Original Research

Treatment of Post-Stroke Dysphagia with Repetitive Transcranial Magnetic Stimulation Based on the Bimodal Balance Recovery Model: A Pilot Study

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Abstract

Background: Brain plasticity and functional reorganization are the main mechanisms of stroke rehabilitation and the theoretical basis for transcranial magnetic therapy. Bimodal balance recovery model suggests that the structural integrity of neural pathways affects the functional reorganization mode of brain recovery after stroke. The principal neural pathway that innervates swallowing is the corticobulbar tract (CBT). The goal is to investigate the impact of corticobulbar tract integrity on swallowing function recovery in post-stroke dysphagia (PSD) patients treated with repetitive transcranial magnetic stimulation (rTMS). **Methods**: Thirty-five patients with high CBT integrity (relative fractional anisotropy (rFA) >0.5) and 32 patients with low CBT integrity (rFA ≤ 0.5) were respectively assigned to three subgroups through a random number table: 5 Hz frequency rTMS group, 1 Hz frequency rTMS group, and Sham rTMS group. The Standardized Swallowing Assessment (SSA), Penetration Aspiration Scale (PAS), and Dysphagia Outcome Severity Scale (DOSS) were analyzed before and after therapy. **Results**: Significant improvements in SSA ($p < 0.05$), PAS ($p < 0.05$), and DOSS scores ($p < 0.05$) were seen in the high frequency (HF) and low frequency (LF) groups compared with the Sham group for patients with high CBT integrity. Increased SSA ($p < 0.05$), PAS ($p < 0.05$), and DOSS scores ($p < 0.05$) demonstrated that the HF group achieved greater remediation than the LF and Sham groups for patients with low CBT integrity. **Conclusions**: Both 5 Hz and 1 Hz rTMS over the contralateral hemisphere are effective for the treatment of swallowing disorders for patients with high CBT integrity after stroke; 5 Hz rTMS over the contralateral hemisphere is more effective than 1 Hz and sham stimulation for patients with low CBT integrity.

Keywords: stroke; repetitive transcranial magnetic stimulation; corticobulbar tract; dysphagia

1. Introduction

Post-stroke dysphagia (PSD) is a common and painful complication following stroke [1]. It is a clinical condition characterized by delayed swallowing, salivation, food residue, choking, and aspiration. Long-term swallowing problems can cause dehydration, malnutrition, aspiration pneumonia, and other conditions that increase medical costs and mortality [2,3]. Currently, treatment for PSD includes modification of diet consistency, eating posture training, swallowing exercises to build strength and coordination, sensory stimulation, drug therapy, neuromuscular electrical stimulation, and noninvasive brain stimulation [4,5]. As a noninvasive intervention to modulate human brain activity, repetitive transcranial magnetic stimulation (rTMS) is commonly utilized to treat PSD patients due to its efficacy and safety [6].

Concerning the application of repetitive transcranial magnetic stimulation in patients with PSD, currently, there are two primary models for the therapy of swallowing dysfunction in stroke patients [7,8]. According to the "interhemispheric competition model", inhibitory low-frequency (1 Hz) rTMS over the contralesional hemisphere benefits the recovery of swallowing function in stroke patients [9,10]. Alternatively, the "vicariation model" suggests that excitatory high-frequency (5 Hz) rTMS over the contralesional hemisphere is also a valid therapeutic option for stroke patients with dysphagia [11]. However, there is no consensus on the most effective modulation or the optimal rTMS application regimen following stroke.

A new theoretical model has recently been presented for the use of rTMS in the treatment of stroke patients. It is known as the "bimodal balance—recovery model" [12]. This model holds that the preeminence of the interhemispheric competitive and vicariation models depends upon the degree of structural reserve.

The corticobulbar tract (CBT) is a central neural pathway regulating swallowing movement [13]. It is the most important contributory factor for structural reserve, which indicates that the selection of the rTMS stimulation protocol for PSD patients could be made according to the integrity of the CBT.

Diffusion tensor tractography (DTT), derived from diffusion tensor imaging (DTI), permits the *in vivo* dissection and quantitative assessment of CBT integrity [14]. In the previous study, the detailed anatomical position of the CBT in the subcortical white matter was determined using DTT, which gives reference lists for this study [15,16]. It was then evaluated whether high frequency (HF) rTMS had an advantage over low frequency (LF) rTMS for PSD patients and the effect of different corticobulbar tract integrities on the swallowing function recovery of stroke patients following treatment with rTMS.

2. Materials and Methods

2.1 Subjects

Subjects were admitted to the rehabilitation medicine department, Liaocheng People's Hospital, Shandong, China. Inclusion criteria were as follows: (1) computerized tomography (CT) or magnetic resonance imaging (MRI) evidence of a first-ever occurrence of unilateral cerebral infarction or haemorrhage [17]; (2) Age 18–80 years; (3) Stroke onset <3 months [18]; (4) Subjects with swallowing difficulties, as well as choking, coughing, wet voice, or nasal regurgitation after swallowing, that persisted for more than two weeks following a stroke [19]; (5) Stable conscious subjects who were able to complete all examinations and treatments; (6) Videofluoroscopic swallowing study (VFSS) confirmed dysphagia. Exclusion criteria included: (1) Insertion of a cardiac pacemaker or metallic implants in the brain; (2) Seizure history; (3) Swallowing disturbances due to subarachnoid hemorrhage, venous infarctions, and other nervous system diseases. This study was approved by the Ethical Committee (XJS2022250), and each subject signed informed consent.

2.2 Grouping of Subjects

According to the integrity of CBT, 35 patients with high CBT integrity (relative fractional anisotropy (rFA) >0.5) were enrolled and assigned to the high CBT integrity group. Correspondingly, 32 patients with low CBT integrity (rFA <0.5) were enrolled and assigned to the low CBT integrity group. Patients within each of the two main groups were further divided into three subgroups: 5-Hz HF group, 1-Hz LF group, and Sham group, to give a total of six groups. Figs. 1,2 presents the research design and flowcharts.

2.3 Diffusion Tensor Tractography

DTI examination was performed at the beginning of the study for all participants. DTI was performed with an 8-channel head coil on a 3.0 T magnetic resonance im-
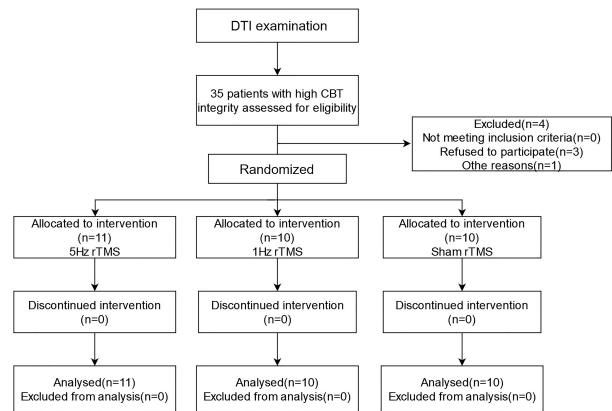

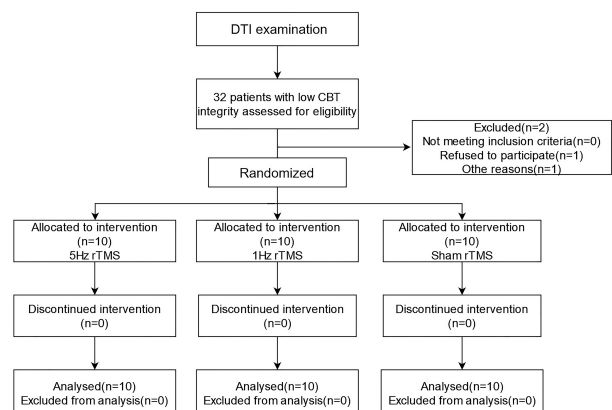**Fig. 1. Patients with high CBT integrity flow chart.**

Fig. 2. Patients with low CBT integrity flow chart.

ager (Ingenia 3.0, Phillips, Amsterdam, Netherlands) before grouping. Imaging parameters were as follows: TR/TE = 4282/100 ms, matrix = 128 × 128; field of view = 224 × 224 mm^2; flip angle = 90°; voxel size = 0.9 × 0.9 × 0.9 mm^3; 60 contiguous slices applying the 32 direction diffusion sensitizing gradients (b value = 1000 s/mm^2) to obtain the diffusion-weighted images and a single unweighted b0 image (b value = 0 s/mm^2) [15]. MRI images were visually inspected and corrected for image distortions and motion artifacts using eddy current correction tools.

IntelliSpace Portal 9.0 (Phillips, Amsterdam, Netherlands) was employed for fiber tracking and DTT data analysis. The seed region of interest for CBT tracking was placed on the inferior pons. The target region of interest was placed on the lower part of the precentral gyrus, which was located on the top of the lateral ventricles [16]. The CBT's fractional anisotropy (FA) was evaluated bilaterally. FA is a metric which ranges from 0 to 1 for quantitatively accessing the integrity of CBT, and a decreased FA on the CBT is related to impaired nerve conduction [20]. The FA ratio between the affected and unaffected sides was defined as relative FA (rFA, rFA = FA$_{ipsilesional}$/FA$_{contralesional}$). An rFA >0.5 was defined as high CBT integrity, whereas an rFA ≤0.5 was defined as low CBT integrity [21] (Figs. 3,4).
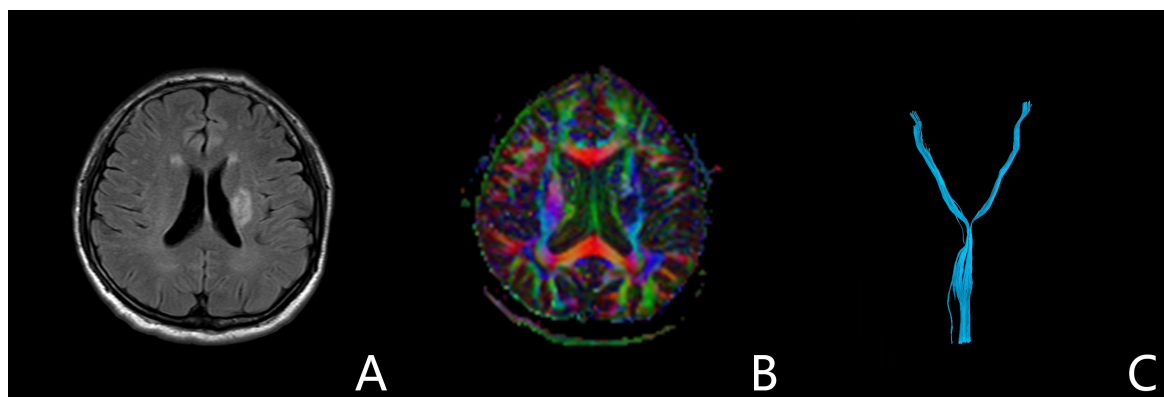
Fig. 3. Patient exemplifying high CBT integrity: A 48-year-old male. (A) Left corona-radiating infarct was detected by MRI flair. (B) Color-coded FA map, whole-brain fiber tracking. (C) DTT diagram shows that the number of CBT fibers in the affected hemisphere decreased slightly (rFA = 0.92).
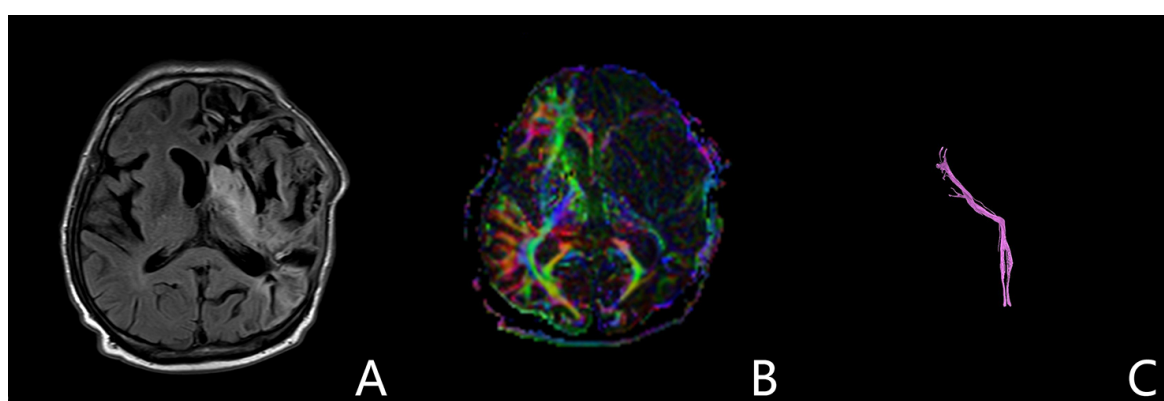

Fig. 4. Patient exemplifying low CBT integrity: A 65-year-old male. (A) An infarct in the right cerebral hemisphere was detected by MRI flair. (B) Color-coded FA map, whole-brain fiber tracking. (C) DTT diagram shows the disruption of CBT in the affected cerebral hemisphere (rFA = 0.07).

2.4 Videofluoroscopic Swallowing Study (VFSS)

VFSS is a superior quality method for diagnosis and quantitative investigation of dysphagia because of its ability to visualize the mouth cavity, pharynx cavity, laryngeal cavity, and upper esophagus during deglutition [22]. VFSS examination was performed before and after treatment. The lateral and posteroanterior images were obtained using VFSS after subjects ingested a 5 mL thick liquid bolus with standardized viscosity and composition.

2.5 Assessment of Swallowing and Functional Outcomes

2.5.1 Standardized Swallowing Assessment (SSA)

SSA was used to evaluate the swallowing function. The SSA consists of three components. SSA scores range from 18 to 46 points, with higher scores suggesting a diminished ability to swallow [23].

2.5.2 Penetration Aspiration Scale (PAS)

The PAS is an eight-point multidimensional indicator of penetration and aspiration that conveys the extent of airway invasion and whether material entering the airway is evacuated, with higher scores associated with a greater chance of aspiration pneumonia [24].

2.5.3 Dysphagia Outcome and Severity Scale (DOSS)

The DOSS scale is used to assess the severity of swallowing. The DOSS scale classifies swallowing function into seven levels, each corresponding to three degrees of swallowing disorder: 4–5 for mild, 2–3 for moderate, and 1 for severe. After treatment, an improvement of 1–2 levels was considered effective, and no change was considered invalid.

2.6 rFA Evaluation

rFA values reflect neural fiber integrity. rFA values are taken in the range of 0 to 1. A value closer to 1 indicates that the neural fiber structure on the affected hemisphere is more intact.

2.7 rTMS Intervention

A 7-cm Magnetic Stimulator (CCY-I, Yiruide, Wuhan, China) was used to deliver rTMS. Surface electrodes were

used to obtain the electromyogram of the mylohyoid muscle. The coil stimulator was placed tangentially at the apex of the skull, then moved 3 cm anteriorly and 5 cm laterally. While moving around in this region, single pulse stimulations were delivered until the maximum motor-evoked potentials of the contralesional hemisphere were obtained [18]. The pulse intensity was subsequently decreased in 2% steps of stimulator output in this region. The minimal stimulation intensity to elicit motor-evoked potential with peak-to-peak amplitude greater than 50 uV in at least 5 of 10 consecutive trials was defined as the resting motor threshold (RMT) [25].

Each participant received rTMS treatment five days per week for two weeks (Fig. 5). Parameters for patients receiving high-frequency stimulation are as follows: 5 Hz, 100% RMT, 2 s stim-10 s rest, with 950 pulses over the contralesional mylohyoid motor cortex for 19 min. Parameters for patients receiving low-frequency stimulation are as follows: 1 Hz, 100% RMT, 15 s stim-2 s rest, with 1005 pulses over the contralesional mylohyoid motor cortex for 19 min. The parameters for patients receiving sham stimulation were the same as the HF group (frequency, time, and noise), but no current was produced in the brain. All patients received the same conventional swallowing treatment before rTMS treatment.

Fig. 5. Subject undergoing rTMS therapy over the contralateral hemisphere.

2.8 Statistical Analysis

Data collected in this study were analyzed using the SPSS 26.0 software (IBM Corp., Chicago, IL, USA) package. The Kolmogorov-Smirnov test was used to ensure the parameters were normally distributed. Quantitative variables are expressed as means $\pm$ standard deviation (SD). Before and after therapy, intra-group comparisons were analyzed using paired t-tests. An Independent t-test was used for comparisons between two groups, and a one-way ANOVA was employed for multiple-group comparisons. A p-value < 0.05 was considered statistically significant.

3. Results

3.1 Clinical Assessment

There were 67 participants recruited in this study. An aggregate of 61 patients completed the study and was included in the final statistical analyses. No significant differences in sex distribution, age, duration of onset of stroke, stroke location, type of stroke, National Institute of Health Stroke Scale (NIHSS), Pneumonia, rFA, and clinical characteristics distribution at baseline among the three subgroups of the same CBT integrity ($p > 0.05$) (Tables 1,2). Changes in SSA, PAS, and DOSS scores at baseline and post-treatment in each subgroup of patients with high and low integrity of CBT are presented separately in Figs. 6,7.

Patients with high CBT integrity improved significantly in three subgroups in the SSA scores after therapy ($p < 0.05$). The further inter-group comparison found that the HF and LF groups had better SSA scores than the Sham group ($p < 0.05$), but the HF and LF groups did not differ significantly ($p > 0.05$). Meanwhile, significant post-treatment improvements in SSA scores were seen in three subgroups of participants with low CBT integrity ($p < 0.05$), with the HF group performing significantly better than the LF and Sham groups ($p < 0.05$), but there were no appreciable changes between the LF and Sham groups statistically.

Regarding patients with high CBT integrity, PAS scores decreased significantly ($p < 0.05$) from pre-treatment to post-treatment for all three subgroups. Multiple comparisons revealed that the decline was more pronounced in the HF and LF groups than in the Sham group ($p < 0.05$), but there were no significant differences between the HF and LF groups ($p > 0.05$). For patients with low CBT integrity, the HF group exhibited a significant decrease in PAS scores from baseline to post-treatment ($p < 0.05$) while also showing significant differences compared to the LF and Sham groups ($p < 0.05$), but the changes were not statistically significant between the LF and Sham groups.

Similar results were observed in patients with high CBT integrity DOSS scores. After two weeks of therapy, the DOSS scores of all three subgroups with high CBT integrity significantly improved compared to pre-treatment ($p < 0.05$). When compared to the Sham group, the HF and LF groups' post-treatment DOSS scores improved considerably ($p < 0.05$), but there was no difference between the HF group and the LF group ($p > 0.05$). For patients with low CBT integrity, DOSS scores significantly increased in all three subgroups after therapy ($p < 0.05$). Further comparisons revealed that the HF group outperformed the LF group and the Sham group ($p < 0.05$), whereas there were no appreciable differences between the LF group and the Sham group ($p > 0.05$).

No serious adverse effects, such as seizures or recurrent strokes, were seen throughout all treatments. During the first few days, two subjects who received high-

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Table 1. Characteristics of patients with high CBT integrity at baseline.

Group	HF ($n = 11$)	LF ($n = 10$)	Sham ($n = 10$)
Sex (M:F)	7:4	6:4	7:3
Age (years)	57.72 ± 8.36	58.10 ± 8.24	57.91 ± 8.72
Time from stroke to recruitment (weeks)	8.31 ± 3.92	8.79 ± 3.67	8.57 ± 3.78
Stroke type (hemorrhagic:ischemic)	4:7	3:7	3:7
Stroke location (cortical:subcortical:both)	1:6:4	0:7:3	1:6:3
Lesion side (right:left)	6:5	5:5	6:4
NIHSS	11.00 ± 3.31	11.40 ± 3.02	11.50 ± 3.90
Pneumonia	1	1	0
rFA	0.71 ± 0.14	0.73 ± 0.11	0.70 ± 0.10
SSA (baseline scores)	26.36 ± 5.34	26.70 ± 4.00	27.10 ± 2.84
PAS (baseline scores)	3.82 ± 0.87	3.80 ± 0.79	3.80 ± 0.77
DOSS (baseline)	4.18 ± 1.17	4.20 ± 1.23	4.20 ± 1.25

NIHSS, National Institutes of Health Stroke Scale; SSA, Standardized Swallowing Assessment; PAS, Penetration Aspiration Scale; DOSS, Dysphagia Outcome and Severity Scale. Mean ± SD.

Table 2. Characteristics of patients with low CBT integrity at baseline.

Group	HF ($n = 10$)	LF ($n = 10$)	Sham ($n = 10$)
Sex (M:F)	6:4	6:4	7:3
Age (years)	58.92 ± 8.47	59.31 ± 8.53	59.40 ± 8.42
Time from stroke to recruitment (weeks)	8.91 ± 3.83	8.96 ± 3.77	8.82 ± 3.75
Stroke type (hemorrhagic:ischemic)	3:7	4:6	3:7
Stroke location (cortical:subcortical:both)	0:4:6	1:4:5	0:5:5
Lesion side (right:left)	5:5	5:5	6:4
NIHSS	23.70 ± 3.02	24.50 ± 3.76	24.30 ± 2.87
Pneumonia	6	7	6
rFA	0.37 ± 0.07	0.36 ± 0.09	0.37 ± 0.12
SSA (baseline scores)	36.90 ± 1.73	37.00 ± 2.36	37.70 ± 1.89
PAS (baseline scores)	6.90 ± 0.74	6.80 ± 0.63	6.90 ± 0.74
DOSS (baseline)	2.50 ± 0.71	2.60 ± 0.69	2.60 ± 0.70

NIHSS, National Institutes of Health Stroke Scale; SSA, Standardized Swallowing Assessment; PAS, Penetration Aspiration Scale; DOSS, Dysphagia Outcome and Severity Scale. Mean ± SD.

frequency stimulation experienced dizziness, and two who received low-frequency stimulation experienced transitory headaches. The symptoms readily disappeared without any particular therapy.

3.2 rFA Value Changes of the CBT

In the case of high CBT integrity patients, the rFA values of HF, LF, and control groups were reduced after two weeks of treatment. Differences were found in the rFA value at post-treatment between the HF and LF groups. Similarly, in the case of low CBT integrity patients, rFA values were lower than pre-treatment in all three groups after two weeks of treatment, there was a statistical difference in rFA values between the HF group and LF group after treatment (Fig. 8). This finding indicates a relative reduction in the integrity of CBT fibers in the affected hemisphere during stroke recovery and that changes in CBT fibers varied at different frequencies of rTMS.

4. Discussion

Current studies on rTMS have demonstrated its efficacy as a therapeutic intervention for neurological rehabilitation of swallowing impairment after stroke [26,27]. rTMS is a noninvasive neurostimulation technique that modulates brain activities using electromagnetic induction. High-frequency rTMS stimulation (>1 Hz) applied over the target cortical areas potentiates cortical excitability, whereas low-frequency rTMS stimulation produces an inhibitory effect in the cortex [28]. Even though many studies revealed its considerable clinical improvement in dysphagia, there is no consensus on the most effective modulation and the optimal application scheme of rTMS after stroke.

Our study shows that the therapeutic efficacy of rTMS in the treatment of PSD is associated with the integrity of the corticobulbar tract in the affected hemisphere. Both high and low frequency rTMS significantly promoted dysphagia recovery compared to Sham stimulation for patients with high CBT integrity. After a stroke, the disturbance of in-
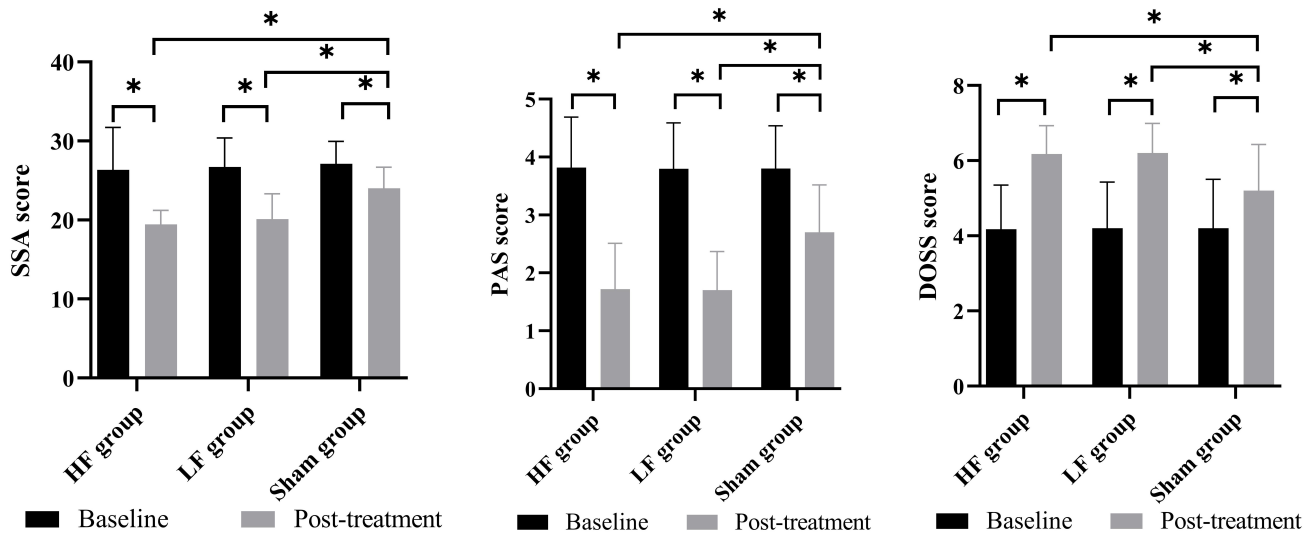
Fig. 6. Changes in baseline and post-treatment swallowing function scores in subjects with high CBT integrity after rTMS stimulation. HF group, 5 Hz-high frequency rTMS group; LF group, 1 Hz-low frequency rTMS group; Sham group, Sham stimulation group; SSA, standardized swallowing assessment; PAS, penetration aspiration scale; DOSS, dysphagia outcome and severity scale. *p < 0.05.
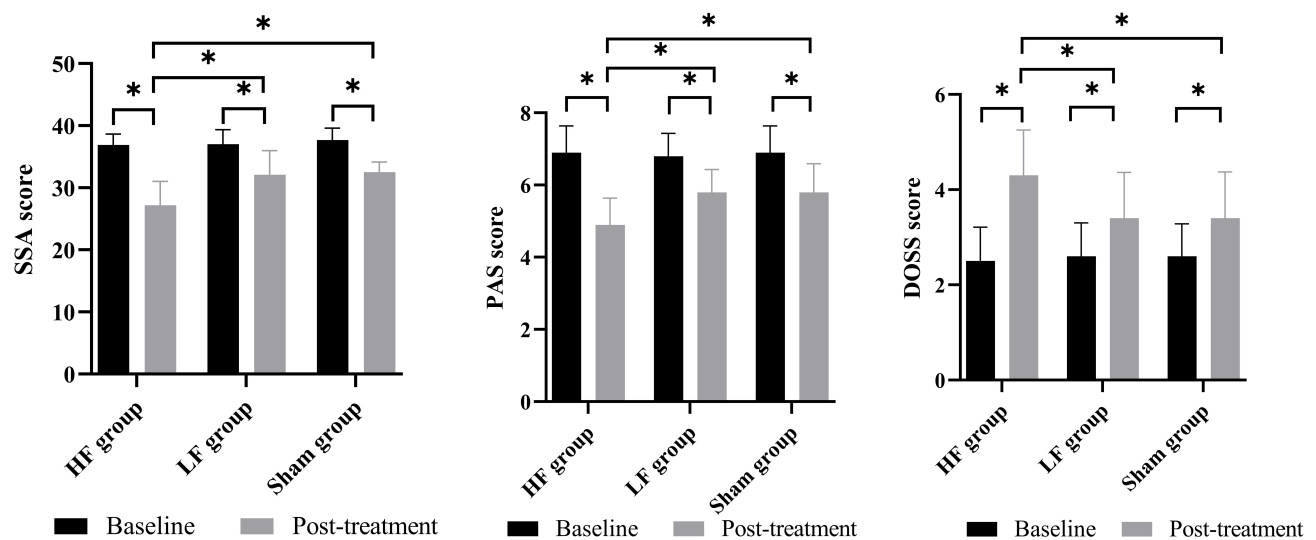

Fig. 7. Changes in baseline and post-treatment swallowing function scores in subjects with low CBT integrity after rTMS stimulation. HF group, 5 Hz-high frequency rTMS group; LF group, 1 Hz-low frequency rTMS group; Sham group, Sham stimulation group; SSA, standardized swallowing assessment; PAS, penetration aspiration scale; DOSS, dysphagia outcome and severity scale. *p < 0.05.

terhemispheric inhibitory balance may contribute to dysphagia because the contralateral hemisphere exerts more interactive inhibition on the affected hemisphere. Reducing transcallosal inhibition exerted on the affected hemisphere will facilitate the recovery of swallowing function when excitability of the contralesional hemisphere is suppressed. However, excitatory 5 Hz rTMS stimulation over the contralateral hemisphere swallowing cortex could also considerably reduce the recovery time of patients with dysphagia and improve rehabilitation outcomes. It was thought that compensatory reorganization occurs in the intact hemisphere after a unilateral hemispheric stroke to promote the

recovery of swallowing function. Nevertheless, there were no differences between HF and LF groups for subjects with high CBT integrity, which indicates that the differences in the effectiveness between the inter-hemispheric competition model and the vicariation model were not significant in this circumstance. It is speculated that it did not matter which theoretical model was dominant as the degree of injuries was relatively mild.

It was discovered that contralesional HF rTMS was superior to contralesional LF rTMS for enhancing swallowing function in patients with low CBT integrity. Park *et al*. [11] reported that high-frequency stimulation delivered
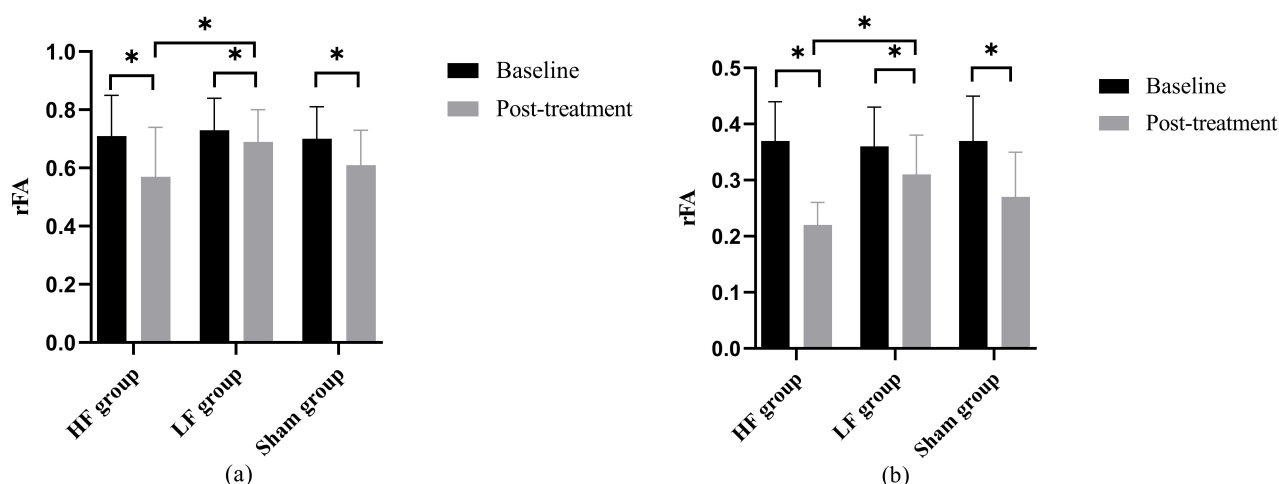
Fig. 8. Baseline and post-treatment rFA values in subjects with high CBT integrity (a) and low CBT integrity (b) after rTMS stimulation. *$p < 0.05$.

to the unaffected hemisphere could promote compensatory reorganization of the contralateral hemisphere and transfer the dominant hemisphere of swallowing function to the unaffected side. Our results demonstrate the efficacy of the vicariation model on dysphagia. Post-stroke dysphagia recovery was associated with the increased activation of swallowing cortical representative areas in the unaffected hemisphere, so it was considered that the up-regulation was more effective than the down-regulation of the intact hemisphere [29]. Corticobulbar projections from both hemispheres innervate swallowing musculatures. Compared with the limb system controlled by the unilateral hemisphere, the transcallosal interaction inhibition is weaker in the swallowing system controlled by the bilateral hemisphere [30]. It was suggested that the compensatory effect of the contralateral hemisphere had advantages in the recovery of swallowing function after stroke in patients with a larger degree of CBT injury.

Secondary white matter degeneration often occurs after brain injury, especially ischemic stroke. Ivana measured the ratio FA between the ipsilesional and contralesional hemispheres 6 and 29 weeks after stroke using the diffusion tensor imaging technique. She found that the rFA value decreased over time, which is consistent with our findings [31]. After brain injury, the longitudinal displacement of water molecules is limited by axon fragmentation. Then the myelin sheath begins to break down, infiltrating microglia cells to clear the axon debris and re-establish parallel diffusion [32]. Cell lysis and structural degradation are accompanied by the replacement of anisotropic microstructures and disordered gliosis [33]. Secondary degeneration is characterized by fiber loss, glial cell proliferation, and extracellular matrix dilatation [34]. Our results support the previously described mechanism of secondary degeneration and suggest that different frequencies of rTMS may have different effects on the progression of secondary white mat-

ter degeneration, which may be related to the recovery of swallowing dysfunction after stroke.

This study indicates that the rTMS regulation of the swallowing motor cortex after stroke can accelerate functional recovery through a bimodal balance recovery model and that for patients with a greater degree of CBT injury, the contralateral compensatory mode may have certain advantages.

Limitation

There are some limitations in the present study. Firstly, the sample size of each subgroup was small. Secondly, the swallowing function at post-treatment was evaluated, but a long-term follow-up was not performed. Thirdly, for patients with high CBT integrity, the baseline NIHSS score of the HF group and LF group were lower than 11.5, while the baseline NIHSS score of the Sham group was equal to 11.5. This could introduce a bias since NIHSS score lower than 11.5 was associated with transient dysphagia, while NIHSS score equal to or superior to 11.5 was related to persistent dysphagia [35]. Future studies should combine DTI with functional Magnetic Resonance Imaging (fMRI) to further explore the mechanism of swallowing function recovery after stroke.

5. Conclusions

Both high-frequency rTMS and low-frequency rTMS over the contralesional hemisphere significantly promoted dysphagia recovery in stroke patients with high CBT integrity. However, contralesional high-frequency rTMS exhibited a more significant treatment effect on swallowing function in stroke patients with low CBT integrity.

Availability of Data and Materials

The data that support the findings of this study are available from the corresponding author

Author Contributions

LW and YLi designed the study. LW, FW, YLin, XG, JW, JL, CF conducted data collection. SX, YW performed image analysis. LW, CG, YM analyzed and interpreted the data. LW wrote the first draft of the manuscript. All authors contributed to manuscript revision and read and approved the final version. All authors have participated sufficiently in the work to take public responsibility for appropriate portions of the content and agreed to be accountable for all aspects of the work in ensuring that questions related to its accuracy or integrity.

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 Liaocheng People's Hospital. The ethics approval number is (XJS2022250).

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Conflict of Interest

The authors declare no conflict of interest.

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