



Increased cortical-medulla functional connectivity is correlated with swallowing in dysphagia patients with subacute infratentorial stroke

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ABSTRACT

Patients with infratentorial stroke (IS) exhibit more severe dysphagia and a higher risk of aspiration than patients with supratentorial stroke. Nevertheless, a large proportion of patients with IS regain swallowing function within 6 months; however, the neural mechanism for this recovery remains unclear. We aimed to investigate possible neuroplastic changes involved using functional magnetic resonance imaging (fMRI) and their relation to swallowing function. We assessed 21 patients with IS (mean age: 59.9 ± 11.1 years) exhibiting dysphagia in the subacute phase and 21 healthy controls (mean age: 57.1 ± 7.8 years). Patient evaluations were based on the functional oral intake scale (FOIS), videofluoroscopic swallow study (VFSS), and fMRI. Temporal swallowing measures and the penetration-aspiration scale (PAS) were obtained using VFSS. Whole-brain–medulla resting-state functional connectivity (rsFC) was calculated and compared between patients and healthy controls. The rsFCs were also correlated with functional measures within the patient group. In patients with IS, whole-brain–medulla rsFCs were significantly higher in the precuneus, the left and right precentral gyrus, and the right supplementary motor area compared to those in healthy controls ($P < 0.001$, family-wise error-corrected cluster-level $P < 0.05$). The rsFCs to the medulla for the left ($r = -0.507$, $P = 0.027$) and right side ($r = -0.503$, $P = 0.028$) precentral gyrus were negatively correlated with the PAS. The rsFC between the left ($r = 0.470$, $P = 0.042$) and right ($r = 0.459$, $P = 0.048$) precentral gyrus to the medulla was positively correlated with upper esophageal sphincter opening durations (UOD). In addition, PAS was also correlated with UOD ($r = -0.638$, $P = 0.003$) whereas the laryngeal closure duration was correlated with the hyoid bone movement duration ($r = 0.550$, $P = 0.015$). Patients with IS exhibited overall modulation of cortical-medulla connectivity during the subacute phase. Patients with higher connectivities showed better swallowing performance. These findings support that there is cortical involvement in swallowing regulation after IS and can aid in determining potential treatment targets for dysphagia.

1. Introduction

Oropharyngeal dysphagia is a common symptom following stroke, with an incidence of 30–78% (Martino et al., 2005; Meng et al., 2020; Takizawa et al., 2016). The severity of dysphagia is closely related to the location of the lesion (Wilmskoetter et al., 2020). Infratentorial stroke (IS¹) leads to more severe symptoms, including increased pharyngeal remnants and a higher score on the penetration aspiration scale (PAS)

than supratentorial stroke (Kim et al., 2019). Physiological and anatomical findings agree with the pathophysiology, because swallowing-related neurons, including the dorsal and ventral swallowing groups, are concentrated in the brainstem region (Jean, 2001). Further, the pontine area has been found to be bundled with corticobulbar projections (Urban et al., 2001). Given the importance of infratentorial regions in swallowing regulation, a lesion in this area may lead to rather resistant swallowing dysfunction (Teasell et al., 2002). Despite

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¹ AAL - automated anatomical atlas, DMN - default mode network, FC - functional connectivity, FOIS - functional oral intake scale, HMD - hyoid bone movement duration, ICC - intraclass coefficient reliability, IS - infratentorial stroke, LCD - laryngeal closure duration, LSMN - left sensorimotor network, MEP - motor evoked potentials, MNI - Montreal Neurological Institute, NIHSS - National Institute of Health stroke scale, OTT - oral transit time, PAS - penetration-aspiration scale, rsFC - resting state functional connectivity, STD - stage transition duration, TMS - transcranial magnetic stimulation, UES - upper esophageal sphincter, UOD - upper esophageal sphincter opening duration, VFSS - videofluoroscopic swallow study.

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this, up to 88–95% of patients with IS recover adequate swallowing and no longer require tube feeding 4–6 months after the episode (Chun et al., 2017; Meng et al., 2000). However, in some patients, the rehabilitation process can last longer than 6 months. This prolonged course and severe risk of aspiration can potentially lead to aspiration pneumonia and be life-threatening. Therefore, elucidating the mechanism underlying neural recovery should be considered crucial to shorten treatment duration and improve long-term outcomes of rehabilitation therapy.

The cortical reorganization observed in patients with post-stroke dysphagia could underlie the recovery of swallowing. Both motor evoked potentials (MEPs) induced by transcranial magnetic stimulation (TMS) and MRI studies have revealed overactivation of the contralesional hemisphere in hemispheric stroke patients with dysphagia during the process of functional recovery (Hamdy et al., 1998; Li et al., 2009). IS patients with dysphagia may exhibit different neural changes compared to patients with hemispheric stroke. An fMRI study that included both hemispheric and brainstem stroke patients identified different plasticity mechanisms between the two groups. Changes in swallowing function were correlated with functional brain connectivity changes in the ventral default mode network (vDMN) of the precuneus in hemispheric stroke patients and in the left sensorimotor network (LSMN) of the left postcentral gyrus in brainstem stroke patients (Huang et al., 2018). However, only six brainstem stroke patients were included, and data regarding neural plasticity for dysphagia patients with IS are quite limited. Whether recovery relies on local reorganization within the infratentorial regions or the mobilization of the entire cortex–medulla swallowing network remains unclear.

The cited studies used fMRI analysis to investigate cortical participation in neural plasticity after stroke. However, not much is known about the involvement of the medulla and other infratentorial regions. A recently developed Bayesian algorithm for segmentation of the brainstem into separate structures, namely the midbrain, pons, medulla, and superior cerebellar peduncle, has improved the methodology considerably (Iglesias et al., 2015). Whole-brain voxel-wise functional connectivity (FC) with the medulla as a novel parameter has been assessed in patients with major depression, and the results revealed that FC between the inferior parietal cortex and the medulla may mediate the control of negative emotions (Luo et al., 2018). Resting-state FC (rsFC) measures temporal correlations between blood oxygenation level-dependent signals in a seed region and specified regions of interest (ROI) in the absence of specific stimulation (Biswal et al., 1995), allowing inferences about the distribution of cerebral functional networks. The rsFCs between different brain regions were found to be associated with, for example, post-stroke depression, aphasia, and motor functions (Egorova et al., 2017; Liu et al., 2015; Yang et al., 2016). Such observations of rsFCs correlating with behavioral outcomes have strengthened the idea that measures of network connectivity might be potential biomarkers for functional recovery. Given the medulla's role in the swallowing neural network of receiving ascending sensory input and relaying descending motor output, whole-brain voxel-wise rsFC with the medulla as a seed region is a prime candidate for exploring neural plasticity changes associated with swallowing recovery.

The cited TMS and MRI studies have primarily considered overall swallowing function, while this motor program is complex with a wide range of components regulated by a distributed neural network including both cortical and medullary contributions. Afferents from the oropharyngeal areas project to supra-medullary structures and to the medulla oblongata, contributing to voluntary modulation and initiation, as well as to the involuntary aspects of the pharyngeal swallow phase. The cerebral cortex orchestrates the swallowing response to external stimuli in the periphery (Rommel and Hamdy, 2016). Based on previous lesion-mapping studies, impairment in a number of cortical regions can cause problems with oral transit, swallowing initiation, and laryngeal closure (Wilmskoetter et al., 2020). For a detailed analysis of different functional elements of swallowing, the VFSS provides quantifiable biomechanical measures of underlying dysphagia symptoms such as

aspiration and pharyngeal remnants (Cabib et al., 2020; Kahrilas et al., 1997). One of the most widely used scales in VFSS analysis is the ordinal Penetration–Aspiration Scale (PAS), running from 1 to 8, with higher scores indicating more severe airway invasion (Rosenbek et al., 1996). Besides the PAS, detailed temporal measures of biomechanical characteristics of the swallowing reaction and muscular movement can be of value (Logemann et al., 2000).

In summary, unveiling the neuroplastic mechanism underlying the recovery of swallowing in patients with IS has been limited by the inherent shortcomings of the techniques used so far. To overcome some of these limitations, we aim to explore the brain–medulla rsFC, and how changes in these parameters associated with changes in different motor components of swallowing function among patients with IS. We then discuss whether functional connectivity should be considered as a biomarker for characterizing swallowing function recovery in future applications.

2. Materials and methods

2.1. Participants

2.1.1. Patient group

We included 23 consecutive inpatients at the rehabilitation department of the Third Affiliated Hospital of Sun Yat-sen University in the patient group that fulfilled the following criteria between March 2021 and November 2021: (a) first ever stroke in the infratentorial region, subacute phase (<6 months after stroke onset; Bernhardt et al., 2017), clinically confirmed by MRI or computed tomography; (b) oropharyngeal dysphagia manifested as impaired efficacy and/or safety during oropharyngeal swallowing confirmed by VFSS; (c) right-handed (d) no prior history of dysphagia caused by any neurological disease or by head and neck structural abnormality or damage; (e) no history of neuropsychological or psychiatric disorders; (f) no tracheostomy; and (g) ability to undergo VFSS and MRI examination.

Written informed consent was obtained from each participant before the MRI examination and clinical evaluations. For each patient, the following clinical characteristics were recorded during admission into the rehabilitation unit: age, sex, time since stroke onset, the National Institute of Health Stroke Scale, affected side, and lesion location. All patients were examined by the same speech-language pathologist on the day of evaluation to determine overall dysphagia severity using the FOIS. FOIS is a 7 points scale (levels 1–7) for assessing the capability for oral intake of food and liquid in stroke patients (Craty et al., 2005). This study was approved by the Ethics Committee of the Third Affiliated Hospital of Sun Yat-sen University (registration number [2021]02–005–01). Data for this paper were obtained from the baseline data of a randomized controlled trial (Trial registration number: ChiCTR2100051627).

2.1.2. Healthy control group

A cohort of 22 healthy individuals without neurological or severe psychiatric history was recruited. These age-matched controls were used to evaluate rsFC changes in the patient group. Relationships between neuroimaging and functional variables were only evaluated in the patient group. Written informed consent was obtained from all participants in accordance with the Declaration of Helsinki. The flowchart of the study is depicted in Fig. 1.

2.2. Videofluoroscopic swallow study (VFSS)

Patients underwent VFSS examination on the day of the MRI examination. Fluoroscopic .avi-videos were recorded at 30 frames/s using an VFSS collection and analysis system (Longest Inc., Guangzhou, China). Patients were asked to swallow two 5-mL of nectar thick liquid diluted as barium sulfate suspension at 60% weight-volume ratio. The mixtures were stirred and left to stand for 5 min before use. Syringes were used to

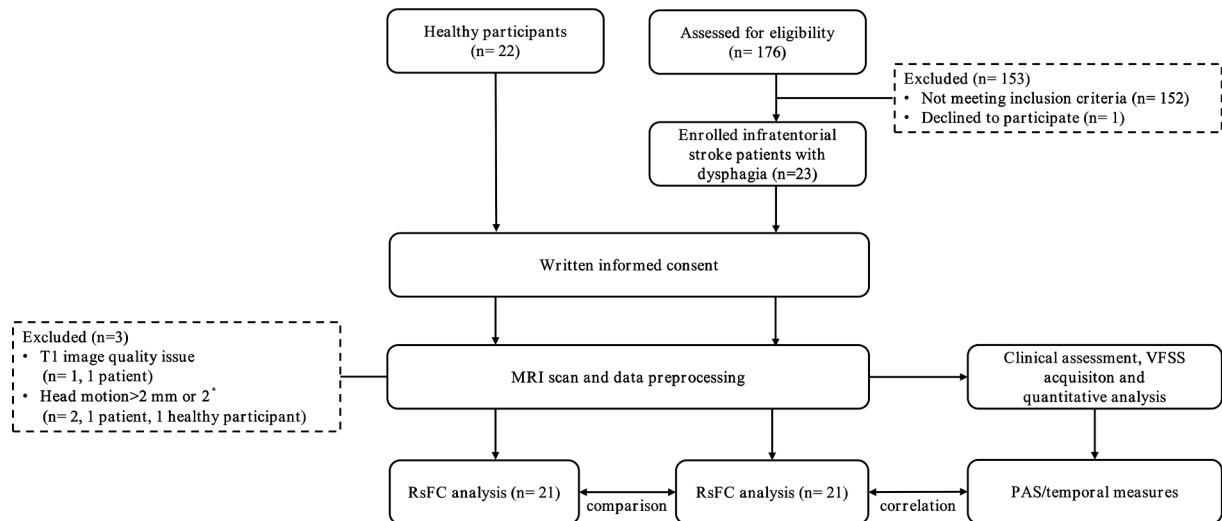


Fig. 1. Flowchart of the study. FOIS, functional oral intake scale; IS, infratentorial stroke; MRI, magnetic resonance imaging; PAS, penetration and aspiration scale; rsFC, resting-state functional connectivity; VFSS, videofluoroscopic swallow study.

measure the volume and introduce the bolus into the patients' oral cavity. Patients were asked to swallow as the stimulus was injected.

All videos were independently assessed by two experienced clinicians (D.M. and C.H.Y.) using the VFSS digital analysis system (Longest Inc., Guangzhou, China), which can play the video frame by frame. Penetration and aspiration scale (PAS) scores (Rosenbek et al., 1996) and all quantitative measures were averaged from the two swallows to better reflect overall swallowing capability. One rater performed all quantitative measures. Inter-rater reliabilities were determined on a random 20% of all swallowing tests through a rating by the second clinician. Both raters were experienced and established consensus on the analysis methods beforehand. Quantitative measures included oral transit time (OTT, Soares et al., 2015), laryngeal closure duration (LCD), hyoid bone movement duration (HMD), stage transition duration (STD) (Molfenter and Steele, 2014; Oommen et al., 2011), and upper esophageal sphincter (UES) opening duration (UOD, Kim et al., 2015). The abbreviations and the definition of starting and ending points for the temporal measures of VFSS are listed in Table 1.

2.3. Resting-state functional MRI

2.3.1. Data acquisition

Functional and structural imaging data were acquired using a 3.0 T

Table 1
Definition, starting and ending point of VFSS temporal measures.

Measure	Abbreviation	Starting point	Ending point
Oral transit time	OTT	The beginning of bolus shape change propelled by the tongue	Arrival of the bolus tail at the fauces
Stage transition duration	STD	Bolus head passing the ramus of the mandible	The onset of hyoid excursion
Laryngeal closure duration	LCD	First contact of the inferior surface of the epiglottis and the arytenoids	Last contact of the inferior surface of the epiglottis and the arytenoids
UES opening duration	UOD	Onset of UES opening	Bolus tail passing through UES and offset of UES opening
Hyoid bone movement duration	HMD	Onset of hyoid bone movement burst	Hyoid bone returns to rest

UES, upper esophageal sphincter.

Siemens Prisma fit MRI scanner (Siemens, Erlangen, Germany) with a 64-channel head coil. Field homogeneity was optimized by a shimming sequence. Functional echo planar images (EPI) were acquired with a gradient echo sequence (52 slices at 3 mm spacing, $3 \times 3 \times 3$ mm isotropic voxels, field of view [FoV] 240 mm, 80×80 matrix, repetition time (TR) 2 s, echo time (TE) 30 ms, flip angle 90° , 240 volumes acquired) to minimize geometric distortions. Slices were obtained in an oblique orientation to ensure coverage of the entire brain including the sensorimotor cortex, cerebellum, and brainstem. During the resting experiment, participants were instructed to relax with eyes closed, but to avoid falling asleep.

A three-dimensional (3D) high-resolution T1-weighted anatomical image was acquired for each participant (magnetization-prepared rapid gradient echo, TR 2530 ms, TE 2.27 ms, flip angle = 7° , FoV 256 mm, voxel size $1 \times 1 \times 1$ mm³, parallel acquisition using a k-space-based algorithm [GRAPPA] with acceleration factor 2, matrix 256×256 , sagittal orientation, 208 interleaved slices).

2.3.2. Data preprocessing

DICOM data were converted to NIFTI format using Dcm2nii (<https://www.nitrc.org/projects/dcm2nii/>). The resting-state fMRI data were also preprocessed using SPM12 (<https://www.fil.ion.ucl.ac.uk/spm/>) and RESTplus V1.22 (<https://www.restfmri.net>) within MATLAB 2013b. To avoid statistical errors, all scans were visually inspected before being preprocessed. The preprocessing steps included the following: (1) discarding the first 10 time points to achieve steady-state magnetization and enable all participants to adapt to the scanning noise; (2) slice timing correction for interleaved slice order; (3) correction for head motion; (4) normalization of images to reduce inter-individual variability and allowing meaningful group analyses by using T1 image unified segmentation, with bounding box $[-90, -126, -72; 90, 90, 108]$ and isotropic voxels of size 3 mm; (5) spatial smoothing by convolution of the 3D image with a 3D Gaussian kernel with a full width at half maximum of 6 mm. One patient and one healthy participant were excluded due to head motion > 2 mm or head rotation $> 2^\circ$ and one patient was excluded due to an issue with the quality of the T1-weighted image.

2.3.3. Lesion segmentation and mapping

Lesions were manually segmented using MRICron software (<https://www.nitrc.org/projects/mricron/>) by inspection of the T1-weighted structural images, simultaneously displayed in atlas space. The average lesion volume was 669.7 mm³ ($[171, 613]$ mm³; Table 2). To

Table 2
Patient demographics and clinical characteristics.

#	Age (years)	Sex	Lesion location	Affected side	Lesion size (mm ³)	Duration since stroke onset (days)	NIHSS	FOIS
1	64	M	Medulla	R	542	24	3	3
2	45	M	Medulla	R	142	51	3	3
3	26	M	Medulla	L	141	22	1	1
4	68	M	Pontine, cerebellum	L	714	96	5	1
5	69	M	Medulla	L	556	29	2	1
6	69	M	Cerebellum, medulla	R	320	145	1	1
7	64	M	Pontine, cerebellum	L	2373	85	9	1
8	63	F	Pontine	L	320	15	8	1
9	75	M	Medulla	R	445	158	2	1
10	55	M	Medulla	L	161	26	4	1
11	53	M	Cerebellum, medulla	R	437	97	6	2
12	67	M	Pontine	L	3244	16	17	3
13	60	M	Medulla	L	502	52	5	3
14	66	M	Medulla	R	181	28	6	3
15	53	F	Medulla	L	535	84	5	2
16	70	M	Medulla	L	116	83	2	1
17	71	M	Medulla	L	235	75	1	3
18	60	F	Medulla	L	2043	97	8	2
19	54	M	Medulla	L	142	55	5	3
20	50	M	Medulla	L	245	122	9	3
21	55	M	Medulla, cerebellum	L	670	108	7	2

F, female; FOIS, functional oral intake scale; L, left; M, male; NIHSS, National Institute of Health Stroke Scale; R, right.

create the lesion overlay map, all lesions of 21 patients were drawn manually and slice by slice on the anatomical images using MRIcron. Native-space T1-weighted images were skull stripped and nonlinearly registered to the Montreal Neurological Institute (MNI) probabilistic template (MNI152_T1_1mm_brain; <https://fsl.fmrib.ox.ac.uk>) using FLIRT and FNIRT in FSL (<https://fsl.fmrib.ox.ac.uk/fsl/fslwiki/>). The generated transform matrices were then used to normalize individual lesions to MNI space. The lesion overlap map (Fig. 2) shows the sum of the aligned binary lesion masks.

2.3.4. Whole-brain voxel-based resting-state functional connectivity

The medulla mask was extracted from a brainstem atlas based on a Bayesian approach to MRI segmentation (Iglesias et al., 2015). In this atlas, the brainstem was segmented into four subregions, the midbrain, pons, medulla oblongata, and superior cerebellar peduncle. The medulla mask included both sides of the medulla region in this atlas.

Whole-brain rsFC analysis (Jia et al., 2019) was performed using RESTplus after data were preprocessed as described above. Voxels in the medulla mask region were selected as seed points for the analysis. Time series for all voxels in this ROI were extracted and their average was calculated. Pearson's correlation coefficient was computed for each voxel in the whole brain relative to this average time series for the medulla. Finally, coefficients were converted to z-scores using Fisher's method to obtain the normally distributed z-rsFC map.

2.3.5. fMRI data statistical analysis

Thresholds of a voxel-wise $P < 0.001$ uncorrected and $P < 0.05$ family-wise error correction at the cluster level (minimum cluster size of 79 voxels) were applied for all analyses. Four spherical ROI (6 mm radius) centered at the peak MNI coordinate of the cortical region that showed significant differences between patients and healthy controls

were extracted. The rsFC of these four ROIs were further used in correlation analysis.

2.4. Statistical analysis

Statistical analysis was performed using SPSS (Version 26, IBM SPSS Statistics for Windows, IBM Corp., Armonk, NY, USA). One-sample Kolmogorov–Smirnov tests were used to determine normality for all parameters, including the rsFCs from the regions with significant inter-group differences, all parameters of videofluoroscopy, and the PAS scores. Values are reported as means \pm SDs or as percentages, where appropriate. To ensure the reliability of videofluoroscopic measures, an inter-rater reliability test was performed for two raters with intraclass correlation coefficients (ICCs). The ICC is based on a two-way random effects analysis of variance, as defined by Shrout and Fleiss (Shrout and Fleiss, 1979). We interpret ICCs and kappa coefficients below 0.4 as indicating poor agreement, 0.4–0.75 as good agreement, and above 0.75 as excellent agreement (Fleiss et al., 2003). Partial Spearman correlation (<https://www.ibm.com/support/pages/partial-rank-correlations-spss>) with age and sex as covariates was calculated between the rsFC data and quantitative swallowing measures. The threshold of significance was set at $P < 0.05$. For interpreting the strength of the correlation coefficient, 0.9–1.0 was considered very high, 0.7–0.9 was considered high, 0.5–0.7 was considered moderate, 0.3–0.5 was considered low and 0.0–0.30 was considered negligible (Mukaka, 2012).

3. Results

3.1. Demographic, clinical, and swallowing functional measures

Demographic and overall clinical evaluation results are presented in

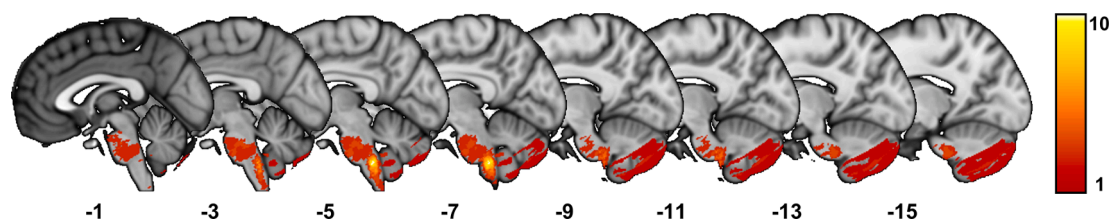


Fig. 2. Representative sagittal slices depicting the lesion overlay density maps of all IS participants ($n = 21$). Y-values shown at the bottom of each slice indicate the y-coordinates in MNI space. Different colors indicate the degree of lesion overlap.

Table 2. Data of 21 patients (mean age: 59.9 ± 11.1 [range: 26–75] years, 18 males, 3 females) and 21 healthy controls (mean age: 57.1 ± 7.8 [range: 42–69] years, 16 males, 5 females) were finally included. No significant differences were found in terms of age ($P = 0.37$) and sex ($P = 0.27$) between the patients and healthy controls. Fig. 2 shows the overlap between the lesion sites of all patients. The results of video-fluoroscopic analysis and ICC are presented in Table 3. OTT, STD, HMD, LCD, and UOD all showed high reliability between the two raters. The results from rater 1 were used for the correlation analysis.

We compared rsFC between patients and healthy controls. Significant differences arising from two-sample *t*-tests (between the two groups) of spatial map regions are presented in Fig. 3. The patient group exhibited significantly increased rsFC with the medulla in the precuneus, the left and the right precentral gyrus, and the supplementary motor area. No cluster showed significantly reduced rsFC in patients compared to the healthy controls.

3.2. The rsFC differences between patients and controls and correlation with functional measures

Four clusters showed significantly higher rsFC in IS patients than in healthy controls. The peak coordinates of the four clusters located in the precuneus, the left and right precentral gyrus, and the right supplementary motor area according to the automated anatomical atlas (AAL). The results are shown in Fig. 3.

The rsFC between the medulla and the left ($r = -0.507$, $P = 0.027$) and right ($r = -0.503$, $P = 0.028$) precentral gyrus showed a moderate negative correlation with PAS and a low positive correlation with UOD (left $r = 0.470$, $P = 0.042$; right $r = 0.459$, $P = 0.048$). We also found a moderate negative correlation between PAS and UOD ($r = -0.638$, $P = 0.003$), and a moderate positive correlation between LCD and HMD ($r = 0.550$, $P = 0.015$). The correlation matrix and scatter plots are shown in Fig. 4.

4. Discussion

In this cross-sectional study, dysphagia patients with subacute IS exhibited enhanced FC between the cortex and the medulla in the precuneus, in the left and right precentral gyrus, and in the right supplementary motor area. rsFC of both sides of the precentral gyrus to the medulla was negatively correlated with PAS and positively correlated with UOD, suggesting that patients with stronger functional connections between the precentral gyrus and the medulla have a lower risk of penetration and aspiration and present with longer UODs. These correlations suggest that the shift in FC values for these regions may be related to neural plasticity changes following IS. We believe that this is the first study to use rsFC based on the segmented atlas of the brainstem to explore neuroimaging measures' relation to swallowing behavior in dysphagia patients with IS.

Table 3

VFSS quantitative measures and results of inter-rater reliability intraclass correlation coefficient.

Measures	Main results from rater 1	ICC
PAS	2.69 (1.28)	0.705–0.951
OTT (ms)	2563.405 (1597.7566)	0.901–0.932
STD (ms)	315 [7.5, 915]	0.931–0.988
HMD (ms)	957.48 [655, 1125]	0.925–0.974
LCD (ms)	581.5 (514.30)	0.954–0.982
UOD (ms)	279.43 [0, 463]	0.911–0.945

ICC, intraclass coefficient reliability; HMD, hyoid bone movement duration; LCD, laryngeal closure duration; OTT, oral transit time; PAS, penetration and aspiration scale; STD, stage transition duration; UOD, upper esophageal sphincter opening duration.

4.1. Increased functional connectivity between cortex and medulla in patients with infratentorial stroke

We found four cortical regions that showed significantly higher rsFC with the medulla in patients when compared to controls. This agrees with other recent findings. Increased FC has been identified in various patient groups with functional deficits after stroke (Liu et al., 2015). It has also been found that voxel-mirrored homotopic connectivity in the pre- and postcentral gyrus increased from day 90 in pontine infarction patients (Shan et al., 2018). FC between the primary motor region (M1) and the contralateral hemisphere has also been shown to be increased in stroke patients compared with controls (Almeida et al., 2017).

Other studies found decreased FC in patients with IS. Patients with acute ischemic brainstem strokes showed significantly decreased FC in the right medial prefrontal cortex and right precuneus within the anterior and posterior default mode network (DMN) (Jiang et al., 2018). Reduced FC within the DMN and between the DMN, executive control network, the salience network, auditory network, and cerebellum were found in patients with acute brainstem ischemic strokes compared to healthy controls. These FC changes were also correlated with measurements of upper limb dysfunction (Geng et al., 2021).

FC changes varied in previous studies, which may be related to different modes of recovery from stroke. Functional and anatomical connections may be directly impaired after a stroke, leading to decreased FC during the acute phase that is reflective of functional loss. In patients with decreased FC between executive control, sensorimotor, and visuospatial networks, overall post-stroke functions have been found to be impaired (Almeida et al., 2017). Dysphagia in hemispheric stroke patients has been related to dysfunctional connectivity among large-scale brain networks in the sensorimotor-insula-putamen circuits and bilateral brain regions related to swallowing (Li et al., 2014).

In contrast, the increased FC in patients with IS may suggest compensatory mechanisms. We found multiple cortical regions with increased FC to the medulla and found these changes to be correlated with different aspects of oropharyngeal swallowing functions, suggesting that the underlying neural plasticity may compensate for functional losses.

4.2. Post-stroke neural plasticity aiding dysphagia recovery

Cortical reorganization is important for the recovery of swallowing function, regardless of the location of the lesion. In hemispheric stroke patients who had recovered from dysphagia, TMS-induced MEP was found to have increased in the area of the pharyngeal representation of the undamaged hemisphere (Hamdy et al., 1998). A fMRI study focused on dysphagia patients in the subacute phase after a brainstem stroke reported that changes in FOIS were related to changes in functional brain connectivity in the sensorimotor network of the left postcentral region (Huang et al., 2018). Network changes related to functional changes in swallowing differed between patients with hemispheric and those with brainstem strokes. Our results are consistent with this study since the left and right precentral gyrus and the right supplementary motor area belong to the sensorimotor network (Smith et al., 2009).

Whole-head magnetoencephalography (MEG) in 8 patients in the early subacute phase after a unilateral brainstem stroke (5 with dysphagia and 3 without) found strong lateralization to the right hemisphere (Teismann et al., 2011). The authors hypothesized early onset compensatory cortical activation on the right side independent of the side of the lesion. We, on the other hand, have found increased cortical FC with the medulla bilaterally. In an fMRI study of normal subjects, dominance was found in both hemispheres for the swallowing task (Mosier et al., 1999). Lesion-symptom mapping also has revealed variations in the hemispheric lateralization of swallowing (Wilmskoetter et al., 2020). These findings all support the notion that compensation for impaired swallowing after an infratentorial stroke can occur bilaterally.

Physiologically, both sides of the cortex project to the medulla

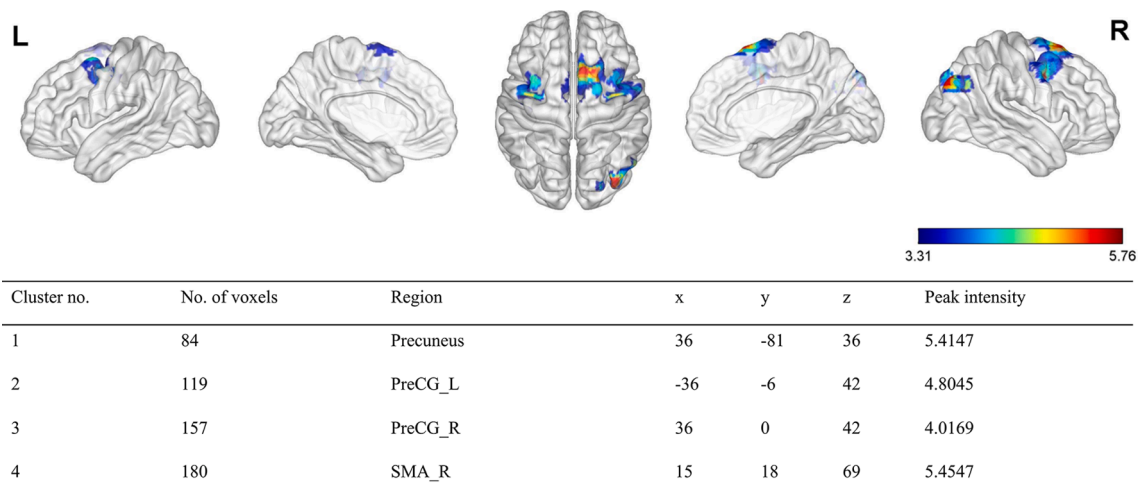


Fig. 3. Altered functional connectivity among patients with infratentorial stroke. PreCG_L, left precentral gyrus; PreCG_R, right precentral gyrus; SMA_R, right supplementary motor area.

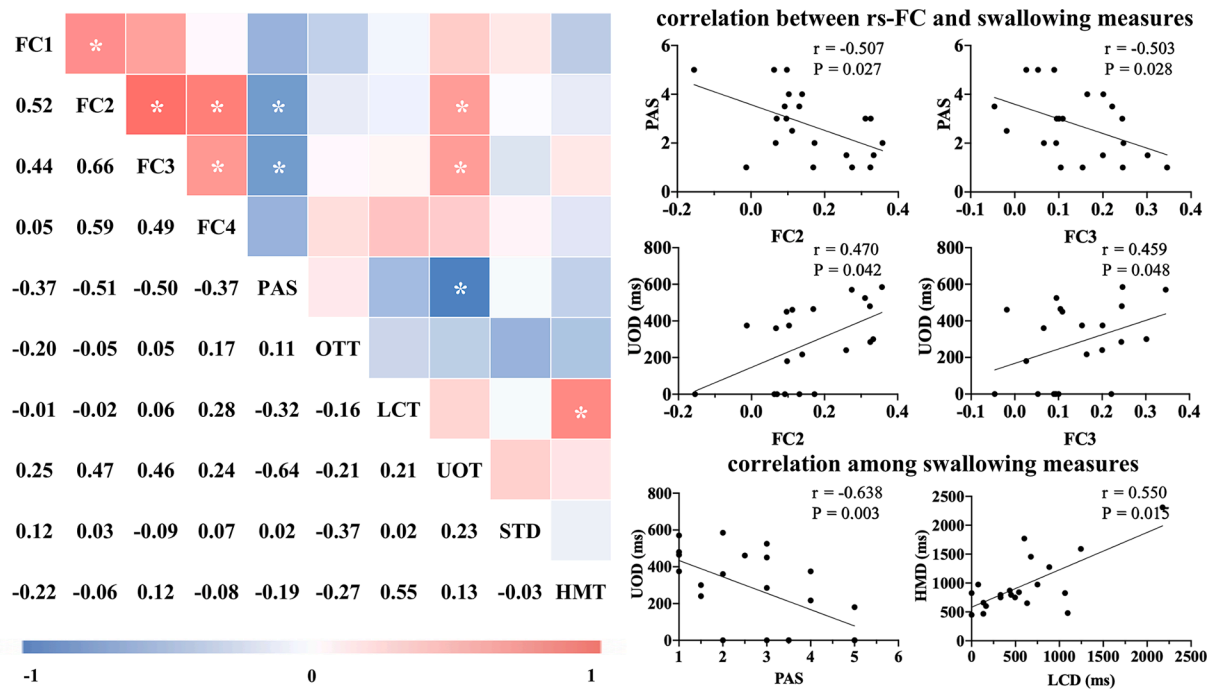


Fig. 4. Spearman correlation matrix between resting-state functional connectivity to the medulla and VFSS functional measures. FC, functional connectivity (FC1 - zFC extracted from the precuneus ROI, FC2 - zFC extracted from the left precentral gyrus ROI, FC3 - zFC extracted from the right precentral gyrus ROI, FC4 - zFC extracted from supplementary motor area ROI); OTT, oral transit time; PAS, penetration and aspiration scale; UOD, upper esophageal sphincter opening duration; * P < 0.05.

through the bilateral corticobulbar tract (Im et al., 2020), allowing the FC to be shifted to one side of the medulla after a lesion occurs. However, previous research did not demonstrate sufficient evidence of such network changes following IS. Our study used an rs-fMRI approach to explore how the whole brain modulates in IS patients with dysphagia and these cortical changes may potentially be the neural compensating changes related to dysphagia.

4.3. Cortical involvement in swallowing function regulation among patients with infratentorial stroke during the subacute phase

We found that the overall PAS score was negatively correlated with rsFC between the medulla and the left and right precentral gyri,

suggesting lower risk of penetration or aspiration in patients with higher rsFC in these two regions. The precentral gyrus has been found to be associated with pharyngeal swallowing in several MRI studies. Prominent and consistent activation of the precentral gyrus has been found in healthy participants in both automatic and volitional swallowing tasks (Wilmkskoetter et al., 2020). Lesion-mapping in stroke patients found that lesions in the primary sensorimotor cortex can present as an impaired laryngeal elevation and closure (Suntrup-Krueger et al., 2017) or as impairments in laryngeal elevation and vestibular closure (Wilmkskoetter et al., 2020). Laryngeal elevation and closure is an important mechanism in airway protection. Based on these findings, our initial hypothesis was that the precentral gyrus may intervene in regulating laryngeal closure and affect the risk of penetration and aspiration.

However, no further correlation was found in either LCD or FC. This may simply be due to the sample size. Another possibility is that aspiration could only be prevented with better laryngeal closure—pharyngeal transportation coordination rather than LCD. Therefore, LCD may not be the only parameter for estimating aspiration risk.

In summary, the precentral gyrus is a key cortical region associated with pharyngeal swallowing and is involved in regulating laryngeal elevation and closure. Increased FC between the precentral gyrus and the medulla is negatively correlated with the severity of aspiration, suggesting an important role for the precentral gyrus in the neuroplastic regulation of pharyngeal swallowing, making this area a potential target for treating aspiration after IS.

In the current study, 6 out of 21 patients showed failed opening of the UES. This conforms to typical manifestations of infratentorial stroke, as impaired UES opening was found to be related to lateral medullary infarctions (Yang et al., 2018). Our correlation analysis also revealed that patients with higher FC between the bilateral precentral gyrus and the medulla showed longer durations of UES opening. UES opening is a complex process that can be impacted by multiple factors, including hyolaryngeal excursion, UES tonicity, neural relaxation, and even the viscosity of the bolus (Kim et al., 2015). Relaxation of the UES is mainly composed of two distinct events: (1) cessation of tonic discharges on the cricopharyngeus muscle by the motor neurons of the nucleus ambiguus and (2) anterior and superior lift of the UES by the contraction of the suprahyoid muscles (Mittal, 2011). The nucleus ambiguus fundamentally controls UES motility. Bilateral TMS stimulation of the motor cortex has been found to induce UES MEP (Ertekin et al., 2001), and the demonstration of volitional control of UES relaxation with high-resolution manometry biofeedback (Nativ-Zeltzer et al., 2019) indicated cortical involvement in the regulation of the UES relaxation. Neuroanatomically, the corticobulbar tract originating from the lateral aspect of the primary motor cortex (Hamdy, 2006) is located within the precentral gyrus, and the cricopharyngeus muscles receive fibers from both sides (Li et al., 2020; Aziz et al., 1996). Our findings on the correlation of UOD with the FC between the bilateral precentral gyrus and the medulla may be related to the role of the precentral gyrus in hyoid movement or to direct regulation of the relaxation aspect of the UES opening.

FC analyses can be used to study stroke patients in a number of ways: voxel-based, seed-based, or independent component analysis of large-scale brain networks. The medulla is the primary regulatory center for swallowing, so it is a natural seed choice for the calculation of whole-brain voxel-based FC to identify involved the cortical regions involved. Unlike the DMN and SMN, no generally accepted network for the control of swallowing has been established yet. Using the medulla as a seed for FC mapping is a promising first step toward this goal.

4.4. Correlations within VFSS quantitative measures

We also found correlations among the quantitative measures included in VFSS. We found a moderate negative correlation between the PAS score and the UOD which is consistent with the literature. Among 13 temporal and kinematic measures of swallowing, only the duration of UES opening has been found in previous work on subacute post-stroke patients with dysphagia to differentiate between aspirators and non-aspirators (Molfenter and Steele, 2014). Impaired UES opening leads to post-swallow pharyngeal residue, which is also a common symptom for dysphagia patients after IS (Shaker et al., 2002) and increases the risk of aspiration. LCD and HMD also showed a moderate positive correlation. The elevation of the hyolaryngeal complex is a crucial event in the pharyngeal phase of swallowing. The motion of the hyoid bone and the closure of the larynx are two aspects secondary to the elevation initiated by the submental muscles (the mylohyoid, geniohyoid, and anterior digastric) and the thyrohyoid muscle (Pearson et al., 2012).

4.5. Limitations

There were several limitations to our study that should be considered when interpreting our results. The number of patients in our study may have been too small to detect more subtle correlations. Moreover, the results might have been biased by the sex ratio. Stroke incidence rate and prevalence are higher in males than in females (Appelros et al., 2009). VFSS temporal measures vary between individuals, and no standard protocol has been set across studies (Molfenter and Steele, 2012). Though it was suggested that 5 mL nectar-thick swallows are useful to obtain physiological measures of swallowing impairment (Martin-Harris et al., 2008), future studies may further investigate cortical participation in the processing of different volumes and viscosities of the bolus stimulus. Additionally, this study was cross-sectional, and no premorbid data of these patients were included. Our results at the group level should be verified through longitudinal studies to determine if our observations may translate into individual biomarkers. Our current data is underpowered for predictive modeling of functional measures of swallowing. In future studies, the predictive value of the functional connectivity between cortical regions and the medulla for swallowing function and recovery should be further investigated. The full identification of cortical regions involved remains an important target for the treatment of dysphagia following IS.

5. Conclusion

We reported that in subacute IS patients with dysphagia, increased functional connectivity between the cortex and the medulla occurred in the bilateral precentral gyrus, the right supplementary motor area, and the left precuneus compared to normal subjects. Some of these increases correlated with videofluoroscopic measures of oropharyngeal swallowing function, highlighting the potential of cortical-medulla FC as a biomarker for characterizing brain network changes related to swallowing. The cortical areas identified are also candidates for future non-invasive strategies for rehabilitation of swallowing. Future research may reveal whether the reorganization of functional network connections can be fostered by targeted therapeutic interventions after a stroke.

CRediT authorship contribution statement

Meng Dai: Conceptualization, Methodology, Software, Writing – original draft, Writing – review & editing, Project administration. **Jia Qiao:** Validation, Data curation. **Xiaomei Wei:** Writing – review & editing, Supervision. **Huayu Chen:** Software, Investigation. **Zhonghui Shi:** Visualization, Investigation. **Zulin Dou:** Supervision, Funding acquisition.

Declaration of Competing Interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

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