require further study (Kim et al., 2019). During TMS treatment, it is necessary to observe whether the patients have head or scalp discomfort, so that the pulse amplitude can be appropriately reduced and the tolerance of patients can be improved. However, whether the effect of reducing the

pulse amplitude on the anti-depression effect needs to be further studied.

5. Conclusion

In conclusion, transcranial magnetic stimulation can promote the synthesis and release of monoamine neurotransmitters in PSD patients, regulate the level of inhibitory/excitatory amino acid neurotransmitters, reduce the inflammatory response, and improve clinical efficacy and immune function. It has clinical application value to improve PSD patients' enthusiasm to receive treatment and promote their physical and psychological rehabilitation.

Declaration of Competing Interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

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