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Central swallowing in normal adults using functional magnetic resonance imaging*****☆*

Shasha Li[1], Cheng Luo[2], Chengqi He[1], Qiyong Gong[3], Dong Zhou[4]

1Department of Rehabilitation Medicine, West China Hospital, Sichuan University, Chengdu 610041, Sichuan Province, China
2School of Science and Technology, University of Electronic Science and Technology of China, Chengdu 610041, Sichuan Province, China
3Huaxi MR Research Center (HMRRC), Department of Radiology, West China Hospital, Sichuan University, Chengdu 610041, Sichuan Province, China
4Department of Neurology, West China Hospital, Sichuan University, Chengdu 610041, Sichuan Province, China

Abstract

BACKGROUND: While brain-imaging studies in healthy adults have indicated that multiple cortical regions are involved in swallowing, these functional imaging techniques have not been extensively applied to the complete understand neurophysiology of swallowing in China. A full understanding of normal swallowing neurophysiology is important for improving functional outcomes for dysphagia due to neurologic disorders or damage with increasing age. Thus the interpretations of the functional contributions of various brain areas in swallowing should be scientifically researched.
OBJECTIVE: To identify the activation and characteristic of swallowing center in healthy adults using functional magnetic resonance imaging.
DESIGN, TIME AND SETTING: An uncontrolled neuroimaging study was performed at the Outpatient Clinic, Department of Radiology, West China Hospital of Sichuan University between March and November 2008.
PARTICIPANTS: Ten healthy right-handed volunteers, aged over 20 years with a mean age of (34.2 ± 8.1) years, a range of 25–45 years and including five males and five females participated. A medical history was obtained from all potential subjects and all subjects were free of systemic diseases and neurological disorders.
METHODS: The healthy volunteers were examined with event-related functional magnetic resonance imaging of blood oxygenation level-dependent while laryngeal swallow-related movements were recorded. Subjects were scanned during voluntary saliva swallowing and water bolus swallowing activation tasks. Data was processed using the General Linear Model. A voxel by voxel group comparison was performed using random effect analysis. Any cluster with a corrected $P < 0.05$ for spatial extent was considered significant.
MAIN OUTCOME MEASURES: The cerebral cortical activation maps of voluntary swallowing of saliva and swallowing of water bolus in healthy adults were observed.
RESULTS: A multifocal cortical representation of swallowing was in the precentral gyrus, postcentral gyrus, insula, anterior cingulate gyrus, thalamus, basal ganglia and cerebellum, in a bilateral and asymmetrical manner, predominantly on the left hemisphere in the volunteers ($P < 0.05$).
CONCLUSION: Activation of the cortex during normal swallowing tasks may be functionally linked to basal nuclei, thalamus, and cerebellum, greatly appearing in the left hemisphere.
Key Words: swallowing; central swallowing; blood oxygenation level-dependent; functional magnetic resonance imaging
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Shasha Li☆, Studying for doctorate, Department of Rehabilitation Medicine, West China Hospital, Sichuan University, Chengdu 610041, Sichuan Province, China

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Corresponding author: Dong Zhou, M.D, Department of Neurology, West China Hospital, Sichuan University, Chengdu 610041, Sichuan Province, China
E-mail: zhoudong66@yahoo.de

INTRODUCTION

Dysphagia, or difficulty in swallowing, is more prevalent with increased age and often results from neurologic disorders, such as stroke, Alzheimer's and Parkinson's diseases, and amyotrophic lateral sclerosis. Research on swallowing disorders has mostly focused on examining the neurophysiology of swallowing to improve the efficiency of diagnosis and treatment. To fully understand the neurophysiology of swallowing disorders we must first understand how it works in healthy individuals.

Although the act of swallowing is thought to be mediated principally by brainstem mechanisms, it is well established that the cerebral cortex plays an important role in the regulation of swallowing[1-2]. Recent technological advances in functional imaging of the human brain have improved our understanding of how the cerebral cortex involves in processing sensory and motor information. In particular, functional magnetic resonance imaging (fMRI) allows for the spatial localization of changes in neuronal activity, in the cortical and subcortical regions of the brain, while performing tasks.

The advent of fMRI has allowed for greater spatial and temporal resolution, offering a more precise identification of structures. The principle underlying fMRI analysis is sensitivity in detecting slight alterations in blood flow within the central nervous system. As neural activity increases, blood flow increases, along with the intensity of the fMRI signal at that locus. This is known as the blood oxygenation level-dependent (BOLD) mechanism[3].

FMRI has been particularly useful in examining brain activity during swallowing in healthy individuals. This is owing to its accuracy in detecting changes across different spatial locations and tissues over time. Also, it does not require the use of radiation or invasive procedures[4]. In addition, fMRI has become increasingly available for research purposes and may shed light on the feasible neural mechanisms of swallowing impairment.

Recent neuroimaging studies have suggested that swallowing is processed within a distributed cortical network[5-10]. The most prominent activation foci correspond to the primary sensorimotor cortex, non-primary sensory and motor cortical regions, the insula and anterior cingulate cortex[5,7-8,10]. It has been hypothesized that these discrete activation foci mediate functionally distinct components of the swallowing action. However, these interpretations of the functional contributions of various brain areas in swallowing have not been fully tested.

The purpose of this study was to define the cerebral cortical representation of voluntary swallowing of saliva and swallowing of water bolus in healthy adults using BOLD-fMRI in order to investigate the motor control of swallowing in a preliminary effort to gain insight into the control scheme of this complex physiologic function.

SUBJECTS AND METHODS

Design

Uncontrolled neuroimaging study.

Time and setting

Imaging was performed at the Out-patient Clinic, Department of Radiology, West China Hospital of Sichuan University, between March and November 2008.

Subjects

Ten healthy volunteers, 5 males and 5 females, aged (34.2 ± 8.1) years (range: 25–45), took part in this study. All participants were strongly right-handed, according to *the Edinburgh Handedness Inventory*[11]. A medical history was obtained from all candidates to ensure all were free from systemic diseases or neurological disorders. Exclusion criteria included a history of oral sensorimotor, swallowing, speech, gastrointestinal, or neurological conditions; surgery to the head/neck; or taking medications known to affect swallowing, or related functions. None of the subjects had previous fMRI experience. The study protocol was approved by the *Administrative Regulations on Medical Institution* published by State Council of the People's Republic of China[12]. The study adhered to the magnetic resonance imaging (MRI) safety depositional guidelines, established by the United States Food and Drug Administration, for clinical scanners. Before scanning, each subject was trained to perform both swallowing tasks according to instructions.

Methods

Swallowing task paradigm

Voluntary saliva swallow task: Each subject participated in functional imaging runs during the event-related experimental session, lasting 200 seconds. Each functional run consisted of two randomly ordered tasks, performed in response to visual cues. The visual cues, which were 3 minutes in duration, were back-projected onto a mirror positioned above the subject's eyes. For the activation task, the "green light" condition was a single voluntary saliva swallow performed in response to the visual cue "swallow". The subject was instructed to swallow his/her saliva once without making exaggerated oral movements to produce extra saliva. For the non-activation task, deemed the "red light" condition, the subject made no overt response following the presentation of the visual cue "do not swallow". The swallowing activation task was performed 15 times during the functional runs. To ensure that the subject understood the experimental procedures, each subject practiced the activation tasks prior to the functional runs.

Water bolus swallow task: Each subject participated in functional imaging runs during wet swallowing, lasting 200 seconds. Subjects were instructed to swallow 3 mL of room-temperature water, delivered through a 3-mm-diameter tube attached to a 20 mL syringe and limitation pressure controlled by MR injection system (MEDRAD, Inc. USA). The tubing was held between the subject's lips, at midline, and stabilized at the chest by the subject's right hand. All subjects were required to limit the movement of their hands. Water was delivered every 20 seconds for six cycles. Subjects were instructed to swallow each volume of water as a single bolus.

Identification of swallowing by surface electromyography (EMG) recording

To verify that the subjects swallowed during the activation periods, and remained motionless during rest periods, the surface EMG was measured with a pair of bipolar Ag/AgCl electrodes attached to the submental and infrahyoid muscle groups. The EMG was recorded using a 10/20 system with the electrodes soldered to 12 kΩ current-limiting resistors, positioned comfortably over the subject's thyroid cartilage. The EMG device was a Mizar 40 amplifier (EBNeuro, Florence, Italy), with two channels adapted for magnetic resonance (MR). The sampling rate was set at 4 096 Hz, which allows a suitable time resolution for picking up the switching effect of the readout gradient in the high slew rate condition. The EMG dynamic range was ±65.5 mV to prevent MRI artifact waveforms saturating the EMG. The EMG device, located inside a shielded box, amplified the signal, and performed A/D conversion. The amplifier was connected to the recording computer outside the scanner room *via* a fiber optic cable. The MR artifact was filtered out and BE-MRI Toolbox (Galileo New Technology, Florence, Italy) software was used. The time at which the swallow-related laryngeal elevation began was recorded for each swallowing task, throughout all fMRI scans.

MRI experiments

MRI data were acquired on a 3.0T MRI system (Excite™, General Electric Company, Milwaukee, USA) to produce BOLD-sensitive echo-planar images, with simultaneous EMG recordings, using a standard 8-channel phased array head coil. This was performed at the Department of Radiology in West China Hospital. T1-weighted images were acquired in axial orientation using a 3-D spoiled gradient recalled (SPGR) sequence [repetition/echo time tje (TR/TE)=8.5 ms/3.4 ms; flip angle=12°], with a voxel size of 0.94 mm × 0.94 mm × 1.00 mm. MRIs sensitized to changes in BOLD signal levels (TR/TE=2 000 ms/30 ms; flip angle=90°) were obtained by a gradient-echo echo-planar imaging sequence. The slice thickness was 5 mm (no slice gap), with a matrix size= 64 × 64, field-of-view (FOV) = 240 mm × 240 mm, which resulted in a voxel size of 3.75 mm × 3.75 mm × 5.00 mm. Each brain volume comprised 30 axial slices and each functional run contained 100 image volumes.

fMRI data analysis

Image preprocessing and statistical analyses were performed using statistical parametric mapping software (SPM2, Welcome Department of Imaging Neuroscience, http://www.fil.ion.ucl.ac.uk). To allow for magnetization equilibrium, the first five images for each subject were discarded. The remaining 95 functional images were first corrected for the acquisition time delay between different slices, and then realigned to the first volume for head-motion correction. If a patient's motion and rotation parameters exceeded 0.5 mm and 0.5°, respectively, the data was excluded from analysis. There was no significant difference in the magnitude of the motion correction parameters between individuals. The images were then spatially normalized to the MNI (Montreal Neurological Institute) template brain. The volumes were resampled, resulting in 3 mm^3 voxels, and the data was spatially smoothed with a 3-D Gaussian kernel of 8 mm full-width, at half-maximum.

After preprocessing, the data was then ready for analysis. According to the EMG, swallowing activity was recorded when the first stimulation-time signal was acquired. Then, the canonical hemodynamic response function (HRF) was modeled by two gamma-variant functions convolved with the stimulation-time pulse signal. Finally, the canonical HRF was specified as an interested regressor in the SPM design matrix. Motion correction parameters were included in the design matrix of six regressive parameters, for each run, as covariates with no interest. The data were then modeled voxel-wise, using a general linear model (GLM)[13].

The statistical threshold was set at $P < 0.05$ at the cluster level (contiguous voxels > 10; lowest threshold; with a t value > 4.79, and a standard voxel level cutoff of $P < 0.05$, corrected). For group analysis, contrast images were created for each subject and entered separately into voxel-wise single-sample student t tests (df=9), implementing a random effects analysis. Every cluster showing a corrected $P < 0.05$ and t value > 4.79 for its spatial extent was considered statistically significant.

Main outcome measures

Observation of the cerebral cortical activation maps of voluntary swallowing of saliva and swallowing of water bolus in healthy adults.

Design, enforcement, and evaluation

All authors participated in study design, conduction, and evaluation.

RESULTS

Verification of swallowing

All subjects tolerated the scanning well, without excess body movements, and all succeeded in swallowing at a consistent rate during fMRI. No excessive head movements occurred for the data sets used in this investigation. Hand movement was restricted during the water bolus to avoid contamination of the signal by motion artifacts. According to the individual EMG recordings, the beginning and end of task-specific muscle activity were marked for every swallow in each individual participant. The laryngeal movement of the EMG indicated that all subjects swallowed once when requested. Furthermore, when the subjects were requested not to swallow, there were no instances of swallowing recorded.

According to the EMGs, swallowing response latencies at baseline showed no significance between individuals, for dry swallowing and wet swallowing tasks (ANOVA analysis, $P > 0.05$).

Both swallowing tasks resulted in a significant increase in fMRI signal intensity, in several cortical regions, during volitional or reflexive swallowing ($P < 0.05$). Cerebral networks activated during swallowing involved 5 primary loci: the primary motor cortex (M1, precentral gyrus, Brodmann areas 4, 6, 44), the primary somatosensory cortex (S1, postcentral gyrus, Brodmann areas 3, 2, 43), the cingulate gyrus (Brodmann areas 30, 32), insular (Brodmann area 13), cerebellum, including frontal lobe, and the temporal lobe. The location of activated areas in each subject was determined by identifying the location of activation in Brodmann areas using established neuroanatomic landmarks[14-15].

Activation associated with voluntary saliva swallow (Table 1, Figures 1, 2)

Table 1 shows the distribution of activation in the cortical and subcortical regions (designated in Brodmann areas) during the volitional swallowing test. The results showed significant activations ($P < 0.05$, corrected) in fMRI signal intensity in the primary motor cortex (Brodmann area 4), the primary somaosensory cortex (Brodmann areas 3, 2, and 43), the supplementary motor cortex (Brodmann area 6), the middle and inferior frontal cortices (Brodmann areas 9 and 47), the transverse, superior and middle temporal gyrii (Brodmann areas 42, 38, and 39), the cingulate gyrus and insular cortex (Brodmann areas 32, 23, and 13), as well areas of the putamen, thalamus and cerebellum.

The voluntary saliva swallow evoked significant activation ($P < 0.05$, corrected) in a number of discrete brain regions (Table 1). The total volume of activated brain in the group map was 11 610 mm^3 ($P < 0.05$, corrected), and the spatial patterns of activation within the left and right hemispheres were clearly asymmetric. The largest activation focus was located within the left pericentral cortex, corresponding to the primary motor (M1), primary somatosensory (S1), and associated cortices.

Table 1 Group analysis for normal subjects: distribution of activation during dry swallowing tasks in Brodmann areas

Region	Brodmann area	Talairach coordinate (local maxima of cluster)			Cluster volume (mm^3)	t value*	Z value
		x	y	z			
Right precentral gyrus	6	54	0	36	2 295	7.18	7.25
	4	45	−15	45		6.71	6.36
Left precentral gyrus	6	−48	−9	54	2 430	7.56	7.04
	4	−58	−16	44		7.24	6.65
Right postcentral gyrus	2	66	−21	30	1 836	7.08	6.65
Left postcentral gyrus	43	−60	−6	18	2 160	7.53	7.01
	3	−51	−12	48		7.25	6.70
Right anterior cingulate	32	3	39	−3	270	6.18	5.88
	23	3	−27	24		4.90	4.78
Right inferior frontal gyrus	47	52	30	−14	162	6.48	5.98
Right superior temporal gyrus	38	57	15	−6	54	7.57	6.66
Right middle temporal gyrus	39	57	−54	12	162	6.82	6.44
	21	60	−54	3		6.76	6.40
Right precuneus gyrus	19	9	−78	39	162	7.15	6.77
Right insula	13	34	10	12	270	6.54	6.30
Left thalamus		9	−6	9	81	5.55	5.38
Left medial frontal gyrus	10	−6	39	−6	81	5.50	5.32
Left superior temporal gyrus	22	−60	−6	6	135	7.04	6.63
Left transverse temporal gyrus	42	−63	−18	9	810	7.20	6.75
Left lingual gyrus	18	−21	−69	0	162	5.54	5.36
Left insula	13	−34	9	12	297	6.65	5.58
Left putamen		−16	2	5	81	5.34	5.16
Left thalamus		−9	−6	9	81	5.35	5.18
Cerebellum		21	−60	−39	243	6.18	5.88

*$P < 0.01$. The statistical threshold was set at $P < 0.05$ at the cluster level (10 contiguous voxels at t value > 4.79, corrected; lowest threshold, t value > 4.79; with a standard voxel level cutoff of $P < 0.05$)

Activation associated with water bolus swallow

The total volume of activated brain associated with the water-swallowing task was 8 802 mm^3 ($P < 0.05$, corrected; Table 2). Water swallow-evoked activation within the left and right hemispheres were distinct, as was the case for the saliva-swallowing task. The largest activation foci corresponded to left postcentral gyrus. Activation of this area was markedly more prominent than for the saliva-swallowing task. Another large region of activation corresponded to the pericentral cortex, particularly in the left hemisphere. Other prominent activation foci corresponded to the bilateral area of the superior temporal gyrus, the right middle frontal gyrus, the middle temporal gyrus, and left transverse temporal gyrus.

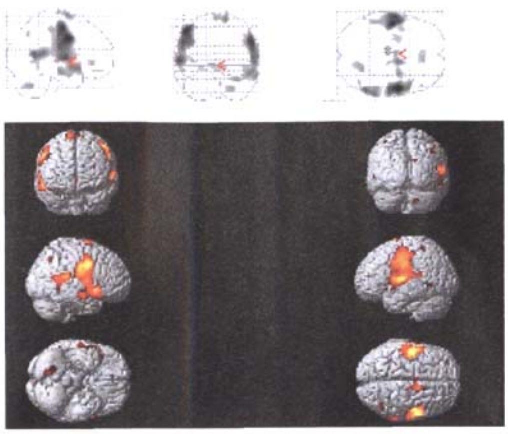

Figure 1 Glass brain images (upper panel) and three-dimensional rendering of areas (lower panel) of significant activation during voluntary saliva swallow task of group analysis of 10 subjects. Talairach coordinates of the activated left-hemispheric brain area are –60, –6, and 18.

Activation was also seen in the cerebellum, and in posterior brain regions, including the precuneus, cuneus and posterior cingulate gyrus.

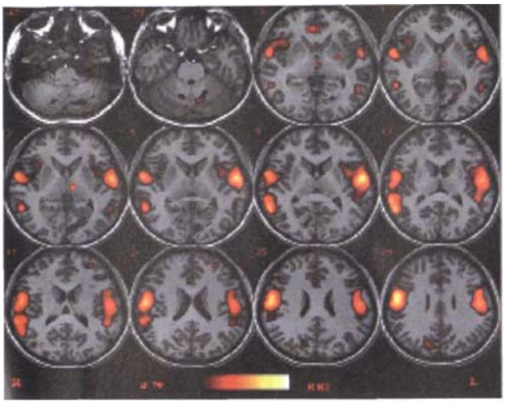

Figure 2 Brain activation associated with voluntary saliva swallow task for group analysis of subjects. The color bar represents *t* value ($P < 0.05$, corrected). Regions of significant activation are displayed on normalized axial brain slices using the Talairach-Tournoux coordinate system. The primary motor cortex, the primary sensory cortex, middle frontal gyrus, middle temporal gyrus, insula, thalamus, basal ganglia and cerebellum were activated. The maximal activation regions were observed in the sensorimotor cortex.

Table 2 Group analysis for normal subjects: distribution of activation during wet swallowing tasks in Brodmann areas

Region	Brodmann's Area	Talairach coordinate Local maxima of cluster			Cluster volume (mm^3)	*t* value*	*Z* value
		x	y	z			
Right precentral gyrus	6	60	–3	27	891	6.24	5.64
	4	36	–18	42		5.58	5.14
Left precentral gyrus	44	–60	12	3	648	5.23	4.86
Right postcentral gyrus	2	66	–21	30	729	5.09	4.75
Left postcentral gyrus	43	–60	–6	18	2 187	5.96	5.43
	3	–51	–12	48		5.68	5.22
Right anterior cingulate	24	3	39	–3	189	6.20	5.93
	32	3	–27	24		4.99	4.88
Right middle frontal gyrus	6	54	9	45	756	5.29	4.91
Right superior temporal gyrus	38	57	15	–6	54	5.46	5.04
Right middle temporal gyrus	37	45	–69	9	162	5.40	4.99
	21	60	–54	3		5.16	4.80
Right cuneus	17	18	–72	12	810	6.62	5.93
	19	9	–90	33		5.36	4.96
Right precuneus gyrus	19	9	–78	39	162	5.50	5.07
Right insula	13	–33	9	11	324	6.68	5.60
Left superior temporal gyrus	38	–57	12	–9	54	5.34	4.94
Left transverse temporal gyrus	42	–63	–18	9	1 080	5.57	5.13
Left cuneus	30	–12	–69	9	270	5.45	5.03
Left posterior cingulate	30	–24	–63	6	270	5.27	4.89
Cerebellum		21	–60	–39	216	5.95	5.70

*$P < 0.01$. The statistical threshold was set at $P < 0.05$ at the cluster level (10 contiguous voxels at *t* value > 4.79, corrected; lowest threshold, *t* value > 4.79; with a standard voxel level cutoff of $P < 0.05$)

Comparison between saliva swallow and water bolus swallow

The two swallowing tasks produced similar regions of activation. However, the total volume of activated brain associated with the water-swallowing task was smaller than the saliva-swallowing task. The contrast analysis identified several regions within the frontal and temporal lobes in which activation associated with the water swallowing task was significantly greater (one-sample Student's *t*-test, $P < 0.05$, corrected) than the saliva-swallowing task. Regions in which activation associated with the saliva-swallowing task exceeded that associated with the water swallowing task were generally stronger and located within the primary motor and somatosensory cortices ($P < 0.05$, corrected).

Hemispheric asymmetry of cortical activation

The number of subjects showing a left- over right-hemisphere activation asymmetry for the pericentral and postcentral cortex were 80% for the voluntary saliva swallow, and 70% for the water swallow. The remaining subjects showed a right- over left-hemisphere asymmetry.

Across all subjects, the mean activations within the left and right pericentral cortex were not significantly different for either of the swallowing tasks.

DISCUSSION

This study used fMRI to investigate the cerebral cortical representation during performance of two different swallowing tasks by healthy subjects. Both voluntary and reflexive swallowing were associated with a multifocal cortical representation in the precentral gyrus, postcentral gyrus, insula, and anterior cingulate gyrus, with a bilateral and asymmetrical pattern, as previously reported using event-related task paradigms[3-10]. In our study we found that voluntary swallowing was associated with activation of a number of spatially and functionally distinct cortical regions in the healthy volunteers. The most prominent and consistent activation foci were located within the precentral gyrus, including Brodmann areas 4 and 6, the postcentral gyrus, anterior cingulate gyrus, insula, and cerebellum. Activation foci within the superior temporal gyrus, middle and inferior frontal gyri, frontal operculum, and thalamus, were also identified, although these were less prominent. Our results support previous reports of cortical activity in the motor areas during swallowing. This area represents a controlling region for oropharyngeal deglutitive muscle activity.

Multiple sites of activation, including those associated with motor processing, suggest that motor control of swallowing may involve several cortical sites to initiate, process, and execute the necessary output for swallowing. Activation of other cortical sites, such as the supplementary motor area, represented in the superior and middle frontal gyri, is believed to be associated with motor planning and, in particular, with planning of sequential movements such as those involved with swallowing[16].

In subcortical areas, activation of the posterior limb of the internal capsule, the insular cortex, and the thalamus was observed in patients during swallowing tasks. Activation of the internal capsule is an expected and important functional feature in swallowing, as the internal capsule serves to functionally connect cortical and brainstem nuclei *via* the cortical bulbar tracts. Vascular injury to these white matter tracts has been associated with oropharyngeal deficits in swallowing[17]. In other areas, the insular cortex is thought to serve a variety of functions, including a role in gustatory sensation, visceral motor activity, and motor association, as well as the processing of motor-associated tasks[18]. Thus activation of the insular cortex during swallowing may be linked to its visceral motor and integrative functions[19].

Regarding hemispheric dominance, our group analysis indicates that swallowing involves both hemispheres, with a larger area involved and more intense activity present in the left hemisphere. The concept of hemispheric dominance in swallowing derives from the clinical observation of dysphagic patients, neuroimaging, and transcranial magnetic stimulation studies in healthy human subjects[5-10, 20-30]. Our findings agree with the earlier observations, using transcranial magnetic stimulation, that the motor cortex representation for swallowing musculature displays degrees of asymmetry and hemispheric dominance, however, appeared to be left hemisphere [27,30].

Inter-task comparison revealed that certain brain regions, including the precentral and the postcentral gyrii, were activated significantly more during the saliva-swallowing task, than the water-swallowing task. The contrast analysis also showed that several regions within the frontal and temporal lobes were activated significantly more in the water-swallowing task than the saliva-swallowing task. A previous study found that the tongue task activated a substantially greater cortical and subcortical brain volume than the swallowing task[31]. Consistent with this, our study revealed a number of brain areas for which voluntary saliva swallowing was greater than water-swallowing task could be activated by voluntary tongue elevation. However, an alternate explanation for the present findings is that this may reflect the cortical processing of water bolus swallowing. The need to control and contain the bolus within the mouth would have been particularly acute for the water swallowing performed within the context of the fMRI experiment since, with the subject in the supine position, the bolus had to be prevented from flowing prematurely from the mouth into the pharynx immediately after water delivery.

In conclusion, this study indicates that the primary motor and somatosensory areas are consistently activated in healthy adult subjects, while performing swallowing tasks. The anterior cingulate cortex and insular cortex were also activated during swallowing. These might include common pathways and functional modules. The results of this study provide an insight into understanding the central nervous system's control over swallowing. These have important implications for future fMRI studies of swallowing that should be performed with a larger sample size. This may provide a means to improving functional outcomes for dysphagia, caused by neurologic disorders or age-related damage. As a valuable method for studying swallowing, fMRI might allow an assessment of cerebral activity associated with functional swallowing and could be a useful tool for the assessment and prognosis of swallowing dysfunction.

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