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ORIGINAL ARTICLE

Can cerebellar theta-burst stimulation improve balance function and gait in stroke patients? A randomized controlled trial

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ABSTRACT

BACKGROUND: The cerebellum is a key structure involved in balance and motor control, and has become a new stimulation target in brain regulation technology. Interference theta-burst simulation (iTBS) is a novel simulation mode of repetitive transcranial magnetic simulation. However, the impact of cerebellar iTBS on balance function and gait in stroke patients is still unknown.

AIM: The aim of this study was to determine whether cerebellar iTBS can improve function, particularly balance and gait, in patients with post-stroke hemiplegia.

DESIGN: This study is a randomized, double-blind, sham controlled clinical trial.

SETTING: The study was carried out at the Department of Rehabilitation Medicine in a general hospital.

POPULATION: Patients with stroke with first unilateral lesions were enrolled in the study.

METHODS: Thirty-six patients were randomly assigned to the cerebellar iTBS group or sham stimulation group. The cerebellar iTBS or pseudo stimulation site is the ipsilateral cerebellum on the paralyzed side, which is completed just before daily physical therapy. The study was conducted five times a week for two consecutive weeks. All patients were assessed before the intervention (T0) and at the end of 2 weeks of treatment (T1), respectively. The primary outcome was the Berg Balance Scale (BBS), while secondary outcome measures included the Fugl Meyer Lower Limb Assessment Scale (FMA-LE), timed up and go (TUG), Barthel Index (BI), and gait analysis.

RESULTS: After 2 weeks of intervention, the BBS, FMA-LE, TUG, and BI score in both the iTBS group and the sham group were significantly improved compared to the baseline (all $P<0.05$). Also, there was a significant gait parameter improvement including the cadence, stride length, velocity, step length compared to the baseline ($P<0.05$) in the iTBS group, but only significant improvement in cadence was identified in the sham group ($P<0.05$). Intergroup comparison showed that the BBS ($P<0.001$), FMA-LE ($P<0.001$), and BI ($P=0.002$) in the iTBS group were significantly higher than those in the sham group, and the TUG in the iTBS was significantly lower than that in the sham group ($P=0.002$). In addition, there were significant differences in cadence ($P=0.029$), strip length ($P=0.046$), gain velocity ($P=0.002$), and step length of affected lower limb ($P=0.024$) between the iTBS group and the sham iTBS group.

CONCLUSIONS: Physical therapy is able to improve the functional recovery in hemiplegic patients after stroke, but the cerebellar iTBS can facilitate and accelerate the recovery, particularly the balance function and gait. Cerebellar iTBS could be an efficient and facilitative treatment for patients with stroke.

CLINICAL REHABILITATION IMPACT: Cerebellar iTBS provides a convenient and efficient treatment modality for functional recovery of patients with stroke, especially balance function and gait.

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KEY WORDS: Cerebellum; Stroke; Gait.

Gait and balance disorders are common complications after stroke, affecting about 2/3 of stroke survivors.[1] These defects are one of the key factors affecting patients' independent living,[2] and also increase the risk of falls.[3] Balance function and gait are the main contents of hemiplegic limb rehabilitation and are extremely important for the overall functional recovery and quality of life of stroke patients.[2] Therefore, improving balance and walking ability is the main goal of post-stroke rehabilitation.[4] However, approximately 50% of stroke survivors still have gait impairment 6 months after receiving conventional treatment.[2] Thus, developing treatment strategies to improve balance and walking ability is one of the primary research focuses in stroke rehabilitation.

The cerebellum is considered a key structure involved in balance and motor control.[5] Neuroimaging studies have shown that walking and balance are physical functions that need complex sensory and motor interactions,[6] and the cerebellar vermis play a significant role in regulation ambulation pattern.[7] Previous study has found extensive fiber connections between the cerebellum and cerebral cortex, and excitability of the primary motor cortex (M1) can be regulated through the cerebellum-thalamus-M1 circuit.[8] In addition, studies have found a close correlation between the functional reorganization of the motor network during stroke recovery[9] and the activation of the contralateral cerebellum, which is positively correlated with gait recovery in patients with stroke.[10] It is worth noting that the cerebellum plays a crucial role in relearning, which is a core issue in every post stroke patient's relearning process.[11] Some studies suggest that this process is mediated by the cerebellum and can be enhanced by non-invasive brain stimulation methods,[5, 12] especially in terms of gait and balance function.[13] Intermission θ-burst stimulation (iTBS) is a novel stimulation mode of repetitive transcranial magnetic stimulation (TMS).[14] Koch *et al.*[15] reported that cerebellar iTBS can regulate excitability in the posterior parietal cortex. Kim *et al.*[16] used 1-Hz repetitive TMS (rTMS) to stimulate the cerebellum and found that conventional inhibitory rTMS can improve walking and balance function in patients with post-stroke ataxia. In addition, Liao *et al.*[17] demonstrated that cerebellar iTBS is able to promote balance and motor recovery in patients with subacute and chronic stroke.

At present, there are few studies on the treatment of lower limb dysfunction in stroke patients with cerebellar iTBS, and the efficacy of iTBS in stroke patients remains to be determined. Therefore, the purpose of this study was to evaluate the effect of cerebellar iTBS on gait and balance function in patients with patients.

Materials and methods

Research design

This study is a randomized, double-blind, sham controlled clinical trial. At the Department of Rehabilitation Medicine of a general hospital where the principal investigators work, stroke patients were recruited and randomized in a ratio of 1:1. Subjects were randomized to either the cerebellar iTBS group or sham iTBS group for 2 weeks. Berg Balance Scale (BBS), Fugl Meyer Lower Extremity Scale (FMA-LE), timed up and go (TUG) test and Barthel Index (BI) were used to evaluate the curative effect. Gait assessment was performed by the 3D gait analysis. Both the subjects and assessors were blinded. This study was reviewed and approved by the local institutional ethics committee (approval number: ky-2023-053) and was conducted in accordance with the declaration of Helsinki. In addition, this study has been registered in the China Clinical Trial Registration Center (Registration Number: ChiCTR2300075860).

Participants

A total of 42 eligible patients were recruited between March 28, 2023, and September 30, 2023, with 4 patients declining to participate after being informed of all study

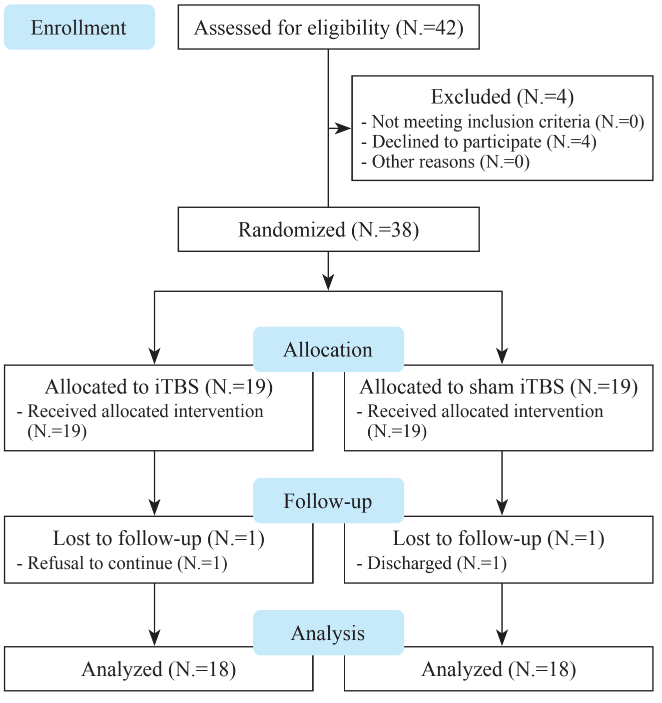

Figure 1.—Flow diagram of the study.

details. Finally, 38 patients were randomly assigned with the method of sample of convenience to either the iTBS or the sham stimulation, as shown in Figure 1. Inclusion criteria included: 1) having stroke symptoms and confirmed by imaging examination as stroke; 2) first unilateral lesion with the course of disease ≥2 weeks; 3) aged between 18 and 80; 4) lower limb dysfunction (gait or balance defect); and 5) willing to sign informed consent. The exclusion criteria were: 1) patients with severe cognitive impairment, such as difficulty in understanding or performing tasks; 2) cerebellar stroke or brainstem stroke; 3) intracranial metal device or skull defect; 4) patients with cardiac pacemakers; 5) history of epilepsy; 6) pregnancy; and 7) in addition to stroke, it is complicated with diseases affecting lower limb function, such as Parkinson's disease.

Blinding and allocation

The study will be a randomized, double-blind, sham-controlled trial. After informed consent was obtained from all subjects, computer-generated random sequences were used, and the random numbers were hidden in opaque numbered envelopes and opened in numerical order by an uninvolved researcher. Thirty-six participants will be randomly assigned to 2 groups in a 1:1 ratio and will receive either real or sham iTBS. Blinding the therapist performing the intervention was not possible due to the nature of the iTBS intervention. Therefore, the study was planned to be blinded to the participants and assessors. The scales and gait assessments were completed by an experienced therapist who was blinded to the group assignments. Data analysis was performed by an independent researcher. Urgent unblinded methods were used only after serious adverse events had occurred.

Intervention

Physical therapy

The standardized physical therapy procedure was completed by professional rehabilitation therapists who did not participate in the study and were unaware of the assignment. Both groups received physical therapy of the same parameters: 60 minutes every day, 5 days/week for a total of 10 days. The content consists of exercises to promote body movement and balance function recovery. Including muscle stretching, active auxiliary exercise, progressive neuromuscular facilitation training, balance and gait training. In gait training, to ensure safety and efficacy, the therapist should walk posterolateral to the patient as a preventive measure.

Cerebellar iTBS

iTBS or sham stimulation was completed 30 minutes before physical therapy in both groups. The area stimulated was the Ipsilateral cerebellum on the paralyzed side (3 cm lateral to the midline and 1 cm inferior to the ipsilateral cerebellum on the paralyzed side). The cerebellum was stimulated by CCY-I fast magnetic stimulator (YIRUIDE, Wuhan, China) and 8-shaped coil. The intensity of iTBS was set to 80% of the active motor threshold (AMT), which is defined as the least intensity to produce motor evoked potentials (MEPs)>200 μ V on for least 5 out of 10 trials.[15, 18, 19] The stimulation parameters were two applications of iTBS per day with a 5-minute interval between them, five times per week for two weeks. Patients receive a total of 1200 pulses per day, and a single iTBS is 600 pulses.[15] For the pseudo stimulation, the intensity of the output magnetic field was reduced to 20% of the true stimulation, and then the stimulation coil was rotated by 90° to make the coil perpendicular to the scalp to reduce the intensity of the magnetic field received by the cerebellum.

Outcomes

The outcome assessments were completed by an experienced therapist who was blind to the grouping. The evaluator assessed each patient at baseline and the end of 2 weeks of treatment. The primary outcome was BBS, the secondary outcome was FMA-LE, TUG test, BI and 3D gait analysis.

Primary outcome

BBS is the most widely used measurement tool for balance, with good reliability and effectiveness.[20] The initial BBS consisted of 38 items, and after modified to be a 14-item scale instrument.[21] Each of these items is scored from 0 to 4, with the total score at 56. The higher the score, the better the balance.

Secondary outcome

FMA-LE is a 17-item instrument[22] as a clinical and research tool for evaluating changes in movement disorders after stroke,[23] and shows good effectiveness,[24] reliability,[25] and internal consistency.[26]

TUG test is a commonly used fall risk screening tool in hospitalized and community settings.[27] It is advocated by the National Institute of Clinical Evidence (NICE) guidelines to assess gait and balance in order to prevent falls.[28] The patient stood up from the armchair (about 46 cm

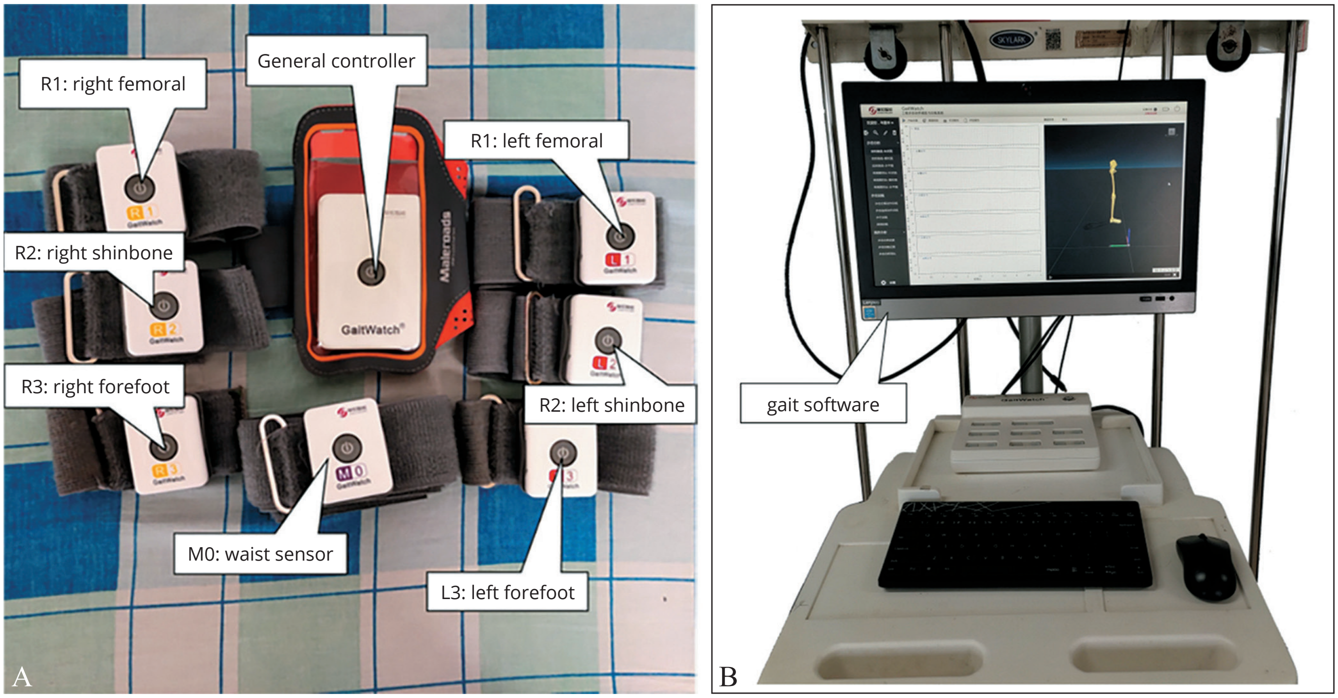

Figure 2.—A, B) Gaitwatch 3D gait motion capture and training system.

high), walked to the floor three meters away at a comfortable and safe speed, turned and walked back to the chair, and then sat down again.[29] The faster the time, the better the performance.[29]

BI is reliable, and most commonly used in clinical and research evaluation of activities of daily living (ADL).[30] BI consists of 10 items with a total score of 100. The higher the score, the better the ability of daily living.[31]

Gait assessment is conducted with the three-dimensional (3D) motion capture system, which is one of the gold standard methods for measuring gait data. Gaitwatch 3D gait motion capture and training system was developed by Zhang He intelligent (Guangzhou, China). It uses advanced wireless position sensors and has the characteristics of high precision, fully automatic acquisition and analysis. It consists of eight sensors, seven bandages and a gait software (Figure 2). During the test, those sensors were placed on the patients' the lower limb to capture the gait parameters during a 12 meters walking (Figure 3).

Figure 3.—Patient wearing 3D motion capture system device for gait assessment.

Sample size

BBS score was the main outcome index. According to a study by Liao *et al.*,[17] the average score of BBS in the conventional treatment group was 47.67±6.58. The mean BBS score of iTBS group was 50.75±4.05, set up α=05 (bilateral), grasp degree=0. 90. The sample size N1=14 in iTBS group and N2=14 in the conventional treatment group were calculated by PASS 15 software (NCSS Corp, Kaysville, UT, USA). Assuming that the loss of follow-up rate of the research object is 20%, the sample size N1=18 cases, N2=18 cases are required. A total of at least 36 patients were included.

Statistical analysis

The data were analyzed using SPSS 26.0 (IBM Corp., Armonk, NY, USA). Continuous variable data are expressed as mean (standard deviation [SD]), and classified variables are expressed as count (N.) or percentage (%). Shapiro Wilk Test was used to test the normality of the data. During baseline comparison, *t*-test, Wilcoxon Mann-Whitney U Test or χ^2 Test were used to compare the differences between the two groups. The paired *t*-test or Wilcoxon Matching Test was used for the intragroup comparison before and after the intervention; Independent sample *t*-test or Mann-Whitney Rank Sum Test were used for intergroup comparison.

Results

Initially, 42 eligible patients were screened and informed of all details of the study, but 4 patients declined to participate. Therefore, 38 patients were included in the study. After the enrollment, 2 patients stopped the therapy, 1 patient refused to continue the intervention, and the other patient decided to be discharged from the hospital. All patients tolerated it well and no adverse effects occurred. Finally, data from 36 patients were analyzed (Figure 1). There was no statistically significant difference between the two groups when comparing the general information such as age, gender, side of lesion, stroke type, duration of disease, Brief Mental State Examination Scale (MMSE), and hypertension (P>0.05) (Table I).

Motor function

After 2 weeks of treatment, BBS, FMA-LE, and BI scores were elevated from baseline in both groups (P<0.05), and TUG was significantly reduced from baseline (P<0.05). Comparing between groups, BBS (T=4.118, P<0.001), FMA-LE (*Z*=-3.933, P<0.001) and BI scores (*Z*=-3.122, P=0.002) were significantly higher and TUG was significantly lower in the iTBS group than in the sham-stimulated group (*Z*=-3.122, P=0.002) (Table II).

Gait analysis

The within-group results revealed that patients in the iTBS group had significant improvement in cadence, stride length, velocity, and step length after 2 weeks of treatment compared with baseline (P<0.05); while in the sham-stim-

TABLE I.—*Baseline characteristics of patients.*

Parameters	Cerebellar iTBS (N.=18)	Sham iTBS (N.=18)	χ^2 (t, Z)	P value
Age (years), mean (SD)	58.67 (7.24)	62.33 (8.78)	*t*=-0.995[a]	0.327
Gender (male/female), N.	14/4	13/5	χ^2=0.148[b]	0.700
Hemiplegic side (left/right), N.	9/9	11/7	χ^2=0.450[b]	0.502
Type of stroke (hemorrhagic/ischemic), N.	13/5	15/3	χ^2=0.643[b]	0.423
course of disease (days), mean (SD)	61.89 (46.72)	52.00 (48.56)	*Z*=-0.699[c]	0.485
Hypertension (with/without), N.	15/3	14/4	χ^2=0.077[b]	0.647
MMSE, mean (SD)	27.94 (2.18)	27.92 (1.48)	*t*=1.163[a]	0.253

iTBS: intermittent theta-burst stimulation; MMSE: minimum mental state examination.
[a]Analyzed by Student's independent *t*-test; [b]analyzed by χ^2 Test; [c]analyzed by Wilcoxon Mann-Whitney U Test.

TABLE II.—*Clinical scale scores of the iTBS and sham itBS groups before treatment (T0), 2 weeks treatment (T1), and changes.*

Parameters		T0	T1	P value (T0 *vs.* T1)	Change	P value (iTBS *vs.* sham iTBS)
FMA-LE	iTBS (N.=18)	20.57 (4.93)	25.11 (5.86)	<0.001[a]*	4.54 (5.45)	<0.001[c]*
	Sham iTBS (N.=18)	23.10 (4.50)	24.63 (4.59)	<0.001[a]*	1.53 (4.56)	
BBS	iTBS (N.=18)	28.05 (10.43)	37.47 (12.08)	<0.001[a]*	9.42 (11.35)	<0.001[d]*
	Sham iTBS (N.=18)	29.47 (8.13)	34.58 (8.34)	<0.001[a]*	5.11 (8.24)	
TUG	iTBS (N.=18)	45.35 (27.37)	31.56 (20.24)	<0.001[b]*	-13.79 (24.59)	0.014[c]*
	Sham iTBS (N.=18)	35.18 (13.70)	29.46 (9.35)	0.002[a]*	-5.72 (12.13)	
BI	iTBS (N.=18)	66.39 (14.23)	83.06 (14.46)	<0.001[a]*	16.67 (14.35)	0.002[c]*
	iTBS (N.=18)	62.02 (14.46)	71.17 (13.39)	<0.001[a]*	9.15 (13.96)	

Values are expressed as mean (SD).
iTBS: intermittent theta-burst stimulation; FMA-LE: Fugl-Meyer score of the lower limbs; BBS: Berg Balance Scale; TUG: timed up and go test; BI: Barthel Index.
*P<0.05; [a]paired *t*-test; [b]Wilcoxon-Matched Pairs Signed-Ranks Test; [c]Mann-Whitney U Rank Sum Test; [d]Independent Samples *t*-test.

Table III.—*Gait outcomes and changes in the iTBS and sham iTBS groups before treatment (T0) and at 2 weeks of treatment (T1).*

Parameters		T0	T1	P value (T0 *vs.* T1)	Change	P value (iTBS *vs.* sham iTBS)
Cadence	iTBS (N.=18)	65.02 (22.18)	76.67 (23.82)	0.002[a]*	11.65 (23.04)	0.029[b]*
	Sham iTBS (N.=18)	69.75 (16.55)	75.86 (14.91)	0.004[a]*	6.11 (15.79)	
Stride length	iTBS (N.=18)	76.56 (33.13)	90.19 (31.11)	0.002[a]*	13.63 (32.17)	0.046[b]*
	Sham iTBS (N.=18)	68.78 (24.31)	74.00 (23.78)	0.057[a]	5.22 (24.05)	
Gait velocity	iTBS (N.=18)	45.44 (30.00)	62.33 (35.19)	0.001[a]*	16.89 (32.90)	0.002[b]*
	Sham iTBS (N.=18)	44.31 (23.24)	46.39 (21.42)	0.496[a]	2.08 (22.39)	
Step length (affected lower limb)	iTBS (N.=18)	34.81 (17.61)	45.31 (18.72)	<0.001[a]*	11.50 (18.20)	0.024[b]*
	Sham iTBS (N.=18)	33.72 (12.95)	36.72 (11.95)	0.160[a]	3.00 (12.48)	
Step length (healthy lower limb)	iTBS (N.=18)	39.75 (15.87)	44.78 (14.65)	0.018[a]*	5.03 (15.30)	0.199[b]
	Sham iTBS (N.=18)	35.67 (13.82)	37.58 (14.25)	0.154[a]	1.91 (14.04)	

Values are expressed as mean (SD).
iTBS: intermittent theta-burst stimulation.
*P<0.05; [a]paired *t*-test; [b]Mann-Whitney U Rank Sum Test.

ulation group only cadence showed significant improvement from baseline(P<0.05).

The between-group results showed that the improvements in cadence (*Z*=-2.188, P=0.029), stride length (*Z*=-1.995, P=0.046), velocity (*Z*=-3.072, P=0.002), and step length of the affected limb (*Z*=-2.251, P=0.024) were statistically significant in the iTBS group compared with those in the sham iTBS group. Gait wise, the mean change values of cadence, stride length, velocity, and step length of the affected lower limb of the patients were significantly higher in the iTBS group than those in the sham stimulation group (P<0.05). However, the difference in step length of the healthy lower limb between the two groups was not statistically significant (Z=-1.283, P=0.199) (Table III).

Discussion

The results of this study concluded that both interventions improved balance, lower limb motor function, gait and daily living skills in hemiplegic patients with stroke. However, iTBS combined with physiotherapy was better than physiotherapy alone for balance, lower limb motor function, and daily living ability. Notably, in terms of gait, physical therapy alone only improved Cadence of gait. However, cerebellar iTBS improves more gait parameters including cadence, stride length, velocity and step length. Therefore, cerebellar iTBS combined with physical therapy may provide more facilitative and accelerative effects to improve functional recovery, especially gait improvement, compared to single physical therapy in patients with stroke.

Cerebellar iTBS on balance function

The results of this study suggest that cerebellar iTBS combined with physiotherapy can significantly improve balance function in post-stroke hemiplegic patients and is more effective than single physiotherapy. This result is consistent with that of Liao *et al.*,[17] who reported an improvement in BBS compared to baseline after treatment in both sham stimulation and iTBS groups, and a more significant improvement in BBS after 2 weeks of iTBS compared to sham-stimulation group. In addition, one study performed cerebellar low-frequency rTMS on 32 patients with acute posterior circulation stroke and found that the BBS scores of patients in the treatment group were significantly improved after 5 days of treatment.[16] Interestingly, although the stimulation parameters as well as the patterns of these studies were different, the stimulation site was the cerebellum, which may account for the fact that they all benefited balance function. The cerebellum is not only a key structure involved in balance and motor control, but also regulates connections between the cerebral cortex through the cerebellum-thalamus-cerebral loop.[32, 33] Therefore, cerebellar iTBS may induce persistent changes in cortical excitability, thereby improving balance function after stroke.

Cerebellar iTBS on lower extremity motor function

In this study, we found that after 2 weeks of treatment, lower limb motor function improved significantly in both groups compared to baseline, and there was a significant difference in FMA between the two groups. This result is controversial with the results of Liao *et al.*,[17] which showed no significant improvement in lower limb motor function in the iTBS group compared to control. However, the cerebellar iTBS group and the control group showed similar mild increases after 1 and 2 weeks of intervention.[17] They believe that these improvements are caused by the same physical therapy.[17] Based on current evidence, it cannot be proven that cerebellar iTBS can improve lower limb motor function in post-stroke hemiplegic patients. Therefore, future research can be extended to design more suitable research protocols to verify the efficacy of long-term cerebellar iTBS stimulation on lower limb motor function in post-stroke patients.

Cerebellar iTBS on Walking ability

Cerebellar iTBS can significantly improve walking ability in patients with stroke. This result is consistent with Kim *et al.*,[16] who found that cerebellar rTMS stimulation significantly improved the patient's 10-meter walking ability. At present, there is almost no research on the walking ability after stroke using cerebellar iTBS. We analyzed that the reason for this result could be an improvement in balance function, which is very important for walking ability. Balance function is closely related to walking ability, and the results of this study show that improved balance function also means a reduced risk of falls.[34] In addition, improved balance function will reduce energy consumption for walking ability in patients with stroke.[35]

Cerebellar iTBS on activities of ADL

Similarly, the results of Koch *et al.*[15] and Liao *et al.*[17] showed no significant difference in ADL between the brain iTBS and sham iTBS groups. However, both Koch *et al.*[15] and Liao *et al.*[17] showed a slight increase in BI compared to before treatment. The results of this study found that compared with sham stimulation, cerebellar iTBS can significantly improve ADL in patients with stroke, and both groups have significantly increased BI compared to the baselines. This result is somewhat controversial compared to previous studies. However, limited walking ability limits patients' ADL at home and in the community,[36] so the improvement of ADL may be related to the improvement of walking ability.

Cerebellar iTBS on gait

One important aspect of gait dysfunction is limited mobility (such as reduced gait velocity and independence),[37] which is associated with decreased community walking and quality of life.[38] This study found that cerebellar iTBS can significantly improve gait parameters (such as cadence, stride length, gait velocity, etc.) in patients with stroke, but there was no difference in step length of healthy lower limb between the two groups of patients. As the main form of assessing stroke disability and recovery of walking function,[39] velocity has been found to be improved by improving cadence and stride length, which can help improve the velocity of patients with stroke.[40] In addition, Koch *et al.*[15] believe from a behavioral perspective that the decrease in stride size after cerebellar iTBS is a clear indicator of improved gait stability. However, an increase in gait velocity can be seen as a strategy to improve gait stability. Rapid walking can reduce step length asymmetry and increase the amplitude of limb swing, knee joint flexion, and hind limb angle in patients with stroke.[38] This phenomenon has also been confirmed to some extent in research, and there is a negative correlation between the increase in gait velocity and the decrease in step size asymmetry in the cerebellar iTBS group. Therefore, current results indicate that cerebellar iTBS can improve the recovery of lower limb motor function, especially balance and gait, in patients with stroke.

Limitations of the study

We acknowledge some limitations of the present study. Firstly, the patients included in this study include patients with hemorrhagic stroke and ischemic stroke, and the efficacy of cerebellar iTBS in patients with different types of strokes cannot be determined. Secondly, although we used a 3D motion capture system to measure gait parameters, we did not measure the angles of various joints in the lower limbs. Thirdly, the outcome indicators of this study cannot explain the potential mechanism of cerebellar iTBS. Future research should include more detection tools such as EEG, functional near-infrared spectroscopy, and functional magnetic resonance imaging to evaluate changes in various cerebral cortex.

Conclusions

The present study concluded that cerebellar iTBS combined with physiotherapy can improve balance, lower limb motor function and activities of daily living in patients with post-stroke hemiplegia. In terms of improving gait, the cerebellum iTBS with physical therapy is more effective than mere physical therapy. Therefore, the application of cerebellar iTBS is an efficient therapeutic modality in accelerating and improving functional recovery in stroke patients, especially balance function and gait.

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Conflicts of interest
The authors certify that there is no conflict of interest with any financial organization regarding the material discussed in the manuscript.

Authors' contributions
Ping-An Zhu share the first authorship; Ping-An Zhu, Zhi-Liang Li, Qi-Qi Lu, Ying-Ying Nie, Howe Liu, Erica Kiernan, Jia Yuan, Lin-Jian Zhang and Xiao

Bao have given substantial contributions to study conception and design, Xiao Bao and Ping-an Zhu to data investigation, Ping-An Zhu to data acquisition, Jia Yuan to study design; Lin-Jian Zhang to data analysis, Zhi-liang Li to data interpretation, Qi-Qi Lu and Ying-Ying Nie to data provision, Howe Liu and Erica Kiernan to manuscript revision. All authors read and approved the final version of the manuscript.

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