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A randomised controlled experiment on stroke patients with dysphagia discovered that recurrent transcranial magnetic stimulation changed their hemodynamic signals and improved their swallowing.

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ABSTRACT
Objective
Using functional near-infrared spectroscopy (fNIRS), our study aims to measure the cortical correlates of swallowing execution in patients with dysphagia following repetitive transcranial magnetic stimulation (rTMS) therapy and to track changes in brain activation patterns in stroke patients with dysphagia following rTMS intervention. Additionally, we attempted to examine how rTMS affected individuals with various lesion sides who had dysphagia in terms of brain activation. This study focused on the effects of 5 Hz rTMS stimulation of the afflicted mylohyoid cortical region, giving clinical support for the use of rTMS to treat dysphagia in stroke patients.
Methods
This was a sham-controlled, single-blind, randomised controlled study with an observer who was blinded. The study included 49 patients who were randomly assigned to the rTMS group (n = 23) or the sham rTMS group (n = 26) using a random number table. The rTMS group got 5 Hz rTMS stimulation to the afflicted mylohyoid cortical region of the brain, while the sham rTMS group received rTMS with the same parameters as the rTMS group except for coil position. Each patient underwent two weeks of stimulation before beginning traditional swallowing therapy. The Standardized Swallowing Assessment (SSA), Fiberoptic Endoscopic Dysphagia Severity Scale (FEDSS), Penetration-Aspiration Scale (PAS), and functional oral intake status were evaluated twice: first at the start of treatment and again two weeks later (after intervention). Meanwhile, we use a fNIRS device to monitor brain hemodynamic changes during the experiment.
Results
After rTMS therapy, the SSA, FEDSS, and PAS scales improved significantly in the rTMS group (all P 0.001). The same analysis was performed on the same scales in the sham rTMS group (all P 0.001). There was no significant difference in clinical assessments between the rTMS group and the sham rTMS group 2 weeks after baseline (all P > 0.05). Except for the SSA score (P = 0.067), there were statistically significant differences between the two groups in the rate of change in the FEDSS score (P = 0.018) and PAS score (P = 0.004). There was no significant difference in the removal rate of the feeding tube between the rTMS group and the sham rTMS group (P = 0.355), however there was a significant difference compared to the baseline characteristics in both groups (PrTMS 0.001, PshamrTMS = 0.002). In fNIRS analysis, the block average result revealed significant differences in brain areas RPFC (right prefrontal cortex) and RMC (right motor cortex) following intervention between the rTMS group and the sham rTMS group (Pchannel30 = 0.046, Pchannel16 = 0.006). In the subgroup analysis, the rTMS group was divided into two groups: left-rTMS and right-rTMS, while the sham rTMS group was divided into two groups: left-rTMS and right-rTMS. The fNIRS results revealed no statistically significant differences in block average and block differential after intervention between the left-rTMS group and the sham left-rTMS group, but differences in block average were statistically significant between the right-rTMS group and the sham right-rTMS group: channel 30 (T = 2.34, P = 0.028) in LPFC and channel 16 (T = 2.54, P = 0.018) in RMC. There was no significance in the left-rTMS group compared to baseline after intervention, but in the right-rTMS group, channel 27 (T = 2.18, P = 0.039) in LPFC and 47 (T = 2.17, P = 0.039) in RPFC exhibited relevance in block differentiation. After intervention, neither the sham left-rTMS group nor the sham right-rTMS group had significant differences in block average and block differential in each brain area (P > 0.05).

Conclusions
The current investigation confirmed that 5-Hz rTMS at the afflicted mylohyoid cortical region is viable in post-stroke patients with dysphagia, and that rTMS therapy can modulate cortical excitability. According to prior research, swallowing has a dominant hemisphere, and the results of our fNIRS investigation appeared to demonstrate a greater increase in cortical activation on the right side than on the left after rTMS of the afflicted mylohyoid cortical region. In the subgroup analysis, however, there was no difference between the left and right hemispheres. Nonetheless, the current work presents a novel and viable way of using fNIRS to assess dysphagia in stroke patients.
KEYWORDS*: Stroke, Dysphagia, Functional near-infrared spectroscopy, fNIRS, Repeated transcranial magnetic stimulation, rTMS*

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I. Introduction

Dysphagia is one of the most prevalent post-stroke consequences, with a prevalence of 37 to 78%. (1). Dehydration, starvation, and pneumonia can all result from improper swallowing. On the other hand, it lengthens hospital stays, raises medical costs, lowers quality of life, and even leads to death (2, 3). Detecting and treating dysphagia as soon as possible is therefore critical for stroke care. Traditional dysphagia treatments such as neuromuscular electrical stimulation, feeding training, and altering meal forms, as well as intervening eating postures, are used to address these issues. Despite the fact that these treatments are routinely used in clinics, no good results have been produced (4–6). Recently, dysphagia rehabilitation treatments have shifted from compensatory tactics to retraining of swallowing function based on the idea of neuroplasticity (7). Cortical dysfunction has been linked to swallowing issues, and the cerebral cortex is important in the start and regulation of swallowing (8, 9). According to earlier assessments of swallowing neurophysiology, swallowing regulation is more bilaterally implemented in the brain (10, 11). Indeed, several research have revealed that one hemisphere may be more dominant when it comes to swallowing (12, 13). However, the concept of hemisphere swallowing dominance was derived from clinical findings of dysphagia patients, which were inferred as a result of neurological examination but not radiologically confirmed (8, 14, 15). Interestingly, Tshetiz proposed that lesions in the left cerebral cortex are related with oral phase swallowing impairment, whereas lesions in the right hemisphere cortex are associated with pharyngeal phase swallowing impairment (16). Repetitive transcranial magnetic stimulation (rTMS), which uses magnetic fields to modify cerebral cortex excitability and accelerate neuroplasticity, has been shown to enhance swallowing function after stroke (17–19). According to J. W. PARK's research, a 5-Hz high-frequency rTMS on the contralesional pharyngeal motor cortex may be beneficial for stroke patients with dysphagia (20).

According to Lee et al. (21), activation of the damaged cortex representing the suprahyoid muscle could enhance swallowing performance. Furthermore, Vasant et al. (22) found that amplitudes of cortical pharyngeal motor evoked potentials (PMEPs) were raised after hemisphere cerebellar rTMS, which was supported by Tshetiz study (23) that found cerebellar rTMS to be a safe and effective treatment for dysphagia after stroke. As a result, determining which stimulation site delivers the best therapeutic results is debatable, and it is based on an understanding of specific parts of the motor cortex involved in swallowing. As a result, assessing brain activity during swallowing is critical for better understanding and treating neural regulation of swallowing. There are numerous clinical evaluation scales for dysphagia, all of which are subjective and ambiguous due to their reliance on clinical measurement and medical history. Functional near-infrared spectroscopy (fNIRS), a relatively new non-invasive imaging technology, monitors variations in oxyhemoglobin (oxy-Hb) and deoxyhemoglobin (doxy-Hb) in cerebral blood flow. fNIRS is a non-invasive and safe approach for assessing cortical activity patterns in individuals with neurological diseases. It can provide a significant imaging foundation for the development of clinical rehabilitation programmes, as well as real-time feedback on the efficacy of rehabilitation intervention, reflecting and judging neurological function reconstruction (24, 25).

Several recent investigations of fNIRS for swallowing function demonstrate that vast areas of the cerebral cortex are active during swallowing activities in healthy participants (26, 27). Several studies have been conducted to investigate if organoleptic testing, such as taste or touch, raises hemodynamic responses in the cortical swallowing network (28, 29). Only one fNIRS study looked at hemodynamic changes in dysphagia patients and healthy controls while doing motor imagery and swallowing motor imagery. In both patients and healthy controls, the highest signal alterations were detected in the inferior frontal gyrus (30). Previous research on brain activation patterns during swallowing relied heavily on data from healthy participants. However, variations in brain activation patterns linked with dysphagia in rTMS patients have received little attention.

This technique has yet to be widely used to investigate changes in cortical activation before and after therapy. Thus, we used fNIRS to investigate the cortical correlates of swallowing in patients with dysphagia following rTMS therapy, as well as to detect the change in brain activation in stroke patients with dysphagia following rTMS intervention (31). Furthermore, we attempted to investigate the effect of rTMS on brain activation in dysphagia patients with various lesion sides. This study also focused on the effect of using 5 Hz rTMS to stimulate the damaged mylohyoid cortical region, giving clinical evidence for rTMS therapy of dysphagia in stroke patients. In response to this issue, we anticipated that patients' swallowing ability improved following rTMS therapy, and the cortical activation signal increased in the affected mylohyoid cortical region treated with 5 Hz rTMS.

II. Materials And Methods

Sample Size Calculation

The required patient sample size for this investigation was computed. A previous related study (23) shown that 5 Hz rTMS therapy significantly improved SSA scores (4.75 4.69) in stroke patients with dysphagia. The sample size was calculated to be at least 44 with the statistical power set to 0.9 and at a two-sided 0.05 level of significance. The probability is 90% that the study will detect a treatment difference at a two-sided 0.05 significance level if the true difference between treatments is 4.75 units. This is based on the assumption that the response variable's standard deviation is 4.69. If 30% of individuals are predicted to drop out at random during the study, a minimum of 57 people must be recruited.

Participants

The study was authorized by the Ethics Committee of the First City Hospital of Poltava, Ukraine, and all subjects provided informed consent before being included. From July 2021 to January 2022, 60 stroke patients with dysphagia were recruited from the Department of Rehabilitation Medicine, First City Hospital of Poltava, Ukraine. Furthermore, each patients was right-handed.

The following parameters were used to choose participants: (1) stroke patients were diagnosed using the updated definition for the twenty-first century (33) and proved to be subcortical stroke by computed tomography (CT) or magnetic resonance imaging (MRI); (2) patients with dysphagia validated by fiberoptic endoscopic assessment of swallowing (FEES); (3) patients with reliable vital signs, disease duration between 1 and 12 months, and ages ranging from 18 to 85 years; and (4) patients not taking the medication.The following were the exclusion criteria: (1) had a history of any other neurogenic diseases, such as epilepsy, tumor, and so on; (2) patients suffering from severe cognitive impairment or aphasia who could not continue to cooperate with treatment; (3) had intracranial metal implants, pacemakers, skull defects, history of seizures, or other contraindications to rTMS treatment; (4) and had a history of sedation, antidepressants, or other drugs that may alter the excitability of the cortex.

Study Layout

This was a sham-controlled, single-blind, randomised controlled study with an observer who was blinded. The individuals were assigned to a TMS group and a sham TMS group using a random number table method. For two weeks, the rTMS group received ten sessions of rTMS. 5 Hz rTMS was used on the afflicted mylohyoid cortical area. The same parameters (including position, stimulation frequency, interval time, and pulse number) were used in the sham stimulation group as in the rTMS group. During the intervention, however, the coil was perpendicular to the surface of the skull to ensure the identical stimulation sound without any effective stimulation. Following rTMS intervention, all patients got the same standard dysphagia treatment for 30 minutes each day, including sensory stimulation, tongue retraction exercises, and oropharyngeal muscle strengthening exercises. The exercises were led by an experienced physical therapist five times per week for ten days. In all cases, a baseline assessment and a follow-up assessment were carried out at two separate times: baseline and 2 weeks after the intervention.

Identifying the resting motor threshold (RMT)

RMT was determined before each patient was treated. Patients sat in a comfy chair in a comfortable position while wearing positioning caps on their heads. To avoid a change in the site, we ask that patients refrain from moving their heads. We next implanted a 90-mm figure-eight stimulating coil of the MagPro CCY-I stimulator (YIRUIDE Company, Wuhan, China) in the afflicted hemisphere's mylohyoid cortical region. Each patient's motor evoked potential (MEP) and RMT were measured by manually manipulating the single pulse output. The optional coil position ("hot spot") is chosen by the location of the maximal MEP recording produced in the mylohyoid cortical area. The RMT is defined as a stimulus intensity that elicited an MEP >50 UV in at least 5 of 10 sequential stimulations across the affected side's first dorsal interosseous muscle. If there is no motor response after maximum stimulation, RMT can be measured by selecting stimulation locations (mirror areas) at the similar spot on the unaffected side.

TMS treatment in the control and treatment groups

A 5-Hz rTMS protocol was applied to the affected mylohyoid cortical region of the affected hemisphere at an intensity of 80% of RMT, a stimulation length of 2 s, and a 10-second gap between each stimulation in the rTMS group. The therapy lasted 20 minutes and included 100 repetitions and 1,000 stimuli. The same stimulation parameters were used in the sham rTMS group. During the intervention, the coil is held at 90° to the scalp to guarantee that it provides the same stimulation sound without actually stimulating the scalp. To establish whether the site of rTMS administration was left or right in these patients with bilateral brain damage, we chose the side of the brain with more extensive injury or the contralateral brain of a more seriously injured limb. The treatment was given once a day, five days a week for two weeks. The rTMS methods employed in our investigation were based on the rTMS safety standards (34).

Outcome Measurements

The major goal was the SSA scale, while additional outcomes included PAS scale, FEDSS scale, and feeding tube removal rate assessments. In the meantime, a fNIRS system detects changes in cerebral hemodynamics during task performance.

Standardized Swallowing Evaluation (SSE)

SSE focuses on clinical evidence. It is divided into three sections. The clinical examination is the first phase, with a total score ranging from 8 to 23, encompassing response level, and so on. Patients were given 5 mL of water three times in the second half. Its points range from 5 to 11. What needed to be examined at this point was whether participants had coughing, choking, dyspnea, or a moist voice. If no difficulties are found, the final phase is to provide 60 mL of water. The results showed that the SSA scores ranged from 18 to 46, with a higher score indicating decreased swallowing capacity (35, 36).

Fiberoptic Endoscopic Dysphagia Severity Scale (FEDSS)

Following the clinical evaluation, each participant underwent a fiberoptic endoscopic evaluation of swallowing (FEES) of their swallowing. Stroke-related dysphagia was classified into a six-point FEDSS scale, with 1 being the best and 6 being the worst, based on the variable consistency of diet detected in their endoscopic examination and the danger of saliva penetration or aspiration (37, 38). Our crew, all of whom have years of experience with this diagnostic device, completed the FEES operations.

Penetration-Aspiration Scale (PAS)

During FEES, each participant in our study was assessed using PAS. PAS used an eight-point scale to assess the severity of dysphagia. This scale, which is often used in endoscopic and radiological assessments, is a semi-quantitative assessment of penetration and aspiration. The greater the PAS score, the weaker the swallowing function (39).

Feeding Tube Intake Status

The Functional Oral Intake Scale (FOIS) was used to determine feeding tube reliance at the time of assessment (40). The FOIS scale has seven levels to describe the functional oral intake of stroke patients with dysphagia. Higher values showed improved swallowing function (41, 42). As a result, a removal rate was determined.

Functional Near-Infrared Spectroscopy (fNIRS) Data Acquisition and Swallowing Task

fNIRS sensors (NirScan Danyang Huichuang Medical Equipment Co. Ltd., China) with wavelengths of 730 and 850 nm were used to detect changes in oxyhemoglobin (HbO) and deoxyhemoglobin (HbR) during rest and voluntary swallowing. Several parts of the cerebral cortex have been reported to be active during swallowing exercises (26, 27). With reference to previous studies, a total of 47 channels were symmetrically positioned over the areas of the prefrontal cortexes (PFCs: LPFC and RPFC), motor cortexes (MCs: LMC and RMC), and occipital lobes (OLs: LOL and ROL) to identify brain regions and their functions and to easily elucidate our study (43, 44). The sampling rate of the NIRS system was set to 10 Hz. The channel configuration of the fNIRS probe set is shown in Figure 1. The optodes were positioned on the scalp surface of participants based on four anatomical positions described by the international 10-20 system (nasion, central zero, left, and right pre-auricular points). NirScan Danyang Huichuang Medical Equipment provided the spatial registration approach, which was based on a standard head model setup that used a 3d localization system to confirm the position of the probe falling on the skull and was then matched into the Broadmann partition. The brain area and channel corresponding to the individual Broadmann division were shown in Supplementary Table S1 in the supplemental information. To limit the impact of noise, the participants were placed in a silent fNIRS examination room. Each optical signal was linked to the skull surface with a custom-made hard plastic cap and covered with a black fabric to prevent ambient light from entering the device.

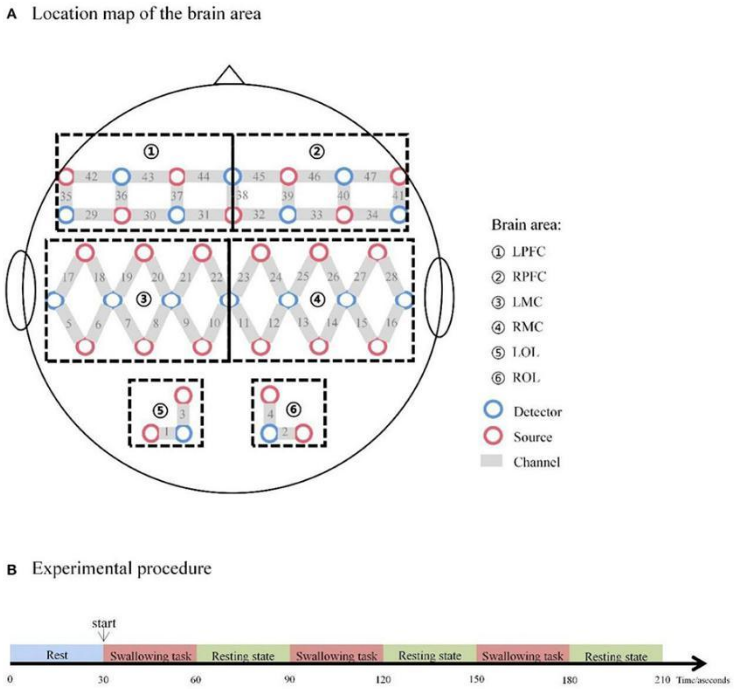


FIGURE 1. (A) Location map of the brain area. **(B)** Experimental procedure. LPFC, left prefrontal cortex; RPFC, right prefrontal cortex; LMC, left motor cortex; RMC, right motor cortex; LOL, left occipital lobe; ROL, right occipital lobe.

The swallowing procedure utilized in this research was divided into two phases: 30-second resting-state periods and 30-second swallowing periods. Rep these two steps three times. The swallowing task required participants to consistently swallow their saliva, as suggested by a computer voice instruction. The number of swallows per participant was not regulated, although during the repetitive saliva swallowing test, all patients swallowed saliva 1 to 5 times (RSST). Each patient practised the swallowing motion before the trial to avoid mouth movement caused by swallowing action. The entire procedure took about 10 minutes (see Figure 1).

fNIRS Data Analysis

The fNIRS data in our investigation were pre-processed and analyzed using the NirSpark programme. To pre-process the data, the following steps were taken: removing irrelevant time intervals and unrelated artefact; converting light intensity to optical density; selecting a band-pass filter to filter noise and interference signals (0.01-0.09 Hz); translating optical density to blood oxygen concentration; and setting the initial time of the hemodynamic response function (HRF) to 0 s and the end time to 30 s. (the time for a single block paradigm). The blood oxygen concentrations from the three-block paradigms were stacked and averaged, providing a block average with a "swallowing" period of 30 seconds. The average of the three-block paradigms of the blood oxygen concentration of swallowing block paradigms minus the blood oxygen concentration of rest block paradigms yielded a block differential result. We used a generalized linear model (GLM) to evaluate the HbO2 time-series data, which had been pre-treated for each channel of each participant, and to perform the t-test (45). For each activity and subject, the GLM could calculate the degree of match between the experimental and ideal HRF values (46). The beta value, which represents the level of cortical activation of the channel, was used to estimate the HRF prediction of the HbO2 signal (47) and can be used to represent the peak value of the HRF function. A two-sample t-test in group statistics was used to examine for differences between groups at baseline and after intervention. The two sample t-test was used to compare differences between the rTMS and sham rTMS groups at the start and end of the trial. We performed a subgroup analysis since the patient's stimulation sites were separated into left and right sides, which could alter the interpretation of fNIRS data. The rTMS group was separated into two groups based on the stimulated hemisphere: left-rTMS and right-rTMS, while the sham rTMS group was divided into two groups based on the stimulated hemisphere: left-rTMS and right-rTMS. Paired t-tests were used to compare these four groups within the study from the beginning to the finish. For stimulation of the left-rTMS group and sham left-rTMS group in the left hemisphere and right-rTMS group and sham right-rTMS group in the right hemisphere, a two-sample t-test was used for the analysis of the between-group differences.

Statistical Analysis

SPSS version 26.0 was used for all statistical analyses (SPSS Inc). To determine the normality of the data distribution, exploratory data analyses and Shapiro-Wilk tests were used. The mean and standard deviation of continuous variables are provided. To investigate between-group differences at baseline and in the change from baseline to the end of the study, unpaired t-tests or the Mann-Whitney U-test were utilised. Within-group comparisons were made using paired t-tests or Wilcoxon tests from the beginning to the completion of the study. Counts and percentages are reported for categorical variables. The X2 test was used to compare between groups in categorical variables at baseline.To investigate the consistency of the data, a post-hoc stimulated hemisphere subgroup analysis was done. To adjust for baseline characteristics, the rate of change was employed in between-group comparisons of swallowing function assessment change from baseline to the conclusion of the trial. The relationship between HbO2 changes in each brain area and SSA improvement in the rTMS and sham rTMS groups was investigated using linear regression analysis. The level of significance was set at a two-sided P-value of 0.05.

III. Results

In this study, we screened 60 patients for eligibility and analyzed only 49 of them who had completed treatment and follow-up assessment (Figure 2). Three patients in the rTMS group dropped out because of dizziness after several interventions, and four patients dropped out of the following intervention due to a lack of time to attend the intervention. In the sham rTMS group, one patient had a change condition so removed from the study and three patients refused to participate in the follow-up assessment.

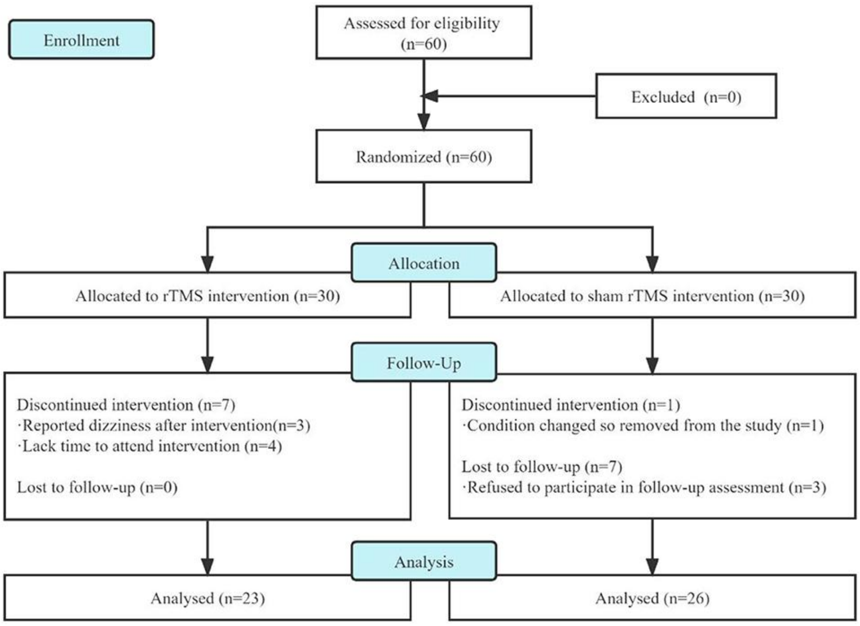


FIGURE 2. Participant flow diagram.

Table 1listed the means or medians of the baseline demographic and clinical characteristics of patients. Intergroup comparisons of baseline characteristics revealed no significant differences ($p > 0.05$, see Table 1). For the function assessment at baseline, no significant differences in the scores of MMSE, BADL, WST, SSA, FEDSS, PAS, and number of people with feeding tubes among the two groups were observed ($p > 0.05$, see Table 1).

Characteristic	Mean ± SD		P-value
	rTMS group	Sham rTMS group	
Age (years)	67.61 ± 11.71	67.73 ± 9.97	0.969
Sex (M: F)	17: 6	20: 6	0.807
Type of stroke (Hemorrhage: Ischemia)	4: 19	5: 21	0.868
Affected hemisphere (Left: Right: Bilateral)	8: 8: 7	13: 10: 3	0.242
Duration of onset of stroke (days)	74.17 ± 88.20	63.38 ± 59.48	0.888
Hypertension, No. (%)	22 (95.7)	22 (84.6)	0.203
Hyperglycemia, No. (%)	14 (60.9)	10 (38.5)	0.117
MMSE	16.96 ± 8.65	15.12 ± 8.00	0.443
BADL	45.00 ± 26.59	49.42 ± 25.43	0.555
WST	4.17 ± 0.89	4.04 ± 0.82	0.541
SSA	29.35 ± 3.83	27.46 ± 3.35	0.141
FEDSS	4.22 ± 1.00	4.27 ± 1.04	0.909
PAS	4.57 ± 1.31	4.58 ± 1.98	0.759
Feeding tube intake status, No. (%)	12 (52.2)	12 (46.2)	0.674

M, male; F, female; MMSE, Mini-Mental State Examination; BADL, Modified Barthel Index; WST, Water Swallowing Test; SSA, Standardized Swallowing Assessment; FEDSS, Fiberoptic Endoscopic Dysphagia Severity Scale; PAS, Penetration-Aspiration Scale.

TABLE 1. Baseline demographic and clinical characteristics.

Swallowing Function Assessments

There was no significant difference observed in the FEDSS score, PAS score, and SSA score at 2 weeks after baseline between the rTMS group and sham rTMS group (all P > 0.05, see Table 2). By contrast, in comparison with the baseline characteristics, two groups exhibited significant improvement across all swallowing assessments 2 weeks after baseline (all P < 0.001, see Table 2). There was also a significant difference between the rTMS group and sham rTMS group in the rate of change in FEDSS score (P = 0.018) and PAS score (P = 0.004), except for SSA score (P = 0.067, see Table 2).

	Mean ± SD		P-value
	rTMS group	Sham rTMS group	
SSA			
Pre	29.35 ± 3.83	27.46 ± 3.35	0.141
Post	25.57 ± 4.34	24.92 ± 3.88	0.587
The rate of change (%)	−13.09 ± 6.67	−9.33 ± 7.29	0.067
P-value	<0.001	<0.001	
FEDSS			
Pre	4.22 ± 1.00	4.27 ± 1.04	0.909
Post	2.65 ± 1.11	3.19 ± 0.98	0.073
The rate of change (%)	−38.26 ± 17.40	−25.13 ± 17.17	0.018
P-value	<0.001	<0.001	
PAS			
Pre	4.57 ± 1.31	4.58 ± 1.98	0.759
Post	2.83 ± 1.47	3.46 ± 1.66	0.105
The rate of change (%)	−39.48 ± 15.95	−23.65 ± 18.57	0.004
P-value	<0.001	<0.001	

SSA, Standardized Swallowing Assessment; FEDSS, Fiberoptic Endoscopic Dysphagia Severity Scale; PAS, Penetration-Aspiration Scale.

TABLE 2. The inter-group comparisons of clinical scale scores after the intervention, the intra-group comparisons of clinical scale scores for each group, and inter-group comparisons of the rate of change in clinical scale scores after intervention.

In the rTMS group, 11 patients pull out the feeding tube successfully after intervention and 10 in the sham rTMS group, which had no significant difference in the removal rate of the feeding tube between groups (P = 0.355, see Figure 3). However, there was a significant difference in feeding tube intake status compared with the baseline characteristics in both groups (PrTMS < 0.001, PshamrTMS = 0.002, see Figure 3).

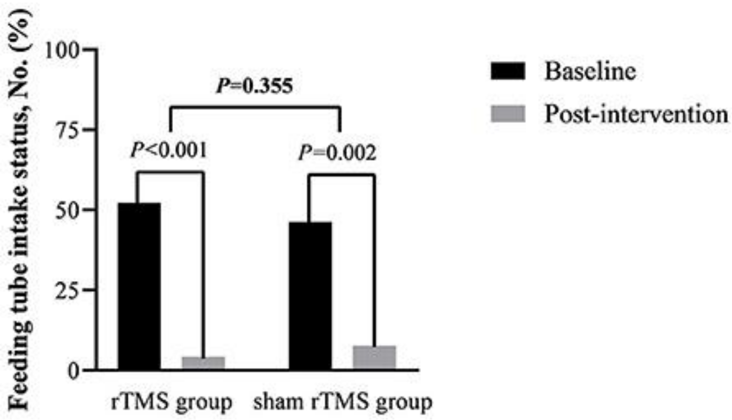
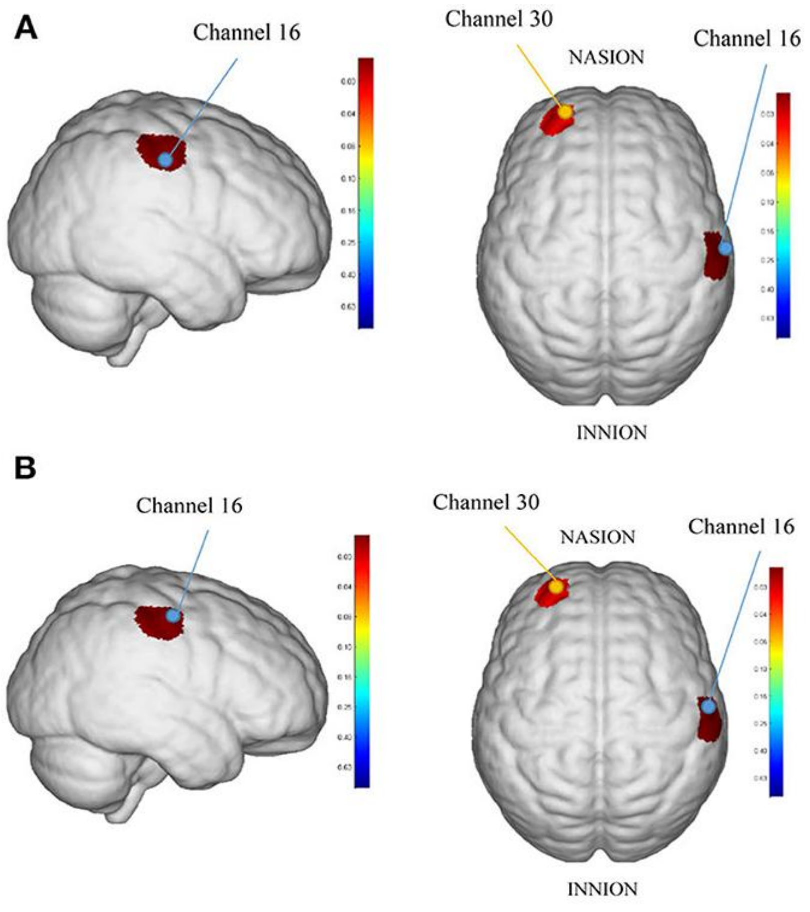


FIGURE 3. Feeding tube intake status, No. (%).

Cortical Activation Analysis of fNIRS Measurements

Intergroup analyses for baseline beta value collection from each brain area between the rTMS group and the sham rTMS group revealed no significant differences (P > 0.05). Following the intervention, the block average result revealed significant differences in brain areas RPFC and RMC between the rTMS group and the sham rTMS group: channels 30 (T = 2.05, P = 0.046) and 16 (T = 2.87, P = 0.006). After intervention, however, there was no significant difference in block differential between the rTMS group and the sham rTMS group (P > 0.05). The beta values of HbO2 before and after intervention for each channel in the rTMS group and Sham rTMS group are provided in Supplementary Table S2 in Supplementary Information, and Figure 4 shows the group analysis cortical maps.



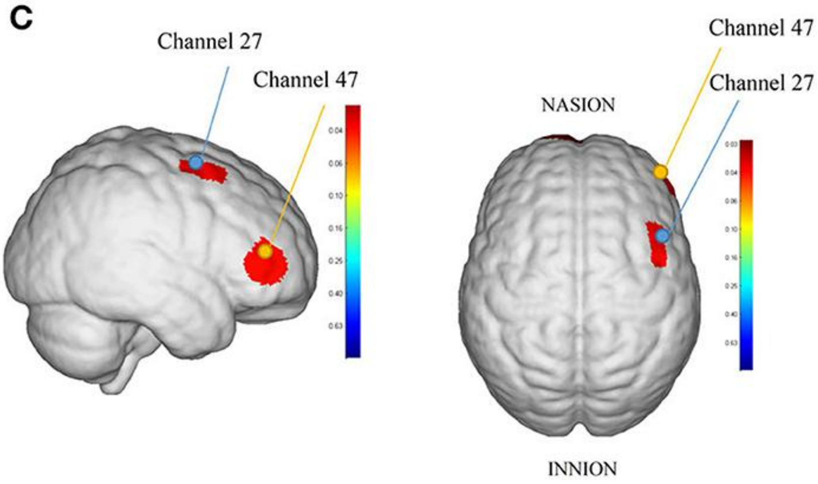
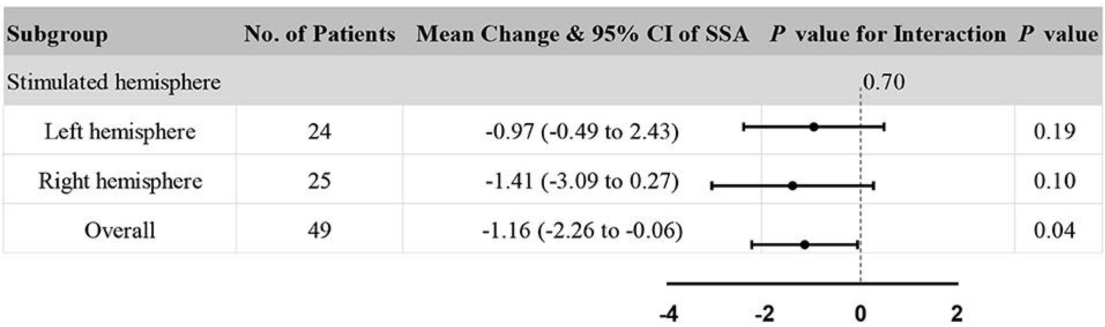


FIGURE 4. The cortical maps based on analyzed HbO2 beta values: **(A)** was the result between rTMS group and sham rTMS group in block average, **(B)** was the result between the right-rTMS group and sham right-rTMS group in block average, and **(C)** was the result between baseline and post-intervention in block differential in the right-rTMS group. The redder color indicates the higher beta value of the channel and the bluer color indicates the lower beta value of the channel.

Subgroup Analysis

We divided the fNIRS findings into left and right and found no difference in block average and block differential after intervention between the left-rTMS group and the sham left-rTMS group. In contrast, the differences in the brain areas RPFC and RMC between the right-rTMS group and the sham right-rTMS group were statistically significant in block average: channels 30 (T = 2.34, P = 0.028) and 16 (T = 2.54, P = 0.018, see Figure 4). There was no difference in HbO2 beta collection from each brain area after the intervention in the left-rTMS group compared to baseline, but in the right-rTMS group, channels 27 (T = 2.18, P = 0.039) and 47 (T = 2.17, P = 0.039) displayed significance in block differential (see Figure 4). In the sham rTMS group, neither sham left-rTMS group nor sham right-rTMS group had significant differences in block average and block differential in each brain area after intervention (P > 0.05).

Accordingly, stimulated hemisphere subgroup analysis in clinical assessments was also performed to explore the consistency of the results. The subgroup analysis showed no significant heterogeneity in the stimulated hemisphere (P = 0.70 for interaction, see Figure 5). In addition, the rTMS group and sham rTMS group had no significant difference in both the stimulated left hemisphere and the right hemisphere (all P > 0.05). Besides, compared to the overall effect (P = 0.04), rTMS therapy appeared to have a diminished effect on improving SSA scores, either in the left or right hemisphere.



Subgroup	No. of Patients	Mean Change & 95% CI of SSA	*P* value for Interaction	*P* value
Stimulated hemisphere			0.70	
Left hemisphere	24	-0.97 (-0.49 to 2.43)		0.19
Right hemisphere	25	-1.41 (-3.09 to 0.27)		0.10
Overall	49	-1.16 (-2.26 to -0.06)		0.04

FIGURE 5. The subgroup analysis of stimulated hemisphere. P-value is not adjusted by covariates.

The correlation between HbO2 change in each brain area and improvement of SSA

According to the linear regression analysis, the regression equation is not significant in the rTMS group (F = 2.161, p = 0.102) or the sham rTMS group (F = 0.288, p = 0.936). The regression analysis produced an adjusted R square of 0.240 in the rTMS group and 0.206 in the sham rTMS group, as well as p-values more than 0.05 for all channels. Furthermore, the tolerance findings were 0.2, indicating that the model could not explain the variance in the SSA improvement.

Safety and Compliance

No serious adverse events or complications were reported during the study. Two patients in the rTMS group reported dizziness after several rTMS interventions. No patients developed seizures during or after therapy.

IV. Discussion

We used fNIRS to compare blood oxygenation levels in swallowing in stroke patients with dysphagia after rTMS therapy to patients after sham rTMS therapy, as well as the effect of 5 Hz rTMS stimulation of the afflicted mylohyoid cortical region. Furthermore, we attempted to investigate the effect of rTMS on brain activation in dysphagia patients with various lesion sides. We discovered changes in cortical activity following rTMS therapy between the rTMS group and the sham rTMS group. After the intervention, the rTMS group demonstrated a substantially greater difference in cortical activation in relevant swallowing motor regions than the sham rTMS group. Furthermore, after the intervention, the rTMS group demonstrated a difference in brain activation. Patients with dysphagia who received left-side rTMS therapy had no change in cortical activation during swallowing after the intervention. Patients with dysphagia who received right-side rTMS therapy, on the other hand, had increased right-side cortical activation during swallowing activities after the intervention. For clinical swallowing function tests, our findings demonstrate that 5-Hz rTMS treatment of the afflicted hemisphere and standard dysphagia treatment can improve post-stroke dysphagia. The difference in clinical efficacy improvement was greater in the rTMS group against the sham rTMS group (P 0.05). Hence, we could show that rTMS applied in the affected mylohyoid cortical region can enhance swallowing function and swallowing motor-related cortical activation in patients with dysphagia after stroke.

CLINICAL ASSESSMENTS

The current study's findings show that rTMS is possible in stroke patients with dysphagia. This finding is consistent with the findings of Liao et al. (48) and Pisegna et al. (49) who found that rTMS improved swallowing function recovery after stroke. High-frequency stimulation of the damaged hemisphere increases cortical excitability, whereas low-frequency stimulation of the unaffected hemisphere decreases cortical excitability (50). Hummel et al. (51) discovered that persons with brain injuries have large interhemispheric imbalances, which may be alleviated by rTMS stimulation, which affects cortical excitability. Furthermore, Gow et al. (52) discovered that 5 Hz rTMS over the swallowing cortex increases cortex excitability. This study was based on the hypothesis that a high-frequency stimulation to the affected hemisphere increases the excitability of this hemisphere and these changes were likely to lead to increases in cerebral blood flow that ultimately would translate into swallowing improvement.

The Block Average Results of fNIRS

Importantly, we used a multi-channel fNIRS device to monitor cerebral blood flow as an evaluation of rTMS intervention in this work. The rTMS group revealed significant differences compared to the sham rTMS group, and the rTMS group showed higher activation in relevant motor regions after rTMS therapy than the sham stimulation group. We discovered significant variations in channels 16 and 30. Channel 16 was in the RMC and was based on the international 10-20 system, while channel 30 was in the LPFC.Previous studies investigated the brain activation patterns related with active swallowing. Using multichannel fNIRS, Kyoko's study (27) discovered extensive cortical activation in 15 healthy subjects during volitional swallowing, including bilateral anterior central gyrus, anterior central gyrus, inferior frontal gyrus, superior temporal gyrus, superior temporal gyrus, and superior temporal gyrus, which was consistent with the findings of Kern's study (8) using fMRI. The extent of cortical activation in healthy persons was the same as in Martin's study (53), but the activated signal of the inferior frontal gyrus was the greatest. Xurui Liu's (54) study showed that the concentration of oxyhemoglobin (HbO2) fell during stimulation and then increased at varied stimulation frequencies. The result is the same as our results which showed that the prefrontal lobe may be involved in swallowing and rTMS therapy can alter cortical excitability.

The Block Differential Results of fNIRS

Previous research indicated that oxy-Hb peaked 15 seconds after task onset in healthy participants (30). However, most patients with dysphagia may take up to 4 to 6 seconds to complete the job, whereas healthy people can swallow in 1 second. Furthermore, as a result of the stroke, blood flow would initially be altered in the lesioned hemisphere, which may impact hemodynamic response assessments. As a result, we compared the difference, which is defined as the difference between patients' resting states following stroke and swallowing tasks. Our findings revealed that there was no change in block differential results after dysphagia patients had left-side rTMS therapy. On the contrary, individuals with dysphagia who received right-side rTMS therapy had greater changes in right-side cortical activation after the intervention. Furthermore, there were changes in right hemisphere activation between the rTMS and sham rTMS groups.

This could be connected to brain activity patterns during swallowing. Previous research has demonstrated primarily bilateral patterns of cortical activation during swallowing, with no evidence of lateralization (26). Recent research, however, suggests that one or the other hemisphere may be dominant in humans following brain trauma. According to Hamdy's study (55), many brain regions are activated asymmetrically during swallowing, most notably the right insula and left cerebellum. Jiahui Tai et al. (56) used fNIRS to identify 22 healthy persons conducting a swallowing task and discovered considerable hemisphere asymmetry in brain activation. It has also been demonstrated that hemisphere dominance appears to differ depending on the swallowing task in some subjects (57). Gallas et al. (58) studied mylohyoid motor evoked potentials (MHMEPs) in stroke patients with or without swallowing problems, determining a dominant hemisphere and presenting evidence for asymmetry in the mylohyoid cortical region of the brain. Kober et al. (30) discovered that dysphagia patients with right hemisphere injuries are more likely to have unilateral patterns of activity during swallowing, which our fNIRS findings support.

However, subgroup analysis of the stimulated hemisphere revealed no significant variation in SSA scores in the stimulated hemisphere ($P = 0.70$ for interaction, see Figure 3). The findings were consistent with a prior review, which identified no significant variations depending on the stimulation site (59). Because both cerebral hemispheres may be involved in swallowing, activating either hemisphere may improve swallowing function. Many prior investigations using fMRI, magneto encephalography (MEG), and fNIRS show that multiple brain areas were active in healthy people during swallowing (26, 60, 61). Previous evaluations have revealed that rTMS therapy in dysphagia can improve swallowing function, whether stimulating the healthy hemisphere, the afflicted hemisphere, or both hemispheres (48, 49). Despite the fact that the rTMS site in our study was on the afflicted hemisphere, there was a significant difference in the block average of both channel 30 and channel 16 in the fNIRS of the rTMS group after the intervention compared to the sham rTMS group. Channel 30 was found in the left prefrontal cortex, while channel 16 was found in the right primary motor cortex, as well as the pre-motor and supplementary motor cortex. If the alterations in channels 30 and 16 found in our work are the result of rTMS, we might hypothesize that high-frequency rTMS stimulation increases cortical activation. In stroke patients with right hemisphere injuries, a recent study discovered a substantial increase in oxy- and deoxy-Hb during swallowing in the damaged hemisphere.

The healthy hemisphere, on the other hand, was less active during swallowing (30). However, just two cases of patients were described in this investigation, and larger-sample studies are still needed. High-frequency rTMS has been shown to raise cortical excitability in the stimulated afflicted hemisphere, which improves motor performance by increasing cerebral blood flow (62, 63). Furthermore, an increase in brain activation in the unaffected hemisphere has been linked to the normal recovery of swallowing after a stroke. Handy et al. (64) reported that patients with dysphagia have lower pharyngeal responses on the unaffected hemisphere than those who can swallow normally after studying the projections from both hemispheres to the swallowing muscles in a large group of patients with pure unilateral stroke. As a result, it is probable that the bilateral cerebral hemispheres play a role in swallowing, and that this may be related to interhemispheric changes in brain morphology, which alters the effects of rTMS. This could explain why rTMS affects diverse cortical areas by regulating cerebral blood flow and reorganizing neural networks.

Given the importance of the intact hemisphere in the recovery of swallowing after stroke, we have a unique chance to explore the plasticity of a normal route. Giovanni et al. (65) previously suggested a bimodal balance-recovery model that links interhemispheric balancing and functional recovery to the structural reserve spared by the lesion. One underlying mechanism for such a model could be a decision between an interhemispheric competition model and a vicariation model of motor recovery after stroke, which leads to the best NIBS therapies suited to individual patients' needs. According to our findings, future high-frequency rTMS therapies to improve swallowing function recovery after stroke may seek to manipulate reorganization on the afflicted side.

Because of the small sample size, the HbO2 change in each brain area was not linked with SSA improvement in the current investigation. Due to the small sample size, we did not perform the linear regression analysis using the change in HbO2 at each brain area as the explanatory variable, instead using the change in HbO2 at each channel. Furthermore, we believed that the identification of explanatory factors was complicated due to the large channel distribution. As a result, bigger sample sizes are required for future correlation research. Although still in its early stages, the use of NIBS and non-invasive neuroimaging techniques to act on or monitor cortical regions is becoming more common. LTP, LTD, changes in cerebral blood flow, enzyme activity, interactions between cortical and subcortical structures, and gene expression may be changed during NIBS therapy and benefit standard therapy (66). In patients with brain damage or neurological disease, fNIRS and other non-invasive neuroimaging techniques can be utilised to evaluate aberrant cortical activation during swallowing and other actions. We can completely grasp the patient's brain mechanisms that choose the appropriate NIBS therapies tailored to them after repeated use of fNIRS or other non-invasive neuroimaging techniques in patients, as was recently done in swallowing.We can completely grasp the patient's brain mechanisms that choose the best NIBS interventions matched to the needs of specific patients after repeated use of fNIRS or other non-invasive neuroimaging techniques in patients, as was recently done in swallowing. Researchers and therapists might imagine how these strategies could be used to improve the effectiveness of established therapies. However, a large number of investigations using neuroimaging and neuro-modulation in clinical research with patients are needed before this technique can be tested and implemented.

Limitations

This research has certain drawbacks. Because of the small sample size, patients with ischemic and hemorrhagic strokes, oral phase swallowing issue, and pharyngeal phase swallowing disorder were put together, despite the fact that these conditions could impair recovery. Unfortunately, recent studies have been unable to overcome this limitation. Second, the stimulation coil was hand-fixed due to a lack of sham coil, which is insufficient blinding. Third, we did not regulate the amount of saliva swallows for each patient or record the precise saliva swallow times for each patient during fNIRS, which may have influenced HbO2 variations. Finally, the use of several fNIRS characteristics as feedback signals, such as oxy-Hb, deoxy-Hb, beta values, and slope values, would be beneficial. Finally, a more valuable experiment would be to use different fNIRS parameters as feedback signals, such as oxy-Hb, deoxy-Hb, beta values, and slope values. This would allow us to see if other parameters will produce different outcomes. As a result, future research must process these subgroups and utilize larger samples to establish the potential benefits of fNIRS and NIBS swallowing intervention for dysphagia patients, as well as use more accurate experimental equipment to reduce experimental error and bias.

V. CONCLUSION

The current investigation confirmed that 5-Hz rTMS at the afflicted mylohyoid cortical region is viable in post-stroke patients with dysphagia, and that rTMS therapy can modulate cortical excitability. According to prior research, swallowing has a dominant hemisphere, and the results of our fNIRS investigation appeared to demonstrate a greater increase in cortical activation on the right side than on the left after rTMS of the afflicted mylohyoid cortical region. In the subgroup analysis, however, there was no difference between the left and right hemispheres. Nonetheless, the current work presents a novel and viable way of using fNIRS to assess dysphagia in stroke patients.

ETHICS STATEMENT

The studies involving human participants were reviewed and approved by the Ethics Committee of the First City Hospital of Poltava, Ukraine. The patients/participants provided their written informed consent to participate in this study.

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CONFLICT OF INTERESTS

The authors declare that the research was conducted in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest.

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