Functional magnetic resonance imaging study on dysphagia after unilateral hemispheric stroke: a preliminary study

S Li,[1,2] C Luo,[3] B Yu,[4] B Yan,[1] Q Gong,[5,6] C He,[7] L He,[1] X Huang,[5] D Yao,[3] S Lui,[5] H Tang,[5] Q Chen,[1] Y Zeng,[1] D Zhou[1]

[1] Department of Neurology, West China Hospital of Sichuan University, Chengdu, Sichuan, PR China; [2] Department of Rehabilitation Medicine, 2nd Affiliated Hospital of Wenzhou Medical College, Wenzhou, Zhejiang, PR China; [3] School of Science and Technology, University of Electronic Science and Technology of China, Chengdu, Sichuan, PR China; [4] Department of Neonatology, 2nd Affiliated Hospital of Wenzhou Medical College, Wenzhou, Zhejiang, PR China; [5] Huaxi MR Research Centre (HMRRC), Department of Radiology, West China Hospital of Sichuan University, PR China; [6] Division of Medical Imaging, Faculty of Medicine, University of Liverpool, Liverpool, UK; [7] Department of Rehabilitation Medicine, West China Hospital of Sichuan University, Chengdu, Sichuan, PR China

Correspondence to:
Professor D Zhou, Department of Neurology, West China Hospital of Sichuan University, No 37 Guo-xue-xiang-Street 610041, Chengdu, Sichuan, PR China;
zhoudong66@yahoo.de

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ABSTRACT

Background: Swallowing dysfunction is common and disabling after acute stroke; however, the mechanism of dysphagia or recovery of swallowing from dysphagia remains uncertain. The purpose of this study was to explore cerebral activation of swallowing in dysphagia using functional MRI (fMRI) to compare the functional anatomy of swallowing in unilateral hemispheric stroke patients and healthy adults.

Methods: In total, five left hemispheric stroke patients with dysphagia, five right hemispheric stroke patients with dysphagia and 10 healthy controls were examined with event related fMRI while laryngeal swallow related movements were recorded. Data were processed using the general linear model.

Results: A multifocal cerebral representation of swallowing was identified predominantly in the left hemisphere, in a bilateral and asymmetrical manner. Cerebral activation during swallowing tasks was localised to the precentral, postcentral and anterior cingulate gyri, insula and thalamus in all groups. Activation of volitional swallowing in dysphagic unilateral hemispheric stroke patients might require reorganisation of the dominant hemispheric motor cortex, or a compensatory shift in activation to unaffected areas of the hemisphere.

Conclusions: The results indicate that unilateral stroke of either cerebral hemisphere can produce dysphagia. Effective recovery is associated with cerebral activation related to cortical swallowing representation in the compensating or recruited areas of the intact hemisphere. Functional MRI is a useful method for exploring the spatial localisation of changes in neuronal activity during tasks that may be related to recovery. Therefore, the subsequent information gleaned from changes in neural plasticity could be useful for assessing the prognosis of dysphagic stroke.

Dysphagia is one of the most vexing clinical problems encountered in stroke patients and is associated with aspiration pneumonia. Depending on the definition and the diagnostic tools used, dysphagia occurs in approximately 25–50% of stroke patients.[1–3] It is now well established that the cerebral cortex plays an important functional role in the regulation of swallowing.[4] While the reflexive component of swallowing depends on swallowing centres in the brainstem, the initiation of swallowing is a voluntary action that relies on the integrity of motor areas of the cerebral cortex.[5]

Indeed, according to a recent review of the neurophysiology of swallowing, damage to the cerebral cortex can have a significant effect on the peripheral swallowing mechanism operating at the level of the brainstem.[6] Several clinical studies have reported that damage to the relevant hemisphere in stroke patients results in increased difficulty in swallowing, as well as corticospinal output that appears to be associated with swallowing problems.[7–10] Malnutrition predicts a poor functional outcome and increased mortality.[11] Although most recovery of normal swallowing function occurs within a few weeks after stroke,[12] the neural mechanisms involved are unclear. In many cases, improvement in swallowing is not matched by an improvement in the degree of hemiparesis.[9]

Within the last few years, an increasing number of brain imaging studies in healthy adults have implicated multiple cortical regions in the control of swallowing.[13–21] However, predictions of the functional contributions made by each of these brain areas have not been fully tested. Although it is now clearly recognised that unilateral stroke of either cerebral hemisphere can produce dysphagia, it is unclear whether one hemisphere is dominant for swallowing and whether damage to a specific hemisphere affects the recovery of swallowing.[22–25]

Functional brain imaging studies may help to elucidate the relevant neural mechanisms underlying swallowing impairment and also provide evidence for functional changes to the cortex resulting from a stroke. Regarding the latter, the functional state of the cerebral cortex of stroke patients with dysphagia has thus far not been fully investigated, particularly using functional MRI (fMRI).

The purpose of this study was to investigate the neurorehabilitation mechanisms responsible for cerebral activation of swallowing following dysphagia. To this end, we examined the functional anatomy of unilateral hemispheric stroke patients and compared it with that of healthy adults. Using blood oxygenation level dependent (BOLD) fMRI, we studied functional neuroimaging features during voluntary swallowing tasks in dysphagic patients, at least 72 h after stroke onset. We focused on both cortical and subcortical activation, so as to gain a greater understanding of the relevant processes that, in turn, might lead to new and effective treatment strategies for dysphagic stroke patients.

METHODS

Subjects

The study protocol was approved by the institutional ethics committee at Sichuan University, and

written informed consent was obtained from all subjects prior to commencing the research. Patients consecutively admitted to the Stroke Centre of West China Hospital from October 2007 to October 2008 were included in the study, based on the criteria that they had only experienced a single cerebral hemispheric ischaemic stroke that was accompanied by a history of mild to severe dysphagia, lasting for up to 3 days. Of these patients, there were five females and five males, with a mean age of 70.9 (3.4) years (age range 62–78). During the initial consultation, we obtained the following information from each patient: sex, age at which the stroke occurred, time since stroke, type of stroke, location and side of the lesion (left or right hemisphere). The 10 stroke patients were enrolled and diagnosed with their first onset of ischaemic stroke, as defined according to World Health Organization criteria (the sudden onset of neurological deficit persisting for >24 h).[26] All patients were assessed for swallowing dysfunction within 24 h of stroke onset by a qualified speech and language therapist. The therapist used the Logemann clinical indicators of dysphagia[27] (ie, coughing, oral residue, delayed swallowing, reduced laryngeal elevation (observed by placing one finger on the hyoid and one on the thyroid), throat clearing and choking).[28] To confirm the diagnosis, patients were subjected to videofluoroscopic swallowing examination (VFSS Imager, Model IA-12LD/HG12; Shimadzu Corporation, Kyoto, Japan). Those who displayed at least one of the following symptoms were considered to have dysphagia[29]: (1) food residue occupying more than 50% of the vallecula or piriform sinus space after swallowing; (2) subglottic aspiration; (3) a pharyngeal transit time >2 s (operationally defined as the time taken for the bolus to move from the point at which the pharyngeal swallow is triggered to the cricopharyngeal sphincter); and (4) impaired cricopharyngeal muscle relaxation. Exclusion criteria included: (1) prior cerebrovascular disease; (2) pre-existing neurological or psychiatric disorders (including a history of seizures, global cognitive impairment, aphasia, neglect, substantial sensory disturbances, severe depression or claustrophobia); (3) use of an electrically sensitive biomedical device (eg, cardiac pacemaker or cochlear implant); (4) metal clips in the brain; or (5) pneumonia at the time of enrolment.

An age and sex matched group of healthy older volunteers (n = 10; five females; mean age 70.3 (4.2) years; range 65–75) served as the control group. All control subjects had a normal neurological examination, no history of a stroke and no significant active neurological problems. They were also free of systemic diseases and neurological disorders. The same exclusion criteria listed above were applied to the control group.

All subjects were strongly right handed, according to the Edinburgh Handedness Inventory. The study adhered to the MRI safety depositional guidelines established by the US Food and Drug Administration for clinical scanners. Before scanning, each subject was trained to perform the voluntary swallowing task according to instructions.

Swallowing task paradigm

Voluntary saliva swallowing task

Each participant was subjected to functional imaging runs of 3 min 20 s duration, during each event related experimental session. Each functional run consisted of two randomly ordered tasks performed in response to visual cues. The visual cues 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 "do 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, no overt response was required of the subject following presentation of the visual cue "don't swallow". The frequency of the visual cue was pseudo-randomly displayed during the scanning time. Between the activation task cues, the resting task cue was displayed. Thus with a mean random interstimulus interval of 10 s (range 8–14), each activation task was performed 15 times during each functional run. To ensure that the subject understood the experimental procedures, each subject practiced the activation task prior to participating in the functional runs.

Identification of swallowing

Electromyography recording

To verify that the subjects swallowed during the activation periods and remained motionless during rest periods, surface electromyography (EMG) was performed, using a pair of bipolar Ag/AgCl electrodes, on the submental and infrahyoid muscle groups.

The EMG was recorded using a 10/20 system with two Ag/AgCl electrodes soldered to 12 kΩ current limiting resistors that were 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. The sampling rate was set at 4096 Hz, which allowed enough time for resolving the switching effect from the readout gradient under the high slew rate condition. The EMG dynamic range was ±65.5 mV, to prevent MRI artefact waveforms saturating the EMG. The EMG device, placed inside a shielded box, amplified the signal and performed analogue to digital conversion. The amplifier was connected to a recording computer located outside the scanner room via a fibreoptic cable. The MR artefact was filtered out using the BE-MRI Toolbox software (Galileo New Technology, Florence, Italy). The time at which the swallow related laryngeal elevation began was recorded for all individual swallows and all fMRI scans.

MRE experiments

MRI data were acquired using a 3.0 T MRI system (Excite; General Electric Company, Milwaukee, USA) with a standard 8 channel, phased array, head coil at the Department of Radiology in West China Hospital. EMG data were acquired simultaneously. Structural images were acquired in axial orientation using a three-dimensional spoiled gradient recalled sequence (repetition/echo time (TR/TE) = 8.5 ms/3.4 ms; flip angle = 12°), with a voxel size of 0.94×0.94×1.00 mm^3. The MR images that were sensitised to changes in BOLD signal levels (TR/TE = 2000 ms/30 ms; flip angle = 90°) were obtained by a gradient echo, echo planar imaging sequence. Slice thickness was 5 mm (no slice gap) with a matrix size of 64×64 and a field of view of 240×240 mm^2, which resulted in a voxel size of 3.75×3.75×5.00 mm^3. Each brain volume consisted of 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). For each subject, all echo planar images were corrected according to slice time, realigned with the first image of the first

Table 1 Clinical data of dysphagic stroke study patients

Patient No	Sex	Age (years)	Lesion side	Infarct location	Lesion extent (A-P/S-I/L-R) (mm)	Lesion volume (cm^3)	NIHSS	Scanning time from stroke (days)	Dysphagia type*	Classification of dysphagia severity	P-A Scale score
1	F	78	Left	Next to central part of lateral ventricle	18/12/12	3.63	10	3	Oral dysfunction	Mild	2
2	M	78	Left	Basal ganglia	10/7/8	2.26	5	3	Oral dysfunction	Moderate	4
3	F	65	Left	Corona radiate	16/5/8	2.55	4	4	Oral dysfunction	Mild	2
4	F	67	Right	Frontal lobe, corona radiate, insular lobe	18/12/10	3.60	11	3	Pharyngeal dysfunction	Moderate	5
5	F	64	Right	Basal ganglia	14/8/14	3.05	11	4	Pharyngeal dysfunction	Moderate	5
6	M	63	Right	Temporal lobe	18/13/12	3.65	10	3	Pharyngeal dysfunction	Moderate	5
7	M	72	Right	Parietal cortex, temporal cortex	15/16/12	3.80	12	4	Oral and pharyngeal dysfunction	Severe	6
8	M	65	Left	Basal ganglia	7/5/18	3.24	14	5	Oral and pharyngeal dysfunction	Severe	6
9	M	68	Left	parietal cortex	12/15/12	3.53	11	4	Oral and pharyngeal dysfunction	Moderate	5
10	F	70	Right	Corona radiate	10/7/9	2.27	5	3	Pharyngeal dysfunction	Mild	2

*Features of oral dysfunction: anterior bolus loss, tongue pumping, delayed initiation of movement and uncoordinated initiation of oral transfer. Characteristics of pharyngeal dysfunction: delayed pharyngeal swallow, reduced laryngeal elevation, penetration, aspiration and stasis.
Dysphagia Severity Rating Scale[34]: mild, oropharyngeal dysphagia present but can be managed with specific swallowing suggestions; moderate, significant potential for aspiration exists. Trace aspiration of one or more consistencies may be seen under videofluoroscopy; severe, more than 10% aspiration for all consistencies.
A-P, anterior–posterior; L-R, left–right; NIHSS Score, National Institutes of Health Stroke Scale[33]; P-A Scale, Penetration Aspiration Scale; S-I, superior–inferior.

series and then unwarped to correct for susceptibility by movement interaction. If a patient's motion and rotation parameters exceeded 0.5 mm and 0.5°, respectively, this run of data was excluded from future analyses. There was no significant difference in the magnitude of the motion correction parameters between the control and study groups.

To allow for magnetisation equilibrium, the first five images were discarded. The remaining 95 images were first corrected to account for the delay in acquisition time among different slices, after which the images were realigned the first volume for head motion correction. The images were subsequently spatially normalised to the MNI (Montreal Neurological Institute) template brain, and spatially smoothed with a three-dimensional Gaussian kernel of 8 mm full width at half maximum. The volumes were resampled, resulting in $3\times3\times3$ mm^3 voxels.

The fMRI data were first preprocessed according to the steps mentioned above. Based on the EMG results, the time point at which swallowing activity coincided with the first stimulation–time signal was acquired. Then, the canonical haemodynamic response function was modelled by two gamma variant functions convolved with the stimulation–time pulse signal. Finally, the canonical haemodynamic response function was specified as an interested regressor in the SPM design matrix. Motion correction parameters for each run were included in the design matrix of six regressive parameters as covariates with no interest. The data were then modelled based on voxels, using a general linear model.[30]

The statistical threshold was set at $p<0.001$ at the cluster level (contiguous voxels >10; lowest threshold; t value >4.29 for controls; t value >7.17 for patients). For patients and healthy controls, contrast images were created for each subject and entered separately into a voxel based one sample Student's t test (df = 4 for patients; df = 9 for controls), to analyse random effects. In addition, the two sample t test was used to compare results (1) between each unilateral hemispheric stroke patient group and the control group; and (2) between all stroke patients and controls, by reversing the maps from the right hemisphere stroke group and combining them with the maps from the left hemisphere stroke group. Each cluster showing an uncorrected $p<0.001$ for its spatial extent was considered statistically significant (contiguous voxels >10; lowest threshold; t value >3.85 for left or right hemispheric stroke patients with dysphagia vs controls; t value >3.61 for 10 stroke patients with dysphagia vs controls).

Hemispheric dominance was quantified using a laterality index (*LI*), defined by the ratio:

$$LI = [\Sigma s \text{ left} - \Sigma s \text{ right}]/[\Sigma s \text{ left} + \Sigma s \text{ right}] \times 100$$

where s = (percentage of activation) × (number of activated pixels). A positive *LI* indicates left hemispheric dominance whereas a negative *LI* demonstrates right hemispheric dominance. Ratios at or close to 0 are thought to represent an indeterminate dominance.[31]

RESULTS

Clinical features and dysphagia examination

The patients' clinical features and lesions are summarised in table 1. There was no significant difference in the distribution of brain infarction between patients with left and right lesions. They had each experienced their first and only cerebral hemispheric stroke up to 3 days prior to admission. The time from stroke onset to the start of the fMRI study ranged from 3 to 5 days. Based on the results of the initial VFSS, four patients were diagnosed with both oral and pharyngeal dysfunction, three with only oral dysfunction and three with only pharyngeal dysfunction. Of these patients, two presented with mild initial Penetration Aspiration (P-A) Scale scores[32] (score of 2), six presented with moderate P-A Scale scores (score of 3–5) and two presented with severe P-A Scale scores (score of 6), indicating at least one aspiration episode.

According to the P-A Scale scores, there was no significant difference in the degree of severity of dysphagia between left and right hemispheric stroke patients ($p>0.05$).

Performance of functional MRI tasks

Verification of swallowing

All subjects tolerated the scanning procedure well, without displaying excess body movements, and all succeeded in swallowing at a consistent rate during fMRI. Head movements were restricted to avoid contamination of the signal by motion artefacts. No gross head motions occurred during data collection in this investigation. The EMG recordings allowed identification of both the beginning and end of task specific muscle activity for each individual swallowing event in all participants (fig 1). The laryngeal movement of the EMG indicated that all subjects swallowed once in response to each of the "do swallow" cues. Furthermore, there were no instances of swallowing in response to "don't swallow" cues in any of the subjects.

According to the EMG results, there was no significant difference in the swallowing response latencies between patients and controls responding to the "do swallow" cues (one sample Student t tests: $p>0.05$).

Group analysis for controls

The MNI coordinates of our results were transformed to Talairach coordinates using mni2tal.m (http://imaging.mrc-cbu.cam.ac.uk/downloads/MNI2tal/) The location of activated areas in each subject was assigned to Brodmann areas based on established neuroanatomical landmarks.[35 36]

Table 2 shows the distribution of activation in cortical and subcortical sites (designated in Brodmann areas, BA) during the volitional swallowing paradigm. The results showed a significant increase ($p<0.001$, uncorrected) in fMRI signal intensity in the primary motor cortex (BA 4), primary somatosensory cortex (BA 3 and 2), supplementary motor cortex (BA 6), middle frontal cortex (BA 10), transverse temporal gyrus, superior temporal gyrus and middle temporal gyrus (BA 42, 22, 38, and 21), anterior cingulate gyrus and the insula (BA 32 and 13), as well as in the areas of the putamen and thalamus.

The voluntary saliva swallow evoked significant activation ($p<0.001$, uncorrected) in a number of discrete brain regions (fig 2A). The total volume of the activated brain region in the group map was 11 718 mm^3 ($p<0.001$, uncorrected), and the spatial patterns of activation within the left and right hemispheres were similar, but clearly asymmetric. The largest activation focus was located within the left pericentral cortex, corresponding to the primary motor (MI) and primary somatosensory (SI) associated cortices. Group analysis of the LI value for the 10 control subjects during performance of the voluntary saliva swallowing task produced a positive value, indicative of left hemispheric dominance ($LI = 21$).

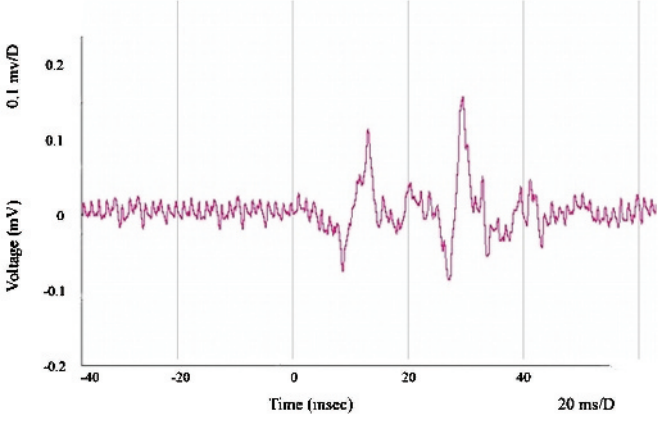

Figure 1 EMG signals from the laryngeal movement during a typical episode of swallowing in one subject. The beginning and end of task specific muscle activity were identified. The visual cue "do swallow" was presented at time = 0.

Group analysis for left hemispheric stroke patients

During the voluntary saliva swallowing task, there was activation of the stronger right side, which included the primary motor cortex (MI, the precentral gyrus, BA 4), the primary somatosensory cortex (SI, postcentral gyrus, BA 3), the superior and middle temporal gyri (BA 22 and 21), insula and thalamus. The right primary motor and primary somatosensory cortices, together with the medial frontal gyrus, and the superior temporal and middle temporal gyri, underwent stronger activation than in the left hemisphere (fig 2B). The total volume of the sensorimotor (SM) cortex activated was 11.556 mm^3. This was 1.3 times the mean value of the control group.

Group analysis for right hemispheric stroke patients

Prominent activation foci corresponded to the SM cortex, middle frontal (BA 10), superior temporal and middle temporal gyri (BA 22 and 21) and the insula (BA 13). However, activation within the undamaged hemisphere was stronger than the infarcted hemisphere (fig 2C). The regions of maximal activation were observed in the bilateral SM cortex, anterior cingulate, insula and right anterior brain regions, including the medial and inferior frontal gyri. Within the left hemisphere, activation was only observed in the thalamus.

Intergroup analysis for each stroke patient group and control group

When a comparison was made with the control group, the left hemispheric stroke patients showed greater activation bilaterally in the precentral gyrus, insula and cingulate gyrus (fig 3A). The only structures in the left hemisphere of this group of stroke patients to be activated more strongly than those in the control group were the postcentral gyrus and middle frontal gyrus. When the right hemispheric stroke patients were compared with the control subjects, the former showed greater activation of the precentral and postcentral gyri, superior temporal gyrus and cingulate gyrus in both cerebral hemispheres. Additional activity was also observed in the right middle frontal gyrus and left insula (fig 3B). By reversing the maps of the right hemispheric stroke group, and then combining them with those of the left hemispheric stroke group, all stroke patients showed a multifocal, large cluster of increased activation in the left precental and postcentral gyri, left middle frontal gyrus and insula compared with the control subjects during the task (fig 3C). Additional activity was also observed in the bilateral cingulate gyrus. The Talairach coordinates of the most activated voxel of these clusters are given in table 3.

DISCUSSION

In this report, BOLD fMRI was used to determine the cortical representations of swallowing in dysphagic stroke patients, and to compare them to those in healthy adults. To our knowledge, this is the first study to use fMRI to investigate cerebral cortical activation during voluntary swallowing in dysphagic stroke patients. Our findings indicate that swallowing in dysphagic stroke patients, similar to healthy older adults, is processed within multiple regions of the cerebral cortex and subcortex. The prominent swallow related activation of the precentral,

Table 2 Group analysis for controls and patients: distribution of activation during voluntary saliva swallowing tasks in Brodmann areas

Cerebral region	Side	Brodmann area	Talairach coordinate (x y z) Local maxima of cluster			Cluster volume (mm^3)	t value	p Value
Distribution of activation of group analysis for controls								
Precentral gyrus	L	4	−58	−16	44	2430	7.59	0.0000***
		6,	−48	−9	54		7.27	0.0000***
	R	4,	45	−15	45	2376	7.15	0.0000***
		6	54	0	36		6.74	0.0000***
Postcentral gyrus	L	3,	−51	−12	48	2187	7.56	0.0000***
		43	−60	−6	18		7.28	0.0000***
	R	2	66	−21	30	1809	6.70	0.0000***
Middle frontal gyrus	L	10	−6	39	−6	81	5.61	0.0000***
Superior temporal gyrus	L	22	−60	−6	6	135	7.04	0.0000***
	R	38	57	15	−6	135	7.55	0.0000***
Middle temporal gyrus	R	21	60	−54	3	405	6.92	0.0000***
							6.76	0.0000***
Transverse temporal gyrus	L	42	−63	−18	9	810	7.17	0.0000***
Anterior cingulate	R	32,	3	39	−3	324	5.2	0.0001
Insula	L	13	−34	9	12	324	6.68	0.0000***
	R	13	34	10	12	297	6.58	0.0000***
Thalamus	L		9	−6	9	81	5.33	0.0000***
Putamen	L		−16	2	5	324	4.5	0.0008
Distribution of activation of group analysis for left hemispheric stroke patients with dysphagia								
Precentral gyrus	L	4	−54	−12	39	3024	15.75	0.0000***
	R	4	50	−12	39	2997	15.15	0.0000***
Postcentral gyrus	L	3	−52	−12	48	2781	12.60	0.0000***
	R	3	52	−13	46	2754	12.30	0.0000***
Superior temporal gyrus	L	22	−60	−8	6	594	9.13	0.0000***
Middle temporal gyrus	L	21	−60	−50	3	1782	10.06	0.0000***
	R	21	57	−50	5	1674	8.51	0.0000***
Anterior cingulate	L	32	−3	39	−5	756	7.83	0.0001
	R	32	3	37	−3	729	7.62	0.0002
Thalamus	R		9	−6	9	81	7.21	0.0009
Distribution of activation of group analysis for right hemispheric stroke patients with dysphagia								
Precentral gyrus	L	4	−40	−12	39	2997	14.2	0.0000***
	R	4	42	−12	39	2970	14.58	0.0000***
		6	54	−9	33			
Postcentral gyrus	L	3	−50	−12	49	2673	12.12	0.0000***
	R	2	65	−22	33	2565	12.84	0.0000***
Middle frontal gyrus	L	10	−6	38	−6	216	10.83	0.0000***
	R	10	12	39	−6	324	10.7	0.0000***
Inferior frontal gyrus	R	47	52	30	−14	297	8.5	0.0000***
Superior temporal gyrus	L	22	−62	−8	6	486	10.86	0.0000***
	R	22	62	−8	6	675	11.23	0.0000***
Anterior cingulate	L	32	−3	39	−5	756	7.80	0.0001
	R	32	3	37	−3	783	7.60	0.0002
Insula	L	13	−33	8	12	324	10.48	0.0000***
	R	13	34	10	12	297	9.28	0.0000***
Thalamus	L		−9	−18	9	81	7.17	0.001

***$p<0.0001$. The statistical threshold was set at $p<0.001$ at the cluster level (10 contiguous voxels), at t value >4.29 ($n = 10$) for the control group and t value >7.17 for the patient group ($n = 5$), uncorrected.

postcentral and anterior cingulate gyri, together with the insula, in a bilateral and asymmetrical manner is consistent with previous event related task paradigm studies in healthy subjects.[14–16 21 37–39] Interestingly, this study also discovered the following features that were distinct to dysphagic stroke patients.

Firstly, group analysis of the healthy control subjects revealed that hemispheric dominance appeared to be associated with the left hemisphere. Our results indicate that although swallowing involves both hemispheres, there is greater and more intense activity in the left hemisphere. The strongest activations were found in the sensorimotor cortices, insula and cingulate gyrus. The concept of hemispheric dominance in swallowing derives from clinical observation of dysphagic patients,[4 23 40–43] neuroimaging[13 14 16 20 21 38] and transcranial magnetic stimulation (TMS) studies[44 45] in healthy individuals and stroke patients. In our study, swallowing recruited multiple cerebral regions, often in an asymmetrical manner, and showed left hemispheric dominance according to the *LI* of group analysis for controls.

The data presented here are mostly descriptive as this is the first attempt to functionally characterise the brains of dysphagic stroke patients using fMRI. Our findings confirm previous

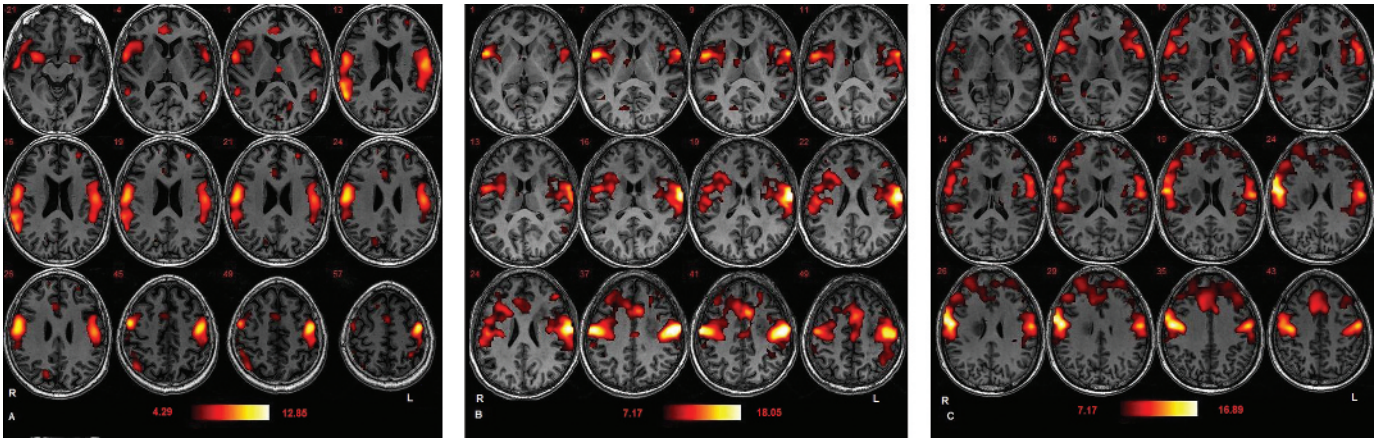

Figure 2 (A) Brain activation associated with voluntary saliva swallow task for group analysis of control. Regions of significant activation are displayed on normalised axial brain slices using the Talairach–Tournoux coordinate system. The spatial patterns of activation within the left and right hemispheres were similar, but clearly asymmetric. The results showed a significant increase ($p<0.001$, uncorrected) in the primary motor cortex (Brodmann area (BA) 4), primary somatosensory cortex (BA 3 and 2), supplementary motor cortex (BA 6), middle frontal cortex (BA 10), transverse temporal gyrus, superior temporal gyrus and middle temporal gyrus (BA 42, 22, 38 and 21), anterior cingulate gyrus and the insula (BA 32 and 13) as well as in the areas of the putamen and thalamus. The largest activation focus was located within the left pericentral cortex, corresponding to the primary motor and primary somatosensory associated cortices. Colour bar represents t value ($p<0.001$, uncorrected). (B) Group analysis of brain activation associated with the voluntary saliva swallow task in patients who suffered ischaemic infarct in the left hemisphere. The primary motor cortex (BA 4), the primary somatosensory cortex (BA 3), middle temporal gyrus (BA 21), insula (BA 13), thalamus and basal ganglia were activated. The maximal activation regions were observed in the right hemisphere. Colour bar represents t value ($p<0.001$, uncorrected). (C) Group analysis of brain activation associated with the voluntary saliva swallow task in patients who suffered ischaemic infarct in the right hemisphere. Prominent activation foci corresponded to the sensorimotor cortex, middle frontal gyrus (BA 10), superior temporal gyrus (BA 22), middle temporal gyrus (BA 21) and insula (BA13). Extensively activated tissue volumes were observed in the left hemisphere. Colour bar represents t value ($p<0.001$, uncorrected).

reports[40–43] that unilateral hemispheric lesions may produce dysphagia in stroke patients. This study provides supporting evidence for the bilateral redistribution of swallowing networks after occurrence of a stroke. The key finding was that dysphagic stroke patients who suffered ischaemic infarct in the left hemisphere showed overactivation in their right cortical maps, over that of the infarcted hemisphere. Conversely, dysphagic stroke patients who suffered ischaemic infarcts in the right hemisphere showed overactivation in their left cortical maps and a shifting from the affected hemisphere. The results demonstrate that swallowing may be prominently lateralised to one specific hemisphere while recovery from dysphagia after a stroke might require reorganisation of the motor cortex in the dominant hemisphere. However, hemispheric dominance in swallowing was still under debate. Our knowledge of the mechanisms that contribute to the dysphagia in unilateral hemispheric stroke is limited, particularly in view of the fact that the stroke patients in this study all presented with mild to

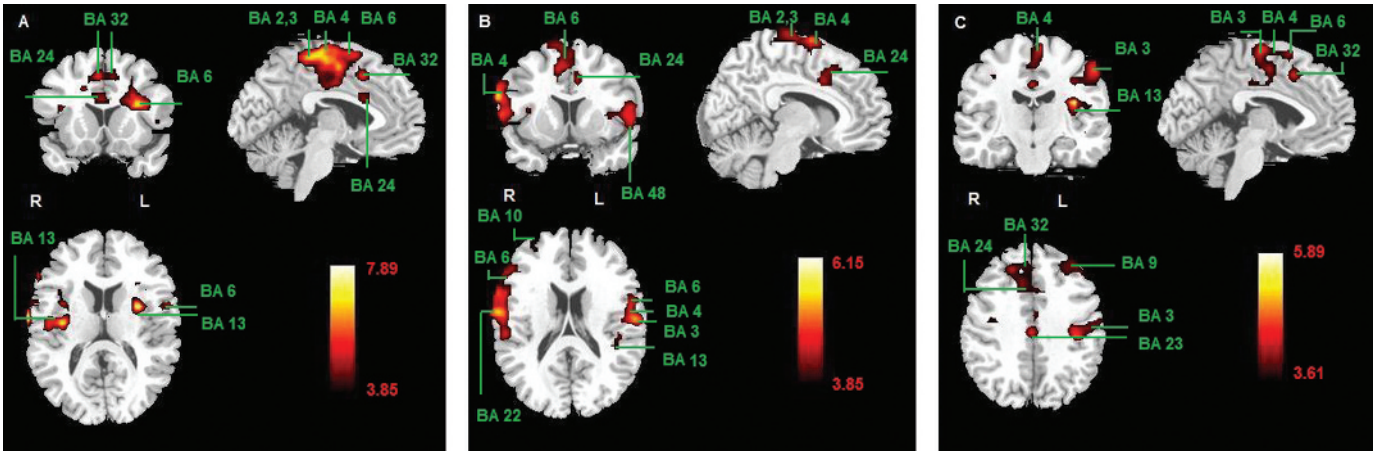

Figure 3 Statistical parametric maps of intergroup comparisons between stroke patients and 10 control subjects. (A) Left hemispheric stroke patients versus control group. The clusters of increased activation were bilaterally centred on the primary motor cortex (Brodmann area (BA) 4), supplementary motor cortex (BA 6), insula (BA 13) and cingulate gyrus (BA 24 and 32). Additional activity was also observed in the right primary somatosensory cortex (BA 3 and 2). (B) Right hemispheric stroke patients versus control subjects. A large multifocal cluster of increased activation is seen in the bilateral primary motor cortex (BA 4), primary somatosensory cortex (BA 3 and 2), superior temporal gyrus (BA 22) and cingulate gyrus (BA 24), compared with control subjects. Additional activity was also observed in the right middle frontal gyrus (BA 10) and left insula (BA 13). (C) Stroke patients with dysphagia versus controls. The increased activation was located in the left primary motor and somatosensory cortex (BA 4 and 3), left supplementary motor cortex (BA 6) and insula (BA 13). Additional activity was also observed in the bilateral cingulate gyrus (BA 32, 24). Colour bar represents t value ($p<0.001$, uncorrected).

Table 3 Cerebral regions exhibiting changes in activation during voluntary saliva swallowing

Cerebral region	Side	Brodmann area	Talairach coordinate (x, y, z) Local maxima of cluster			Cluster volume (mm^3)	t value	p Value
Intergroup comparison: increased activation (left hemispheric stroke patients with dysphagia versus controls)								
Precentral gyrus	L	4.6	−60	−12	45	216	6.44	0.0000***
	R	4.6	42	−12	40		5.83	0.0000***
Postcentral gyrus	L	2	−51	−18	45	189	6.28	0.0000***
Middle frontal gyrus	L	6	−27	−6	48	729	4.26	0.0003
Insula	L	13	−34	8	13	135	6.32	0.0000***
	R	13	33	10	12	162	6.23	0.0000***
Cingulate gyrus	L	24	−2	10	26	108	3.91	0.0009
	R	24	2	11	26		3.88	0.001
Intergroup comparison: increased activation (right hemispheric stroke patients with dysphagia versus controls)								
Precentral gyrus	L	4	−40	−12	39	324	4.82	0.0000***
	R	4	44	−12	39		5.16	0.0000***
Postcentral gyrus	L	3	−50	−12	47	216	4.42	0.0001
	R	3	56	−12	48		4.59	0.0000***
Middle frontal gyrus	R	10	12	39	−6	135	4.06	0.0006
Superior temporal gyrus	L	22	−62	−10	6	162	5.56	0.0000***
	R	22	62	−10	6		5.62	0.0000***
Insula	L	13	−42	3	−6	108	4.23	0.0003
Cingulate gyrus	L	24	0	14	29	135	3.9	0.0009
	R	24	2	16	25		4.05	
Intergroup comparison: increased activation (stroke patients with dysphagia versus controls)								
Precentral gyrus	L	4	−56	−17	40	351	5.33	0.0000***
Postcentral gyrus	L	3	−51	−16	47	297	5.54	0.0000***
Middle frontal gyrus	L	6	−3	16	46	405	3.86	0.0002
Insula	L	13	−37	−16	16	162	5.82	0.0000***
Cingulate gyrus	L	32	−36	37	40	162	4.21	0.0000***
	R	24	2	−21	40	189	4.08	0.0001

***$p<0.0001$. The statistical threshold was set at $p<0.001$ (uncorrected) at the cluster level (10 contiguous voxels), at t value >3.85 for left or right hemispheric stroke patients with dysphagia versus controls or t value >3.61 for stroke patients with dysphagia versus controls.

moderate lesions. In order to confirm these preliminary findings, a prospective, longitudinal study is needed that contains a larger sample of unilateral stroke patients and includes patients both with and without dysphagia.

Secondly, we found that, compared with controls, a number of cortical regions in dysphagic stroke patients were overactivated by volitional swallowing where the most consistent of these areas included the lateral pericentral and postcentral gyri and multiple subcortical sites. Based on the theory that the brain undergoes neurofunctional adaptation after a stroke,[46] the presence of a lesion in the dominant hemisphere would cause cortical activation to shift to the unaffected hemisphere. Compared with control subjects, left hemispheric stroke patients with dysphagia showed overactivation bilaterally in the precentral gyrus, insula and cingulate gyrus. Moreover, right hemispheric stroke patients with dysphagia showed increased activation compared with healthy controls, particularly in the precentral and postcentral gyri, superior temporal gyrus and cingulate gyrus. Interestingly, during volitional swallowing, there was increased activation in the left precentral and postcentral gyri, left medial frontal gyrus and insula of all of the stroke patients, compared with control subjects. Due to the presence of significantly different activation modes from intergroup comparisons, it might be postulated that the cerebral cortex is involved in the execution of, or sensory feedback processing for, voluntary swallowing. Our study corroborates previous reports of cortical activity in the motor areas during swallowing. These areas control oropharyngeal deglutitive muscle activity. Multiple sites of overactivation, including those associated with motor processing, suggest that the motor control of swallowing may involve several cortical sites that initiate, process and execute the necessary output for swallowing.

Furthermore, lesion studies have demonstrated that swallowing behaviours may differ between left hemispheric and right hemispheric damage strokes. We also found that patients with left and right hemispheric strokes may have different dysphagic characteristics. In agreement with Robbins and Levine,[23 24] our results showed that pharyngeal dysmotility was more prominent in patients with right hemispheric damage strokes, and reduced oral coordination was more prominent in patients with left hemispheric damage. This finding was consistent with previously published work.[8]

Thirdly, this is our initial effort to show the relationship between the cerebral activation of swallowing following unilateral ischaemic stroke and the severity of dysphagia. These findings indicate that patients with left hemisphere lesions may have more severe dysphagia, and that their cerebral activation was therefore smaller during the swallowing task than patients with right hemispheric damage. Our results support the hypothesis that lesions to the left hemisphere may result in more severe impairment of swallowing due to the greater relative importance of the left hemisphere in mediating this function. The cortical representation asymmetry may explain why the development of dysphagia following a stroke is variable in degree and duration. This suggests that compensatory contralateral hemisphere reorganisation might be responsible for the improvement in swallowing seen in patients after

occurrence of a unilateral stroke. Although the number of patients studied is too small for firm conclusions to be made, these observations may have implications for the diagnosis, prognosis and treatment of stroke related dysphagia. Considering the brain's plasticity, and our observations of the changes to these functional maps, a novel insight from our work is that increased bilateral activation may indicate a good prognosis for acute mild or moderate strokes. Furthermore, improvement in the dysphagia of stroke patients may be associated with a compensatory recruitment and bilateral activation of areas that are involved in the cortical representation of swallowing.

The present study has several limitations. For dysphagic stroke patients, it may be difficult to complete the water bolus swallowing task in the supine position. Taking the safety of patients and older controls into consideration, we only used the dry swallowing task in this pilot study. Furthermore, these experimental tests do not accurately represent ''normal'' swallowing conditions. Subjects were required to swallow repeatedly while lying supine, for several seconds. Due to the strict training before study, all subjects showed swallow related movements, as determined by EMG. Although possible confounding variables such as age, lesion location and disease duration were carefully matched between groups, we acknowledge the modest sample size of this study and recognise that a large cohort study would be required to verify the current findings.

CONCLUSIONS

In conclusion, the fMRI scanning results indicate that the primary motor and somatosensory areas are consistently active across healthy adult subjects when swallowing. The anterior cingulate and insular cortices are also highly active during swallowing. To further our understanding of the function of these anatomical regions and systems in swallowing, we demonstrated that swallowing function in dysphagic stroke patients is associated with a compensatory recruitment and activation of regions of the cerebral cortex in the intact hemisphere. Given that the intact hemisphere plays an important role in the recovery of swallowing after a stroke, we are provided with an interesting opportunity to study the plasticity of an intact pathway. Thus any future rehabilitation therapies aimed at enhancing the recovery of swallowing should target reorganisation of the intact side.

Finally, functional MRI is among the fastest growing brain imaging technologies. It is advantageous because it is minimally invasive, compared with some other brain imaging systems, and it is also becoming increasingly accessible to researchers. As a valuable method for studying swallowing control, this approach allows assessment of the cerebral activity associated with functional swallowing, and could serve as a useful prognosticator for dysphagic stroke conditions.

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Neurological picture

Double depressor palsy caused by bilateral paramedian thalamic infarcts

A 45-year-old woman with Coffin–Lowry syndrome, but without risk factors for cerebrovascular disease, awoke with double vision and unsteadiness on her feet. Examination revealed a skew deviation of the eyes and diplopia on downgaze due to a "double depressor" palsy of the inferior rectus and superior oblique muscles. Her gait was unsteady with a tendency to veer left. Brain computed tomography (CT) and MRI confirmed bilateral paramedian thalamic infarcts (figs 1, 2). CT angiogram of the aortic arch and extracranial and intracranial carotid arteries, thrombophilia screen and 24 h ambulatory electrocardiogram were normal. An echocardiogram

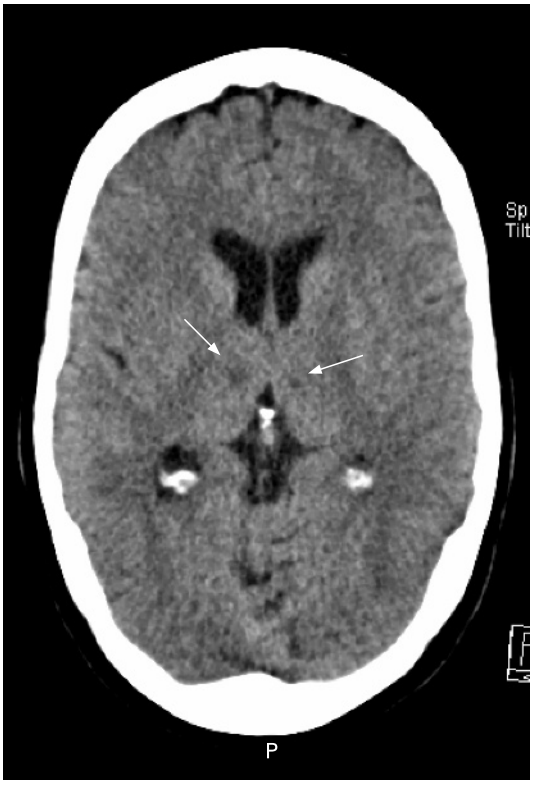

Figure 1 Brain computed tomogram, showing bilateral low-intensity lesions in the thalami (arrows).

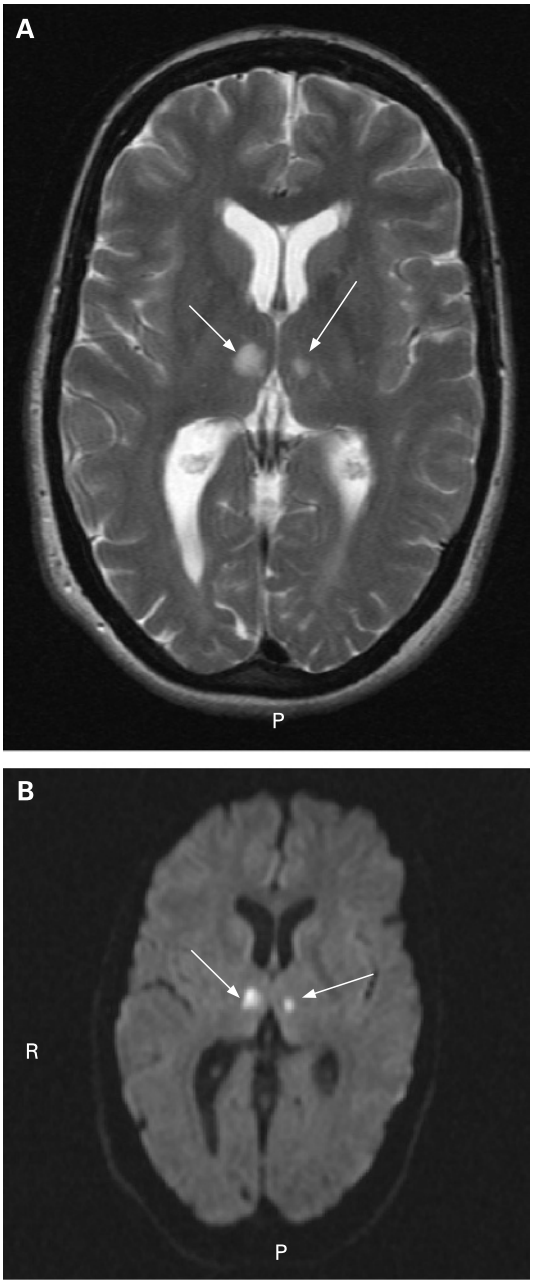

Figure 2 Brain MRI, showing bilateral paramedian thalamic infarcts (arrows) on (A) T2-weighted and (B) diffusion-weighted imaging.

Functional magnetic resonance imaging study on dysphagia after unilateral hemispheric stroke: a preliminary study

S Li, C Luo, B Yu, B Yan, Q Gong, C He, L He, X Huang, D Yao, S Lui, H Tang, Q Chen, Y Zeng and D Zhou

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