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Effects of Low-Frequency (0.5 Hz) and High-Frequency (10 Hz) Repetitive Transcranial Magnetic Stimulation on Neurological Function, Motor Function, and Excitability of Cortex in Ischemic Stroke Patients

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Background: Repetitive transcranial magnetic stimulation (rTMS) is a noninvasive neuromodulation technique. The purpose of our study is to explore the effects of low-frequency (0.5 Hz) and high-frequency (10 Hz) rTMS on neurological function, motor function, and excitability of cortex in Chinese ischemic stroke patients.

Materials and Methods: A total of 240 ischemic stroke patients were collected. The National Institutes of Health Stroke Scale (NIHSS), modified Rankin Scale (mRS), motor-evoked potential (MEP) cortical latency, central motor conduction time (CMCT), Fugel-Meyer assessment (FMA), Berg balance scale (BBS), and modified Barthel index (MBI) scores were recorded.

Results: After treatment, the NIHSS, mRS, MEP cortical latency, CMCT, FMA, BBS, and MBI scores of the high-frequency group and low-frequency group were significantly improved than the sham stimulation group, and the changes in the low-frequency group were more significant (adjusted $P < 0.05$). Compared with the sham stimulation group, high-frequency stimulation reduced the NIHSS score by 9.5%, mRS score by 12.6%, MEP latency by 2.5%, and CMCT by 5.8%, and increased the upper limb FMA scale by 16.4%, lower limb FMA scale by 8.8%, BBS by 26.3%, and MBI by 9.3%, while low-frequency stimulation reduced the NIHSS score by 23.8%, mRS score by 25.3%, MEP Latency by 11.7%, and CMCT by 9.1%, and increased the upper limb FMA scale by 24.1%, lower limb FMA scale by 18.4%, BBS by 27.4%, and MBI by 23.7% in our cohort.

Conclusions: Low-frequency rTMS is better than high-frequency rTMS stimulation in improving neurological function, motor function, and excitability of cortex in ischemic stroke.

Key Words: ischemic stroke, transcranial magnetic stimulation, prognosis, nervous system physiological phenomena, motor cortex

(*The Neurologist* 2023;28:11–18)

Stroke is the second leading cause of death in the world, based on the 2016 Global Burden of Disease Study.[1] The study emphasizes that East Asia has the highest age-standardized incidence of stroke, especially in China (354/100,000 person-years).[1] The number of stroke patients was 80.1 million worldwide in 2016, of which ischemic stroke accounted for 84.4%.[1] Ischemic stroke has the characteristics of high disability and high mortality.[2] Up to 62% of ischemic stroke survivors are suffering from motor and neurological deficits worldwide.[3,4]

Transcranial magnetic stimulation (TMS) is a painless and noninvasive neurological examination and treatment technique.[5] The effects of TMS on the human body have been discovered as follows: (1) Regulate the excitability of the cerebral cortex;[6] (2) Regulate the secretion of neurotransmitters in the brain (such as glutamate, γ-aminobutyric acid, serotonin, and dopamine);[7] (3) Promote the repair of nerve cells;[8] (4) Promote the secretion of nerve factors;[9] (5) Promote brain metabolism and increase brain blood flow.[10] According to the stimulation mode, TMS can be divided into single-pulse TMS, paired-pulse TMS, and repetitive TMS (rTMS). The single-pulse TMS and paired-pulse TMS stimulation modes are mainly used for clinical disease evaluation and prognosis judgment, while rTMS is mostly used for clinical treatment. According to frequency, rTMS can be divided into low-frequency rTMS and high-frequency rTMS. Low-frequency rTMS has an inhibitory effect on the cerebral cortex, and high-frequency rTMS has an excitatory effect on the cerebral cortex.[11]

At present, the recommended frequency of rTMS for ischemic stroke patients remains to be clarified.[12–14] In this study, a total of 240 ischemic stroke patients were included. On the basis of receiving routine rehabilitation training, the patients were randomized to receive sham stimulation, 0.5 Hz rTMS, and 10 Hz rTMS. In terms of assessing the patient's neurological function, the National Institutes of Health Stroke Scale (NIHSS) and modified Rankin scale (mRS) were performed. In terms of assessing the patient's motor function, the Fugel-Meyer assessment (FMA) scale was used to assess the patient's upper and lower limb motor function; the modified Barthel index (MBI) scale was used to assess the patient's ability of daily living; the Berg balance scale (BBS) was used to evaluate the patient's balance function. In assessing the excitability of the patient's cortex, motor-evoked potential (MEP) cortical latency and central motor conduction time (CMCT) were tested. Finally, we objectively evaluated the effects of 0.5 Hz/10 Hz rTMS on the neurological function, motor function, and excitability of the cortex in Chinese ischemic stroke patients.

MATERIALS AND METHODS

Inclusion and Exclusion of Ischemic Stroke Patients

A total of 240 ischemic stroke patients treated in the Department of Rehabilitation Medicine of The People's

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The authors declare no conflict of interest.

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ISSN: 2331-2637/23/2801-0011
DOI: 10.1097/NRL.0000000000000435

Hospital of Longhua District from August 2020 to May 2021 were included. The selection of all patients met the inclusion and exclusion criteria of this study. This study was conducted in accordance with the Declaration of Helsinki (as revised in 2013). Our study was reviewed and approved by the Ethics Committee of The People's Hospital of Longhua District (approve no.: E2020-06-1705A).

The inclusion criteria include: (1) Comply with the diagnostic criteria for ischemic stroke in the 2018 American Heart Association (AHA)/American Stroke Association (ASA) Guidelines;[15] (2) computed tomography or magnetic resonance imaging examination confirmed the presence of cerebral hemispheric infarction lesions, and MEP can be recorded in the M1 area of the affected cortex; (3) Course of disease ≤ 2 months; (4) Those who have a unilateral disease for the first time or who have had previous attacks but have not left neurological dysfunction; (5) The patients gave informed consent to this study.

Grouping of Ischemic Stroke Patients

By using a random number table method, 240 ischemic stroke patients were divided into three groups: high-frequency group (10 Hz rTMS, n = 80), low-frequency group (0.5 Hz rTMS, n = 80), and sham stimulation group (n = 80).

Routine Rehabilitation Treatment and rTMS Treatment for Ischemic Stroke Patients

In addition to the routine rehabilitation treatment for the 3 groups, high-frequency group patients were given 10 Hz rTMS treatment for the M1 area of the central anterior motor cortex of the affected side; low-frequency group patients were given 0.5 Hz rTMS treatment for the M1 area of the uninfected central anterior motor cortex, and sham stimulation group patients were given sound stimulation with the same stimulation frequency as the high-frequency group, but there was no energy output.

Routine rehabilitation treatment: the main applications are exercise therapy, exercise relearning therapy, Bobath therapy, Brunnstrom therapy, Rood technology, proprioceptive neuromuscular facilitation, occupational therapy, physical factor therapy (intermediate frequency pulse electric therapy and low-frequency pulse electric therapy), acupuncture, and other treatment methods. The above treatment items are treated for a total of 3 weeks, 6 days a week, 120 minutes per day.

rTMS treatment: in the high-frequency group, 10 Hz rTMS was given to the M1 area of the central anterior gyrus of the cortex on the side of the lesion. The patients were treated for 15 minutes each time, once a day, and 6 times a week for a total of 3 weeks. The low-frequency group was treated with 0.5 Hz rTMS for the M1 area of the central anterior gyrus of the contralateral cortex. Patients were treated for 40 minutes each time, once a day and 6 times a week for a total of 3 weeks. The sham stimulation group was given sound stimulation at the same frequency as the high-frequency group in the M1 area of the central anterior gyrus of the cortex on the lesion side. At this time, the magnetic field therapy instrument only displays the normal operation interface, but there is no energy output during the period. The course of the above-mentioned sham stimulation treatment is 3 weeks, 6 times/week, 15 minutes/time.

Evaluation Method of Rehabilitation Effect for Ischemic Stroke Patients

The neurological function evaluation methods include the NIHSS score[16] and the mRS score.[17] The motor function evaluation methods include the FMA scale,[18] the BBS scale,[19] and the MBI scale.[20] Cortical excitability assessment methods include MEP cortical latency measurement and CMCT measurement.[21]

Statistical Analysis

Results were represented as the mean ± SD or median (interquartile range) or percentage (%). The differences between normally distributed numeric variables were evaluated by the Student *t* test, whereas non-normally distributed variables were analyzed by Mann-Whitney *U* test. One-way analysis of variance was used for the comparison among multiple groups if the variance was homogeneous, while non-normally distributed variables were evaluated by Kruskal-Wallis variance analysis. Multiple comparisons between the groups were performed using the *S-N-K* method. The Benjamini-Hochberg procedure was performed for all *P*-values at each taxonomic rank to control the false discovery rate.[22] The categorical variables were analyzed using the χ^2 test. A multinomial logistic regression model was built to assess the magnitude and direction of the association between stimulation subtypes and neurological function, motor function, excitability of

TABLE 1. General Information Among the 3 Groups of Patients (n = 240)

Indicators	High-Frequency Group	Low-Frequency Group	Sham Stimulation Group	$F/\chi^2/Z$	*P*
Number of patients	80	80	80		
Sex (n)				0.258	0.879
Male	54	51	52		
Female	26	29	28		
Age (mean ± SD, year)	63.85 ± 9.54	63.92 ± 10.28	64.10 ± 9.96	1.165	0.314
Body mass index (n)				0.445	0.801
< 24 kg/m^2	48	44	47		
≥ 24 kg/m^2	32	36	33		
Smoking (n)	47	50	48	0.244	0.885
Drinking (n)	63	65	66	0.377	0.828
Hypertension (n)	55	57	60	0.780	0.677
Diabetes (n)	29	34	31	0.665	0.717
Hyperlipidemia (n)	22	19	24	0.802	0.670
Infarct volume (IQR, mL)	21 (12, 29)	20 (11, 29)	20 (9, 28)	1.672	0.417
Mean course of disease (mean ± SD, day)	21.32 ± 2.87	21.25 ± 3.30	21.42 ± 3.05	1.076	0.343
Hemiplegia side (n)				0.634	0.729
Left	42	39	37		
Right	38	41	43		

IQR indicates interquartile range.

cortex indicators (3 groups: high-frequency group, low-frequency group, and sham stimulation group. Choose the sham stimulation group as a reference). Data were analyzed using SPSS version 22.0 (IBM Corporation) software. $P<0.05$ indicates that the difference is statistically significant.

RESULTS

General Information of Patients

The general information of the 3 groups of patients is shown in Table 1. Results showed that the differences in general information between the 3 groups were not statistically significant ($P>0.05$), indicating that the groups are comparable.

Comparison of the Neurological Function Before and After Treatment Among the 3 Groups of Patients

There was no markedly significant difference in the NIHSS and mRS scores of the 3 groups before treatment ($P>0.05$, Table 2). After treatment, the comparison between the groups showed that the NIHSS score and mRS score of the high-frequency group and the low-frequency group were lower than those of the sham stimulation group (adjusted $P<0.05$, Table 2). Compared with the high-frequency group, the NIHSS score and mRS score of the low-frequency group improved significantly (adjusted $P<0.05$, Table 2). Compared with the NIHSS score and mRS score before treatment, the NIHSS (Fig. 1A) score and mRS (Fig. 1B) score of the 3 groups after treatment were significantly reduced (adjusted $P<0.05$, Table 2).

Comparison of the Motor Function Before and After Treatment Among the 3 Groups of Patients

After statistical analysis, there was no remarkably significant difference in the MBI scale and FMA scores of the upper and lower limbs of the 3 groups before treatment ($P>0.05$, Table 3). After treatment, the comparison between the groups showed that the MBI scale and FMA scores of the upper and lower limbs of the high-frequency group and the low-frequency group were significantly higher than those of the sham stimulation group (adjusted $P<0.05$, Table 3). Compared with the high-frequency group, the improvement of the MBI scale and FMA scores of the upper and lower limbs of the low-frequency group were more significant (adjusted $P<0.05$, Table 3). Compared with the MBI scale and FMA score of the upper and lower limbs before treatment, the MBI scale (Fig. 2D) and FMA scores of the upper and lower limbs (Figs. 2A and B) of the 3 groups of patients statistically increased after treatment (adjusted $P<0.05$, Table 3).

The analysis results also showed that there was no observably significant difference in the BBS score of the 3 groups before treatment. After treatment, the comparison between the groups showed that the BBS score of the high-frequency group and the low-frequency group were signally higher than those of the sham stimulation group (adjusted $P<0.05$, Table 3). However, compared with the high-frequency group and the low-frequency group, there was no significant difference in the degree of improvement of the BBS score ($P>0.05$, Table 3). Compared with the BBS score before treatment, the BBS score (Fig. 2C) of the 3 groups after treatment were significantly improved compared with those before treatment (adjusted $P<0.05$, Table 3).

Comparison of the Cortical Excitability Before and After Treatment Among the 3 Groups of Patients

Before treatment, there was no statistically significant difference in the MEP latency and CMCT levels of the 3 groups of patients. After treatment, the comparison between the groups showed that the MEP latency and CMCT level of the high-frequency group and low-frequency group were markedly shorter than those of the sham stimulation group (adjusted $P<0.05$, Table 4). Compared with the high-frequency group, the MEP latency and CMCT level in the low-frequency group were shortened significantly (adjusted $P<0.05$, Table 4). Compared with the MEP latency and CMCT level before treatment, the MEP latency (Fig. 3A) and CMCT (Fig. 3B) levels of the 3 groups were significantly reduced (adjusted $P<0.05$, Table 4).

Associations Between Function Indicators and Stimulation Subtypes From Multinomial Regression Analyses

When stimulation subtypes were considered in multinomial logistic regression models, neurological function, motor function, and excitability of cortex showed significant

TABLE 2. Comparison of the Neurological Function Among the 3 Groups of Patients (n = 240)

Indicators	High-Frequency Group	Low-Frequency Group	Sham Stimulation Group	*F*	*P*
Number of patients	80	80	80		
NIHSS (mean ± SD)					
Before treatment	10.85 ± 2.87	10.67 ± 2.66	10.78 ± 2.54	1.209	0.300
After treatment	7.67 ± 2.33	6.24 ± 2.05*	8.96 ± 2.19*†	10.283	< 0.001
t	7.423	10.969	8.220		
P	< 0.001	< 0.001	< 0.001		
FDR-adjusted *P*‡	< 0.001	< 0.001	< 0.001		
mRS (mean ± SD)					
Before treatment	2.98 ± 0.57	2.90 ± 0.49	2.93 ± 0.52	0.984	0.375
After treatment	2.14 ± 0.69	1.89 ± 0.45*	2.48 ± 0.63*†	12.092	< 0.001
t	7.147	9.936	3.711		
P	< 0.001	< 0.001	< 0.001		
FDR-adjusted *P*‡	0.001	< 0.001	0.001		

*Compared with high-frequency group, $P<0.05$ (*P*-values were corrected for multiple comparisons using the Benjamini-Hochberg procedure to control the FDR ≤ 5%).

†Compared with low-frequency group, $P<0.05$ (*P*-values were corrected for multiple comparisons using the Benjamini-Hochberg procedure to control the FDR ≤ 5%).

‡*P*-values were corrected for multiple comparisons using the Benjamini-Hochberg procedure to control the FDR ≤ 5%.

FDR indicates false discovery rate; mRS, modified Rankin scale; NIHSS, National Institutes of Health Stroke Scale.

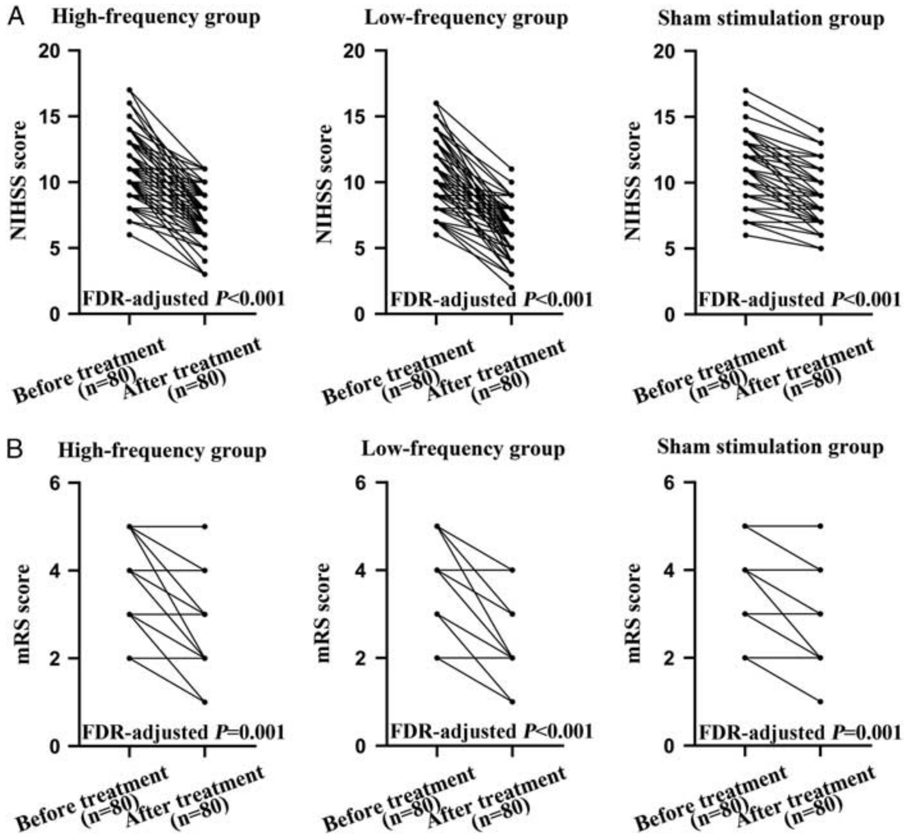

FIGURE 1. Comparison of neurological function in patients with the high-frequency group, low-frequency group, and sham stimulation group before and after treatment. (A) Comparison of NIHSS scores before and after treatment in the 3 groups of patients. (B) Comparison of mRS scores before and after treatment in the 3 groups of patients. FDR indicates false discovery rate; mRS, modified Rankin scale; NIHSS, National Institutes of Health Stroke Scale. *P*-values were corrected for multiple comparisons using the Benjamini-Hochberg procedure to control the FDR $\leq 5\%$.

associations with high-frequency stimulation and low-frequency stimulation (Table 5). Compared with the sham stimulation (referent), high-frequency stimulation reduced the NIHSS score by 9.5%, the mRS score by 12.6%, the MEP Latency by 2.5%, and the CMCT by 5.8%, and increased the upper limb FMA scale by 16.4%, the lower limb FMA scale by 8.8%, the BBS by 26.3%, and the MBI by 9.3% in our cohort (Table 5). Moreover, low-frequency stimulation reduced the NIHSS score by 23.8%, the mRS score by 25.3%, the MEP Latency by 11.7%, and the CMCT by 9.1%, and increased the upper limb FMA scale by 24.1%, the lower limb FMA scale by 18.4%, the BBS by 27.4%, and the MBI by 23.7%, compared with the sham stimulation group in our cohort (Table 5).

DISCUSSION

Recent studies have shown that 0.5 Hz is better than 1 Hz and 2 Hz low-frequency rTMS treatment to increase the excitability of the affected cortex and improve the motor function of the limbs.[23–26] Possible reasons include the following: (1) 0.5 Hz rTMS treatment has a stronger inhibitory effect on the contralateral cortex than 1 Hz low-frequency stimulation, and is more conducive to regulating the inhibitory response between the 2 hemispheres, so as to better reconstruct the balance of brain functions on both sides.[23] (2) The total stimulation time of 0.5 Hz rTMS is prolonged with higher frequency rTMS, which further enhances the inhibitory effect on the excitability of the contralateral cortex.[24] (3) Preliminary research pointed out that 0.5 Hz rTMS narrowed the synaptic gap by increasing the synaptic contact area and increasing the thickness of the postsynaptic membrane, thereby increasing the synaptic transmission capacity of the uninvolved side.[25] On the basis of the above analysis, 2 rTMS frequencies, that is, 0.5 and 10 Hz were selected in this study.

Our study showed that the neurological function scores (NIHSS and mRS), SpTMS indicators (MEP cortical latency and CMCT), limb motor function scores (FMA and BBS), and activities of daily living scores (MBI) were significantly improved compared with before treatment. In addition, we also found that the improvement of the above indicators in the low-frequency group and the high-frequency group was better than that of the routine rehabilitation treatment group. Interestingly, 0.5 Hz low-frequency rTMS treatment is better than 10 Hz high-frequency rTMS treatment in improving patients' NIHSS, mRS, MEP cortical latency, CMCT, FMA, and MBI ($P < 0.05$). However, 0.5 Hz and 10 Hz rTMS treatments have similar effects in improving patient balance. The above results found that the routine rehabilitation methods and 0.5 Hz, 10 Hz rTMS treatment was able to improve the neurological function, motor function, and ability of daily living in patients with hemiplegia after ischemic stroke, but the improvement of the 2 groups of rTMS treatment groups was more significant. Our study also demonstrates that the 0.5 Hz rTMS treatment is better than the 10 Hz rTMS treatment to improve neurological function, motor function, and excitability of cerebral cortex in ischemic stroke patients.

TABLE 3. Comparison of the Motor Function Among the 3 Groups of Patients (n = 240)

Indicators	High-Frequency Group	Low-Frequency Group	Sham Stimulation Group	*F*	*P*
Number of patients	80	80	80		
Upper limb FMA scale (mean ± SD)					
Before treatment	23.28 ± 6.14	23.11 ± 6.17	23.17 ± 6.09	1.117	0.329
After treatment	34.63 ± 7.22	36.80 ± 5.64*	29.33 ± 6.21*†	4.652	0.010
t	−10.711	−14.648	−6.335		
P	< 0.001	< 0.001	< 0.001		
FDR-adjusted *P*‡	< 0.001	< 0.001	0.002		
Lower limb FMA scale (mean ± SD)					
Before treatment	11.73 ± 3.27	11.60 ± 3.21	11.69 ± 3.32	0.877	0.417
After treatment	16.02 ± 3.38	18.71 ± 4.78*	14.93 ± 3.44*†	6.873	0.001
t	−8.159	−11.045	−6.247		
P	< 0.001	< 0.001	< 0.001		
FDR-adjusted *P*‡	< 0.001	0.001	0.002		
BBS (mean ± SD)					
Before treatment	16.20 ± 4.11	16.42 ± 4.07	16.47 ± 3.98	2.017	0.135
After treatment	24.43 ± 5.87	24.72 ± 5.16	19.18 ± 4.80*†	8.937	< 0.001
t	−10.273	−11.296	−3.457		
P	< 0.001	< 0.001	< 0.001		
FDR-adjusted *P*‡	0.001	< 0.001	0.004		
MBI scale (mean ± SD)					
Before treatment	39.47 ± 9.19	39.63 ± 7.43	39.94 ± 10.62	1.530	0.129
After treatment	58.13 ± 11.34	66.37 ± 12.73*	53.83 ± 11.95*†	13.009	< 0.001
t	−11.434	−15.383	−9.437		
P	< 0.001	< 0.001	< 0.001		
FDR-adjusted *P*‡	< 0.001	< 0.001	< 0.001		

*Compared with high-frequency group, $P < 0.05$ (*P*-values were corrected for multiple comparisons using the Benjamini-Hochberg procedure to control the FDR ≤ 5%).
†Compared with low-frequency group, $P < 0.05$ (*P*-values were corrected for multiple comparisons using the Benjamini-Hochberg procedure to control the FDR ≤ 5%).
‡*P*-values were corrected for multiple comparisons using the Benjamini-Hochberg procedure to control the FDR ≤ 5%.
BBS indicates Berg balance scale; FDR, false discovery rate; FMA, Fugel-Meyer assessment; MBI, modified Barthel index.

Previous research showed that rTMS treatment was able to improve motor dysfunction in ischemic stroke patients by improving the excitability of the cerebral cortex of the affected side.[26] It is worth noting that rTMS participates in regulating the expression of brain-derived neurotrophic factors to promote the proliferation of endogenous neural stem cells, and affects the

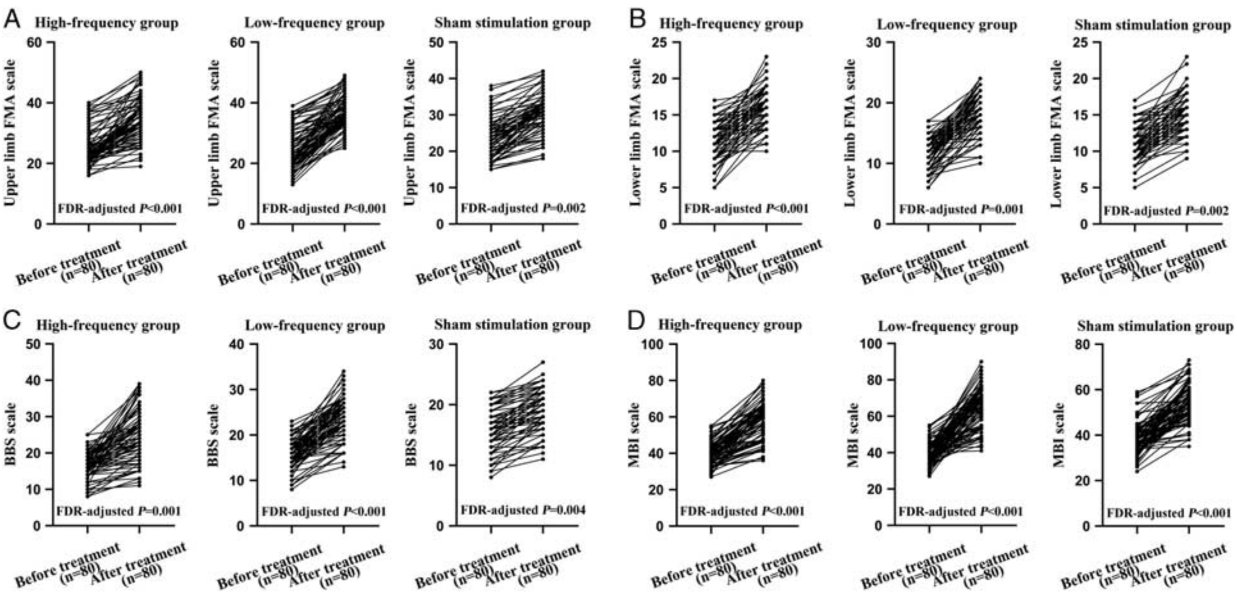

FIGURE 2. Comparison of motor function in patients with the high-frequency group, low-frequency group, and sham stimulation group before and after treatment. (A) Comparison of upper limb FMA scales before and after treatment in the 3 groups of patients. (B) Comparison of lower limb FMA scales before and after treatment in the 3 groups of patients. (C) Comparison of BBS scores before and after treatment in the 3 groups of patients. (D) Comparison of MBI scales before and after treatment in the 3 groups of patients. *P*-values were corrected for multiple comparisons using the Benjamini-Hochberg procedure to control the FDR ≤ 5%. BBS indicates Berg balance scale; FDR, false discovery rate; FMA, Fugel-Meyer assessment; MBI, modified Barthel index.

TABLE 4. Comparison of the Cortical Excitability Among the 3 Groups of Patients (n = 240)

Indicators	High-Frequency Group	Low-Frequency Group	Sham Stimulation Group	*F*	*P*
Number of patients	80	80	80		
MEP latency (mean ± SD, s)					
Before treatment	24.42 ± 2.06	24.26 ± 1.99	24.33 ± 1.47	0.953	0.388
After treatment	22.38 ± 1.98	20.37 ± 1.67*	23.04 ± 1.84*†	3.417	0.034
t	9.425	12.315	3.392		
P	< 0.001	< 0.001	< 0.001		
FDR-adjusted *P*‡	< 0.001	< 0.001	0.001		
CMCT (mean ± SD, s)					
Before treatment	11.86 ± 0.75	11.88 ± 0.79	11.73 ± 0.92	1.036	0.356
After treatment	10.63 ± 0.60	10.01 ± 0.65*	11.06 ± 0.78*†	3.267	0.040
t	9.387	16.412	4.968		
P	< 0.001	< 0.001	< 0.001		
FDR-adjusted *P*‡	0.001	< 0.001	< 0.001		

*Compared with high-frequency group, $P < 0.05$ (*P*-values were corrected for multiple comparisons using the Benjamini-Hochberg procedure to control the FDR ≤ 5%).

†Compared with low-frequency group, $P < 0.05$ (*P*-values were corrected for multiple comparisons using the Benjamini-Hochberg procedure to control the FDR ≤ 5%).

‡*P*-values were corrected for multiple comparisons using the Benjamini-Hochberg procedure to control the FDR ≤ 5%.

CMCT indicates central motor conduction time; FDR, false discovery rate; MEP, motor-evoked potential.

function and metabolism of nerve cells.[26] In vivo experiments further pointed out that rTMS treatment was able to excite or inhibit neuronal activity by changing the excitability of nerve cells, thereby producing a series of physiological effects.[27] Kakuda et al[28] applied 1 Hz low-frequency rTMS treatment to the contralateral cerebral cortex of 39 patients with spastic hemiplegia after stroke. After 15 consecutive days of treatment, the patient's modified Ashworth scale score significantly decreased, the FMA score increased significantly, and the time to complete the Wolf Motor Function Test (WMFT) was also evidently reduced. Their study showed that low-frequency rTMS significantly reduced the degree of spasticity in patients with cerebral infarction and

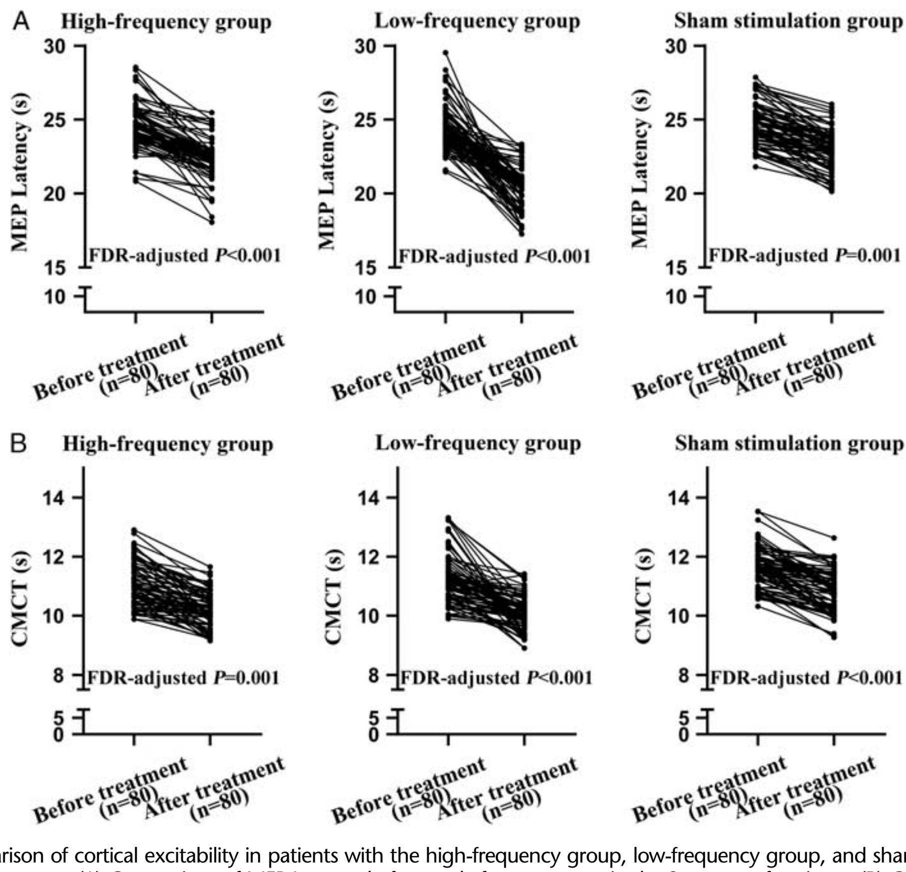

FIGURE 3. Comparison of cortical excitability in patients with the high-frequency group, low-frequency group, and sham stimulation group before and after treatment. (A) Comparison of MEP Latency before and after treatment in the 3 groups of patients. (B) Comparison of CMCT before and after treatment in the 3 groups of patients. *P*-values were corrected for multiple comparisons using the Benjamini-Hochberg procedure to control the FDR ≤ 5%. CMCT indicates central motor conduction time; FDR, false discovery rate; MEP, motorevoked potential.

TABLE 5. Multinomial Logistic Regression Analysis of Stimulation Subtypes and Neurological Function, Motor Function, Excitability of Cortex Indicators

	Odds Ratio (95% CI)		
Indicators	**High-Frequency Group**	**Low-Frequency Group**	**Sham Stimulation Group**
NIHSS	0.905 (0.831-0.987)	0.762 (0.549-0.991)	Reference
mRS	0.874 (0.756-0.991)	0.747 (0.553-0.942)	Reference
Upper limb FMA scale	1.164 (1.028-1.272)	1.241 (1.003-1.482)	Reference
Lower limb FMA scale	1.088 (1.002-1.153)	1.184 (1.046-1.330)	Reference
BBS	1.263 (1.127-1.458)	1.274 (1.119-1.466)	Reference
MBI	1.093 (1.008-1.184)	1.237 (1.148-1.389)	Reference
MEP Latency	0.975 (0.952-0.996)	0.883 (0.804-0.957)	Reference
CMCT	0.942 (0.895-0.993)	0.909 (0.822-0.984)	Reference

BBS indicates Berg Balance Scale; CI, confidence interval; CMCT, central motor conduction time; FMA, Fugel-Meyer assessment; MBI, modified Barthel index; MEP, motor-evoked potential; mRS, modified Rankin scale; NIHSS, National Institutes of Health Stroke Scale.

improved motor function. Khedr et al[29] treated patients with acute cerebral infarction with rTMS at 3 and 10 Hz for 5 days. Their results demonstrated that the NIHSS score and mRS score of the patient treated with 3 and 10 Hz rTMS was remarkably improved compared with the control group. The above research indicated that high-frequency and low-frequency rTMS improved the limb dysfunction and neurological function of ischemic stroke patients, which was also consistent with the results of this study. What is more, our study also found that 0.5 Hz rTMS was more effective than 10 Hz rTMS to improve the excitability of the cerebral cortex, thereby further improving the neurological and motor functions of patients with hemiplegia.

Under normal circumstances, the inhibition between the cerebral hemispheres on both sides maintains a dynamic equilibrium state, which is called the interhemisphere inhibition model. A stroke usually disrupts the balance of inhibition between the cerebral hemispheres on both sides. Therefore, when an infarction occurs in one cerebral hemisphere, the excitability of the cerebral cortex of the affected side is reduced not only because of the stroke itself, but also because of the suppression of the corpus callosum. Stimulating the M1 area of the motor cortex of the contralateral cerebral hemisphere with low-frequency rTMS inhibited the excitability of the contralateral cortex, while stimulating the M1 area of the lesion side with high-frequency rTMS increased the excitability of the affected side cortex.[30] This study was carried out based on the above research and further verified the effect of rTMS on nerve function, motor function, and cortical excitability. It should be pointed out that there are still some shortcomings in this study. We only included patients with detectable MEP on the affected side. In addition, the sample size of our cohort was small, and none of the patients had a disease course of more than 2 months. More importantly, we did not systematically study the stratification of hemorrhagic stroke, brainstem infarction, cerebellar infarction, and stroke rehabilitation. Therefore, follow-up studies will conduct a stratified study of patients and more comprehensively study the therapeutic effect of rTMS on patients with different types of stroke. In addition, the next study should expand the sample size and conduct follow-up 3 and 6 months after the end of treatment to more systematically study the effect of rTMS on stroke patients.

In conclusion, our study found that compared with the routine rehabilitation therapy for ischemic stroke patients, both the contralateral low-frequency rTMS treatment and the ipsilateral high-frequency rTMS treatment significantly improved the patient's neurological function, motor function, and cortical excitability. The cortical excitability, neurological function, and motor function of the contralateral M1 area of the lesion treated with low-frequency rTMS (0.5 Hz) were better than high-frequency rTMS stimulated the lesion side M1 area.

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