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Original Research

Effects of corticospinal tract integrity on upper limb motor function recovery in stroke patients treated with repetitive transcranial magnetic stimulation

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Abstract

Background: The bimodal balance-recovery model predicts that corticospinal tract (CST) integrity in the affected hemisphere influences the partterns of brain recovery after stroke. Repetitive transcranial magnetic stimulation (rTMS) has been used to promote functional recovery of stroke patients by modulating motor cortical excitability and inducing reorganization of neural networks. This study aimed to explore how to optimize the efficiency of repetitive transcranial magnetic stimulation to promote upper limb functional recovery after stroke according to bimodal balance-recovery model. **Methods**: 60 patients who met the inclusion criteria were enrolled to high CST integrity group (n = 30) or low CST integrity group (n = 30), and further assigned randomly to receive high-frequency rTMS (HF-rTMS), low-frequency rTMS (LF-rTMS) or sham rTMS in addition to routine rehabilitation, with 10 patients in each group. Outcome measures included Fugl-Meyer scale for upper extremity (FMA-UE), Wolf Motor Function (WMFT) scale and Modified Barthel Index (MBI) scale which were evaluated at baseline and after 21 days of treatment. **Results**: For patients with high CST integrity, the LF group achieved higher FMA-UE, WMFT and MBI scores improvements after treatment when compared to the HF group and sham group. For patients with low CST integrity, after 21 days treatment, only the HF group showed significant improvements in FMA-UE and WMFT scores. For MBI assessment, the HF group revealed significantly better improvements than the LF group and sham group. **Conclusions**: For stroke patients with high CST integrity, low-frequency rTMS is superior to high-frequency rTMS in promoting upper limb motor function recovery. However, only high-frequency rTMS can improve upper limb motor function of stroke patients with low CST integrity.

Keywords: Stroke; Corticospinal tract integrity; Diffusion tensor imaging; Repetitive transcranial magnetic stimulation

1. Introduction

Motor deficits is one of the most common and serious disabling sequelae of stroke [1]. Approximately 80% of stroke survivors suffer from upper limb dyskinesias, with particular influences on manual dexterity and coordination [2]. These restrictions can reduce patients self-care capability and result in decreased living ability and quality of life [3].

In recent years, there have been many new intervention methods in upper limb motor function recovery of patients with stroke [4]. Repetitive transcranial magnetic stimulation (rTMS), as a non-invasive neurostimulation technique, can alter the plasticity of cortex and modify synaptic excitability through magnetic field [5]. It causes an motor-evoked potential generated to peripheral neurons and target muscles through the corticospinal tract (CST), which is a new direction for the motor functional recovery of stroke patients [6].

The classic stimulation scheme of rTMS in clinical practice is based on the theory of interhemispheric competition model, which through applying low frequency stimulation to suppress the motor cortex of the unaffected hemisphere or high frequency stimulation to improve the cortical excitability of the affected hemisphere to promote motor recovery of stroke patients [7]. However, this theory is not applicable to all patients, especially for those with severe motor deficits. Theilig *et al*. [8] reported that low-frequency rTMS stimulation over M1 of the contralesional hemisphere could not improve patients' severely impaired motor function, while another study applied high-frequency rTMS on contralesional M1 of patients with severe hemiplegia and found noteworthy motor function recovery, which was explained through improving contralesional cortical function to achieve compensatory effect [9].

At present, the scholars proposed bimodal balance-recovery model which considered the integrity of corticospinal tract determined interhemispheric imbalance or contralateral compensation was more dominant [10]. This suggested that the selection of rTMS protocol for motor dysfunction after stroke could be made according to the integrity of CST. The CST is a major neural pathway regulating voluntary movement, its structural integrity affects the prognosis of limb motor function and the hemispheric activation pattern of stroke patients [11]. Diffusion tensor imaging (DTI) is a MRI modelling technique used to evaluate integrity of the white matter tracts [12], and intuitively show the spatial relationship between the lesions and corticospinal tract [13]. The magnitude and directionality of anisotropic diffusion yields DTI metrics of tract integrity such as fractional anisotropy (FA). In this study, we firstly compared the mean FA of the CST within the ipsilesional and the contralesional hemisphere, termed relative FA (rFA), to divided the patients into high CST integrity group or low CST integrity group. Different rTMS intervention were then peformed over the unaffected motor cortex of the stroke patients. The aim of current study was to investigate the influence of corticospinal tract integrity on upper limb motor function recovery of stroke patients, which would provide guidance for clinical application of repetitive transcranial magnetic stimulation.

2. Materials and methods

2.1 Patients

Patients were recruited for the study between January 2020 to January 2021 from the inpatients of Department of Rehabilitation Medicine, the Affiliated Hospital of Qingdao University. Inclusion criteria included: (1) First-ever unilateral ischemic or hemorrhagic stroke documented by computed tomography (CT) or magnetic resonance imaging (MRI) within 2 weeks to 3 months; (2) Patients in a stable condition with clear consciousness, who can complete all examinations and treatments; (3) Age 30–80 years; (4) unilateral upper limb motor deficits. Exclusion criteria included: (1) metal implants in the brain or use of a pacemaker; (2) history of seizures; (3) severe aphasia or cognitive impairment; (4) apply drugs that alter cortical excitability; (5) associated severe medical complication.

2.2 Diffusion tensor imaging (DTI)

DTI was obtained before grouping using a TRIO 3.0T magnetic resonance imaging system (Siemens, Germany). A total of 60 contiguous slices (slice thickness = 2.3 mm) was acquired through applying the 32 noncollinear diffusion sensitizing gradients (matrix = 256 $\times$ 256, FOV = 240 mm $\times$ 240 mm, echo time = 76 mm, repetition time/echo-plannar imaging factor = 9500/92 ms, b = 1000 s/mm^2, number of excitations = 1, scanning time = 452 s) [14]. No interval scanning and the scan covered the whole brain. Eddy current correction was applied to correct the head motion effect and image distortion [15]. Syngo. Via MR 3D software (Siemens, Germany) was used for fiber tracking. In order to analyze the CST, the seed region of interest 1 (ROI 1) was placed on the cerebral peduncle in which the CST passed through, and the target ROI 2 was placed on the CST location in the posterior limb of the internal capsule (threshold: factional anisotropy more than 0.2; direction threshold less than 60°) [16]. CST was determined by selection of fibers passing through two regions of interests. The fractional anisotropy (FA) of the CST in both hemisphere was calculated through the "tract statistics" function of the software. A single blinded expert analyzed all patients' DTTs and rebuild the Color-coded Fractional Anisotropy (cFA) graphs. FA is a parameter to quantitatively evaluate the integrity of white matter microstructures, such as axons, myelin, and microtubules. The range of FA is 0-1 and decreased FA within the CST is associated with poor nerve conduction ability [14,17]. To minimize the effects of age and individual variation (inter-subject variability), we use relative FA (rFA, rFA = $FA_{ipsilesional}/FA_{contralesional}$) to evaluate the CST integrity of ipsilesional hemisphere [18], rFA $>$0.5 was defined as high CST integrity, and rFA $\leq$0.5 was defined as low CST integrity (Figs. 1,2).

2.3 Grouping of patients

DTI examination was performed before treatment for all enrolled subjects. According to corticospinal tract integrity, the patients were allocated into either the high CST integrity group (rFA $>$0.5) or the low CST integrity group (rFA $\leq$0.5). Patients in each group were further randomly assigned into the high frequency group (HF group), the low frequency group (LF group) or the sham group by using a computer-generated sequence.

2.4 Outcome assessment

The following outcomes of enrolled patients were evaluated at baseline and post-interventions. All assessments were performed by the same therapist blinded to the randomization.

2.4.1 Fugl-Meyer Assessment-Upper Extremity (FMA-UE)

Upper-limb motor functions were evaluated with FMA-UE, which included 33 items such as shoulder, elbow, wrist and finger coordination and separation movement, with 0~2 points for each item and a maximum of 66 points. A higher score indicated a better motor function of upper-limb [19].

2.4.2 Wolf Motor Function Test (WMFT)

WMFT consisted of 17 items, which included 15 function-based tasks and 2 strength-based tasks with 0~5 points for each item and a total of 85 points. A higher score implied a better functioning level [20].

2.4.3 Modified Barthel Index (MBI)

MBI was mainly used to evaluate the ability of daily life activities based on the patient's actual daily performance. This scale includes 11 items, such as eating,

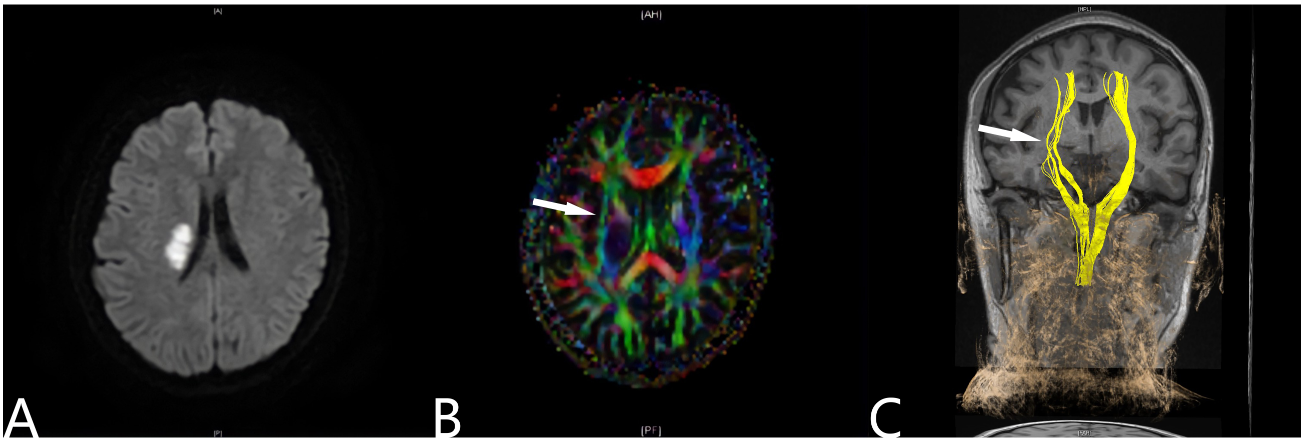

Fig. 1. Example of patient with high CST integrity: A 47-year-old female. (A) DWI showed an infarct in the right corona-radiating. (B) FA map, arrow showing compression and thinning of CST on the right. (C) DTT diagram, arrow showing a reduction in the number of CST fibers at the right (rFA = 0.73).

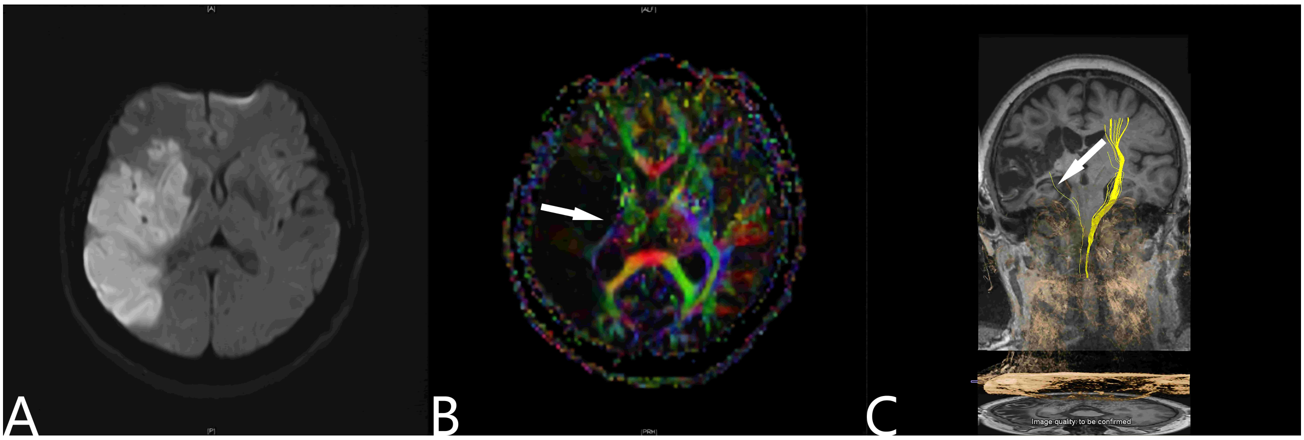

Fig. 2. Example of patient with low CST integrity: A 61-year-old female. (A) DWI showed an infarct in the right basal ganglia. (B) FA map, arrow showing the thinning of CST on the right. (C) DTT diagram, arrow showing sparse and interrupted CST fibers at the right (rFA = 0.15).

bathing, grooming and dressing, etc., and each item is scored at 5 levels with a full score of 100. A higher score indicated a better ability of daily life activities [21].

2.5 Routine rehabilitation treatment

The patients in all the 6 groups received routine rehabilitation treatment aimed at restoring upper limb motor functions. All treatment sessions were individually designed according to patients' moter function of the affected upper limb and performed based on Bobath principles. The exercise protocols included shoulder flexion-extension, abduction-adduction, internal-external rotation, elbow flexion-extension, forearm pronation-supination, hand-digit motion. The treatment was performed by experienced therapists 25 mins twice a day, for 21 days.

2.6 rTMS intervention

Transcranial magnetic stimulation (TMS) was conducted using a 7-cm Magnetic Stimulator (figure-8 circular coil, Yiruide, Wuhan, China) positioned tangentially to the surface of patient's skull. The rTMS was conducted to stimulate the area over the primary motor cortex (M1) of the unaffected hemisphere [22]. The resting motor threshold (RMT) was defined as the minimum stimulus intensity that produced a motor evoked potential (MEP) response of at least 50 μV peak-to-peak amplitude in five out of ten trials in the abductor pollicis brevis muscle of the unaffected side [23].

Each patient received rTMS daily for 21 days. Patients in the HF group were treated as follows: 5 Hz stimulation for 2 s per session, intertrain interval 8 s, with pulses at 90% RMT over M1 of the unaffect hemisphere for a total of 18 mins. For the LF group, patients receiced rTMS as follows: 1 Hz stimulation for 15 s, intertrain interval 2 s, with pulses

Table 1. Characteristics of patients with high CST integrity.

Group	HF Group (n = 9)	LF Group (n = 10)	Sham Group (n = 10)
Gender			
Male	6	6	6
Female	3	4	4
Age (years) ($\bar{X} \pm$ S)	55.89 ± 7.27	55.00 ± 7.34	55.40 ± 7.82
Time from stroke to recruitment (weeks) ($\bar{X} \pm$ S)	8.11 ± 2.74	8.80 ± 2.82	8.00 ± 2.98
Type of the stroke			
hemorrhagic	3	3	4
ischemic	6	7	6
Stroke location			
cortical	2	3	2
subcortical	5	5	6
brain stem	2	2	2
rFA	0.70 ± 0.09	0.73 ± 0.07	0.75 ± 0.07
FMA-UE score	29.33 ± 5.52	29.10 ± 5.40	30.10 ± 5.37
WMFT score	34.33 ± 5.81	34.20 ± 5.49	35.10 ± 5.15
MBI score	63.33 ± 11.29	63.50 ± 11.26	63.50 ± 11.21

at 90% RMT over M1 of the unaffect hemisphere for a total of 18 mins. The sham group received rTMS with the same parameters (noise, time, and frequency) as the 1 Hz rTMS group over the unaffected hemisphere but with the coil rotated 90° away from the scalp so that minimal current was induced in the brain. All rTMS intervention were performed by the same therapist blinded to group allocation.

2.7 Statistical analysis

At the baseline assessment, the mean values among the three groups were compared by either a one-way ANOVA for continuous data or chi-squared test for categorical data. Paired *t*-tests were used for intra-group comparisons before and after treatment. Inter-group comparisons after treatment were conducted using one-way ANOVA, Bonferroni correction was applied for post hoc tests. A value of $p < 0.05$ was considered statistically significant. All data analyses were performed using the SPSS 26.0 soft package (IBM Corp., Armonk, NY, USA).

3. Results

60 patients who met the inclusion criteria were enrolled to high CST intergerity group (n = 30) or low CST integrity group (n = 30), and further divided randomly into the high frequency group (HF group), the low frequency group (LF group), and the sham group with 10 patients in each group. 2 patients were unable to tolerate the pain caused by rTMS and requested to withdraw, The remaining 58 patients completed this study and were included in the final analyses. The patients flowchart was shown in Fig. 3. There were no significant differences among the groups in their baseline demographic and clinical characteristics (Tables 1,2).

Changes in FMA-UE, WMFT, and MBI scores at baseline and post-treatment in each group of patients with high CST integrity and with low CST integrity were presented in Fig. 4 and Fig. 5 separately.

For patients with high CST, all three groups showed significant improvements in FMA-UE scores after 21 days treatments (all $p < 0.05$). Further inter-group comparison revealed that FMA-UE scores were better in the LF group compared with the HF group and sham group (all $p < 0.05$). However, there were no significant differences between the HF group and sham group ($p > 0.05$). For patients with low CST, only HF group revealed significant post-treatment improvements in FMA-UE scores ($p = 0.02$), which were significant better than LF group ($p < 0.05$) and sham group ($p < 0.05$).

With regard to patients with high CST, the WMFT scores increased significantly from baseline to post-treatment for all three groups (all $p < 0.05$). The multiple comparisons showed that the LF group achieved higher WMFT scores when compared to the HF group and sham group (all $p < 0.05$), while no significant differences were found between the HF group and sham group ($p > 0.05$). For patients with low CST, only HF group exhibited increased WMFT scores from baseline to post-treatment ($p < 0.05$), which were significant higher than LF group ($p < 0.05$) and shame group ($p < 0.05$)

Similar results were recorded in MBI scores of patients with high CST. After 21 days treatment, MBI scores in all three groups were significantly improved compared with pre-treatment (all $p < 0.05$). In the intergroup analysis, the MBI scores measured at post-treatment were significant higher in LF group compared to HF group ($p < 0.05$) and sham group ($p < 0.05$), while no significant differences were found between the HF group and sham group ($p > 0.05$). For patients with low CST, significant improvements in MBI score were found in all three groups after treatment (all $p < 0.05$). The further inter-group comparison results indicated that the HF group obtained better MBI scores when compared to the LF group($p < 0.05$) and sham group ($p < 0.05$), while no significant differences between the LF group and sham group were found ($p > 0.05$).

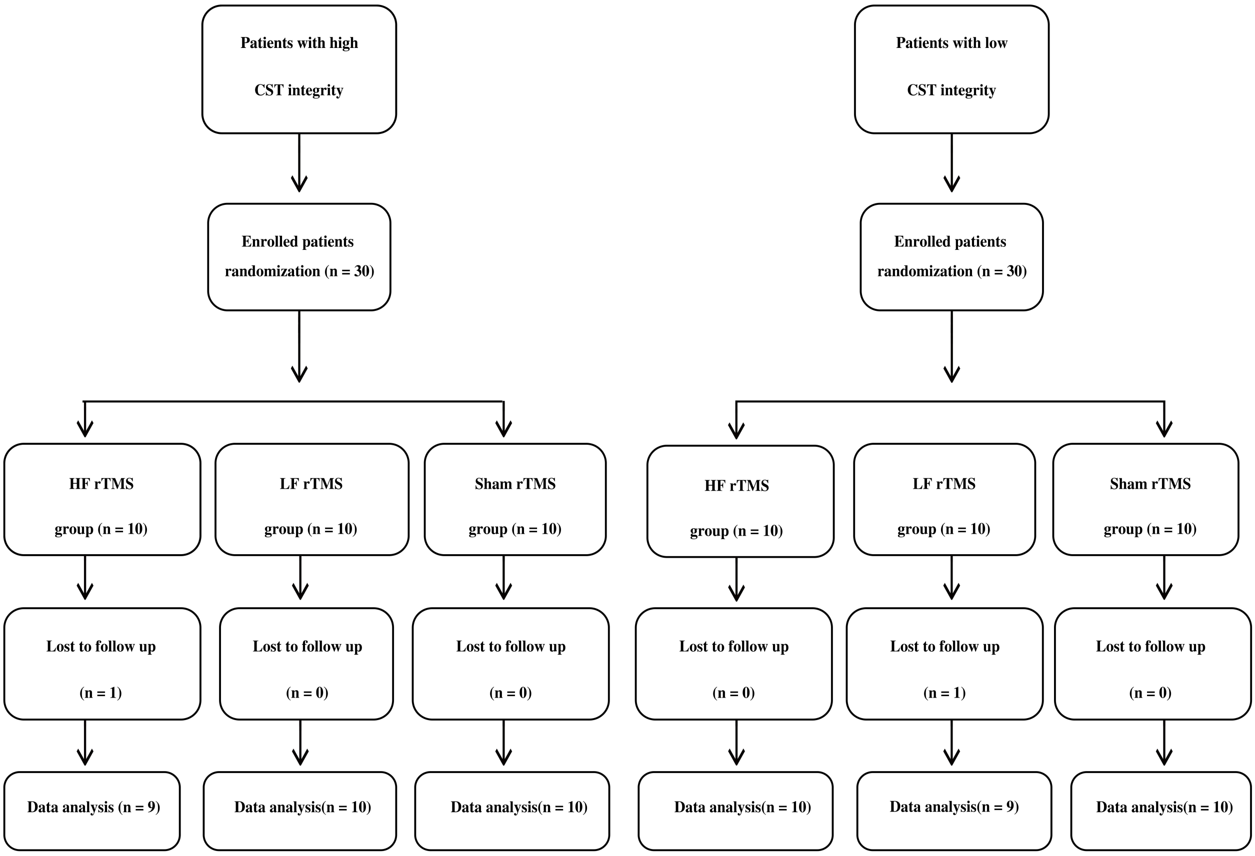

Fig. 3. The patients flowchart.

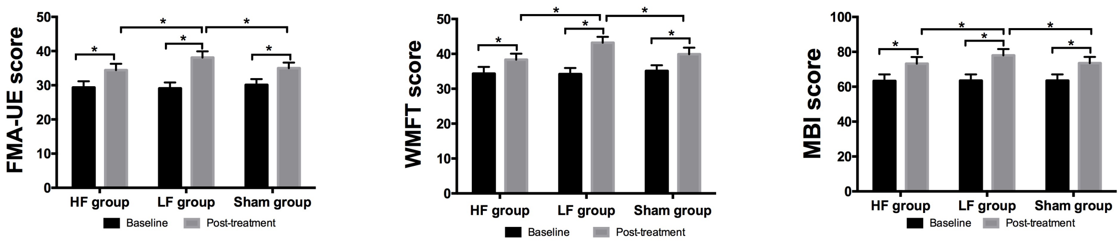

Fig. 4. Changes in FMA-UE, WMFT, and MBI scores at baseline and post-treatment in each group of patients with high CST integrity. FMA-UE, Fugl-Meyer scale for Upper Extremity; WMFT, Wolf Motor Function Test; MBI, Modified Barthel Index; HF group, high frequency rTMS group; LF group, low frequency rTMS group; *: $p < 0.05$.

There were no severe adverse reactions such as seizures or recurrent stroke happened during all treatments. Only one patients in the HF-rTMS group experienced dizziness at the first few sessions of stimulation. No special treatment was performed, the symptom disappeared soon after intervention.

4. Discussion

The recovery of motor function of patients with stroke is associated with cortical reorganization and synaptic plasticity. Both hemispheres participate in the recovery processes, which are highly active during the first few months after stroke [24]. The corticospinal tract is the most important voluntary motor conduction pathway, and its structural and functional integrity can predict the potential for motor recovery after stroke [25,26]. Meanwhile, the reorganization of motor function after stroke is associated with the integrity of the imparied corticospinal tract. Therefore, this study took the integrity of the corticospinal tract as the target to explore its impact on the neural regulation mechanisms of rTMS.

Current studies suggested that rTMS could promote motor-function recovery in stroke patients through regulation of cortical excitability and interhemispheric inter-

Table 2. Characteristics of patients with low CST integrity.

Group	HF Group (n = 10)	LF Group (n = 9)	Sham Group (n = 10)
Gender			
Male	6	6	5
Female	4	3	5
Age (years) ($\bar{X} \pm$ S)	56.40 ± 7.81	55.78 ± 7.38	56.30 ± 7.12
Time from stroke to recruitment (weeks) ($\bar{X} \pm$ S)	8.20 ± 2.63	8.33 ± 2.59	8.10 ± 2.87
Type of the stroke			
hemorrhagic	4	3	5
ischemic	6	6	5
Stroke location			
cortical	2	2	2
subcortical	6	5	6
brain stem	2	2	2
rFA	0.33 ± 0.11	0.30 ± 0.10	0.29 ± 0.09
FMA-UW	8.70 ± 1.70	8.56 ± 1.89	8.72 ± 1.77
WMFT	11.70 ± 1.06	11.33 ± 1.58	11.70 ± 1.73
MBI	39.00 ± 5.32	40.00 ± 5.33	39.00 ± 5.16

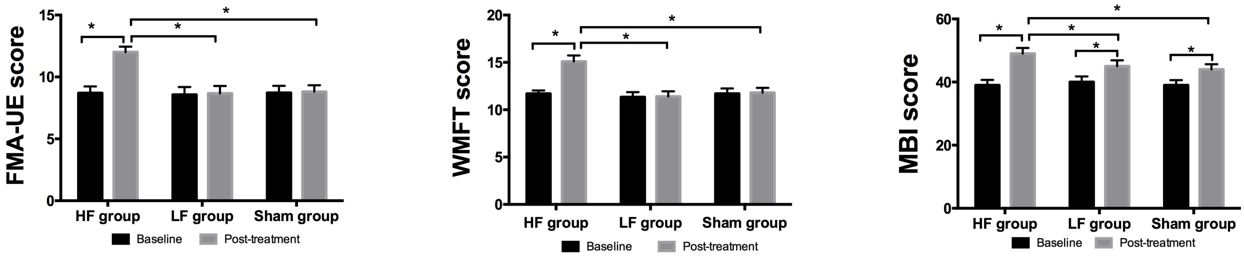

Fig. 5. Changes in FMA-UE, WMFT, and MBI scores at baseline and post-treatment in each group of patients with low CST integrity. FMA-UE, Fugl-Meyer scale for Upper Extremity; WMFT, Wolf Motor Function Test; MBI, Modified Barthel Index; HF group, high frequency rTMS group; LF group, low frequency rTMS group; *: $p < 0.05$.

actions. Stimulation frequency ≤1 Hz was considered as low-frequency, which generated an inhibition effect, while stimulation frequency ≥5 Hz was considered as high frequency, which generated an excitatory effect. In clinical practice, classic rTMS protocol was performed based on the theory of interhemispheric inhibition modle [27]. However, this theory may not be applicable to patients with severe motor function impairment. Wang *et al*. [9] applied high-frequency rTMS stimulation over M1 of the contralesional hemisphere of patients with ischemic or hemorrhagic stroke, which through regulation compensatory activity of unaffected hemisphere to promote the recovery of motor function of patients, suggesting that the contralesional hemisphere plays an significant role in the recovery of motor function.

Our findings showed that, for patients with high CST integrity, LF-rTMS was superior to HF-rTMS and sham stimulation in upper limb motor rehabilitation after stroke. Inhibition of hyperexcitability of the contralesional hemisphere through performing low-frequency rTMS to restore the interhemispheric balance could promote the recovery of motor function. For patients with low CST integrity, the application of HF-rTMS to the contralesional hemisphere improved motor functionin patients with severe hemiplegia. It could be explained that when severe unliateral damage hemisphere happened, the residual neurons may insufficient to compensate for the lost function, in this condition the functional recovery was dominated by contralateral hemisphere. For thoses patients with severe unilateral injury, lost functions are partly relocalized in the unaffected side [28,29]. The remodeling and reorganization of brain function involved all the surviving neurons of bilateral hemispheres. It was considered that in the case of unilateral brain is severely damaged, unlike the previous HF-rTMS excitation of the affected cortex or the LF-rTMS suppression of the intact side, the high frequency stimulation of contralateral brain could improve its compensation function to help restore the impairment. Suppressing the activity of the contralesional hemisphere with LF-rTMS may not beneficial for patients with low CST integrity. The role of the contralateral hemisphere in stroke recovery are double-sided. In addition to interhemispheric inhibition, the contralateral hemisphere also has compensatory potential. Based on the results of our study, we considered that the leading role in the process of recovery was associated with lateral corticospinal tract integrity. That is, for patients with high CST integrity, inhibition of hyperexcitability of the contralesional hemisphere with low-frequency rTMS to restore the interhemispholar balance could promote the recovery of motor function. For patients with low CST integrity, through exciting the affected cortex with HF-rTMS can promote hemiplegia recovery after stroke.

After the occurrence of stroke, different kinds of changes happened at cellular and neural network levels. Previous animal studies reported that axonal extension and sprouting in the CST play a significant role throughout the whole recovery process [30,31]. The recrossing of the corticospinal axon projecting from the contralesional hemisphere to the ipsilesional spinal cord which innervate forelimb or more caudal body part and corticospinal neurons originally innervating the ipsilesional body part acquire the output to the contralesional body part. These results suggested that axonal remodeling of the CST in the contralateral hemisphere could be an important mechanism for the recovery of upper limb motor function after stroke.

The connectivity of neural functional network is extensive and complex [32]. Post-stroke neurological recovery included cortical and subcortical functional reorganization, which was affected by a variety of factors. Studies have shown that the vestibular spinal tract and reticular spinal tract can replace the corticospinal tract in the recovery of lower limb motor function after stroke, but their roles in the recovery of upper limb motor function remain to be further explored. To our knowledge, this is the first first study that explore the influence of the CST integrity on the therapeutic effect of rTMS on upper limb moter function recovery. For future study, it is necessary to increase sample size and follow up period combined with functional MRI to provide more objective and reliable evidence.

5. Conclusions

For stroke patients with high CST integrity, low-frequency rTMS is superior to high-frequency rTMS in promoting upper limb motor function recovery. However, only high-frequency rTMS can improve upper limb motor function of stroke patients with low CST integrity.

Abbreviations

CST, corticospinal tract; R-TMS, repetitive transcranial magnetic stimulation; DTI, Diffusion tensor imaging; DTT, Diffusion tensor tractography; CT, computed tomography; MRI, magnetic resonance imaging; ROI, region of interest; FA, fractional anisotropy; RFA, relative FA; FMA-UE, Fugl-Meyer Assessment-Upper Extremity; WMFT, Wolf Motor FunctionTest; MBI, Modified BarthelIndex; RMT, resting motor threshold; MEP, motor evoked potential.

Author contributions

These should be presented as follows: LW and QXZ designed the research study. LW, QXZ, MHZ, RZZ, XQL performed the research. NST, XCF provided help and advice on the study. CFG, MHZ analyzed the data. LW, CFG wrote the manuscript. All authors contributed to editorial changes in the manuscript. All authors read and approved the final manuscript.

Ethics approval and consent to participate

All participants signed a written informed consent before-hand, which abided by Helsinki Declaration, and all research activities were authorized by the Affiliated Hospital of Qingdao University. The study was approved by the Ethics Committee of the Affiliated Hospital of Qingdao University (QYFYWZLL26418) and registered in the Chinese Clinical Trial Registry (ChiCTR2100043590).

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Conflict of interest

The authors declare no conflict of interest.

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