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ORIGINAL ARTICLE

Structural and functional changes mapped in the brains of amyotrophic lateral sclerosis patients with/without dysphagia: A pilot study

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Abstract

The purpose of this study was to explore cerebral structural and functional changes in amyotrophic lateral sclerosis (ALS) patients with or without dysphagia compared with healthy adults. In total, five ALS patients with dysphagia, five ALS patients without dysphagia and 10 healthy controls were evaluated using diffusion tensor magnetic resonance imaging (DTI) and event-related functional magnetic resonance imaging (fMRI) while laryngeal swallow-related movements were recorded. The fMRI data were analysed using the general linear model to gain the differential statistical map (two-sample *t*-test) for each group. Maps of fractional anisotropy (FA) and mean diffusivity (MD) were calculated within the masks that corresponded to the different statistical functional maps of intergroup comparisons. During the voluntary saliva swallowing, prominent activation of foci corresponded to the primary sensorimotor (SM) cortex in both ALS and controls, while decreased activation of the SM cortex was observed in ALS patients with dysphagia. DTI analysis revealed that FA was significantly reduced and MD was typically increased in the posterior limb of the internal capsule, thalamus, and anterior cingulate gyrus, as well as in the insula of ALS patients compared with controls. However, in ALS patients with dysphagia, FA and MD were more sensitive to these changes than ALS patients without dysphagia. This study highlights the potential of DTI and fMRI for monitoring structural degeneration and functional changes in patients with ALS. This study is the first to demonstrate that cerebral activation map changes correspond to distribution patterns of diffusion abnormalities. Combined non-invasive neuroimaging techniques may be useful tools to assess prognosis and study rehabilitation strategies for dysphagic ALS patients, especially for patients who are MRI-negative by conventional methods.

Key words: *Dysphagia, amyotrophic lateral sclerosis (ALS), functional magnetic resonance imaging (fMRI), diffusion tensor imaging (DTI)*

Introduction

Dysphagia is one of the most problematic clinical features of amyotrophic lateral sclerosis (ALS). Approximately 20–30% of ALS patients present with bulbar dysfunction (1), and malnutrition has been shown to be an independent prognostic factor for survival – ALS with malnourished condition showing a 7.7-fold increased risk of death (2,3).

Functional magnetic resonance imaging (fMRI) studies have found altered patterns of cortical activation during motor tasks in ALS (4–8). However, the swallowing action of ALS patients with dysphagia has not been fully studied, and there is limited knowledge about functional compensation or neural reorganization in ALS. An understanding of the neural processes involved in swallowing is required to assess prognosis and study rehabilitation strategies for bulbar onset ALS.

Currently, diffusion tensor imaging (DTI) allows investigation of the orientation and integrity of brain pathways in vivo by virtue of the water diffusion characteristics within them (9,10). DTI has been used to quantitatively assess tissue damage to the corticospinal tracts in ALS (11–16), and thus it provides an objective morphological marker for

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these structural properties that may complement the findings from functional imaging studies.

The purpose of this study was to determine whether DTI and fMRI could be used together in ALS patients to give useful insights into the neurophysiological mechanisms of dysphagia. Using fMRI combined with DTI, we studied cerebral activation during voluntary swallowing and assessed the diffusion abnormalities in ALS patients with or without dysphagia. We hypothesized that the functional and structural findings will allow the comprehensive characterization of neural compensation in ALS patients with or without dysphagia compared to normal individuals.

Patients and methods

Subjects

The study was approved by the institutional ethics committee at Sichuan University, and all subjects gave written informed consent. A total of 20 right-handed subjects were recruited including five ALS patients without dysphagia, five ALS patients with dysphagia and 10 age- and sex-matched healthy controls. Table I presents demographic and clinical characteristics for all subjects. All the patients were consecutively admitted to the Neurology Department of West China Hospital from May 2005 to October 2008 and diagnosed with definite ALS, according to El Escorial criteria (17). Disease severity was estimated by the ALS Functional Rating Scale-Revised (ALSFRS-R) score (18). Following neurological evaluation, the speech and language therapist assessed the feature of swallowing dysfunction using the Logemann clinical indicators (21) of dysphagia. To confirm the diagnosis, patients who showed at least one of the following findings in the videofluoroscopic swallowing study (VFSS Imager, Model: IA-12LD/HG12, Shimadzu Corporation, Kyoto, Japan) were considered to have dysphagia (22): 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; and 4) impaired cricopharyngeal muscle relaxation.

All controls were free of systemic diseases and neuropsychiatric disorders. The study adhered to the magnetic resonance imaging safety depositional guidelines established by the United States Food and Drug Administration for clinical scanners.

Swallowing task paradigm

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". For the non-activation task, deemed the 'red light' condition, the subject made no overt response following presentation of the visual cue "don't swallow". Thus, the swallowing activation task was performed 15 times per run. To ensure that the subject understood the experimental procedures, each subject practised the activation task prior to the scanning according to instructions.

fMRI and DTI data acquisition

MRI data were acquired on a 3.0 Telsa MRI system (Excite™, General Electric Company, Milwaukee, USA) with a standard 8-channel phase array head coil. EMG data were acquired simultaneously. Structural images were acquired in the axial orientation using a three-dimensional (3D) spoiled gradient

Table I. Clinical characteristics of patients with amyotrophic lateral sclerosis (ALS).

Patient No./Age (y)/Sex	Duration (mo)	ALSFRS-R	P-A scale score	Dysphagia type‡	Classification of dysphagia severity§	EIESC
1/49/M	16	39	1	None	None	Definite
2/44/F	15	34	3	Oral dysfunction	Moderate	Definite
3/48/F	33	42	5	Oropharyngeal dysfunction	Moderate	Definite
4/58/M	20	42	1	None	None	Definite
5/55/M	22	40	3	Oral dysfunction	Moderate	Definite
6/42/M	24	38	1	None	None	Definite
7/52/F	18	36	1	None	None	Definite
8/40/M	16	34	4	Pharyngeal dysfunction	Moderate	Definite
9/32/M	28	39	1	None	None	Definite
10/38/F	22	40	5	Oropharyngeal dysfunction	Moderate	Definite

Note: ALSFRS-R indicates ALS Functional Rating Scale-Revised (18). ‡: 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 (19). 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. P-A scale score: penetration-aspiration scale (20). EIESC, El Escorial (17).

recalled (SPGR) sequence (repetition/echo time (TR/TE) = 8.5 msec/3.4 msec; flip angle = 12°; voxel size = 0.94 × 0.94 × 1.00 mm^3). Subsequently, the functional images were obtained by a gradient-echo, echoplanar imaging (EPI) sequence (TR/TE = 2000 msec/30 msec; flip angle = 90°). The slice thickness was 5 mm (no slice gap) with a matrix size of 64 × 64, and a field-of-view (FOV) measuring 240 × 240 mm^2, which resulted in a voxel size of 3.75 × 3.75 × 5.00 mm^3. Each brain volume comprised 30 axial slices, and each functional run contained 100 image volumes.

DTI data were acquired using a single-shot, spin-echo, echoplanar image (SE-EPI) sequence. The diffusion sensitizing gradients were applied simultaneously in 15 non-collinear directions (b = 1000 s/mm^2); acquisition without diffusion weighing (b = 0) was also carried out. Moreover, 42 contiguous slices, each with a slice thickness of 3 mm, were acquired without gaps. The other acquisition parameters were: TR = 10,000 ms; TE = 70.8 ms; number of excitations (NEX) = 2; matrix = 128 × 128; and FOV = 24 × 24 cm^2. The total acquisition time was 5 min 40 s.

Identification of swallowing

To verify that the subjects swallowed during the activation periods and remained motionless during rest periods, surface electromyography (EMG) was measured with a pair of bipolar Ag/AgCl electrodes in the submental and infrahyoid muscle groups. 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 allows a suitable time resolution for differentiating the switching effect of the readout gradient under the high slew rate condition. The EMG dynamic range was ±65.5 mV to prevent MRI artifact waveforms from saturating the EMG. MR artifacts were filtered out using the BE-MRI Toolbox (Galileo New Technology, Florence, Italy) software. The time at which the swallow-related laryngeal elevation began was recorded for all individual swallows throughout all fMRI scans.

fMRI data analysis

Image pre-processing and statistical analysis were performed using statistical parametric mapping software (SPM2, http://www.fil.ion.ucl.ac.uk/spm/software/). To allow for magnetization equilibrium, the first five images were discarded for each subject. The remaining 95 functional images were first corrected for the acquisition time delay among different slices, and then the images were realigned, for head-motion correction. The images were then spatially normalized to the MNI (Montreal Neurological Institute) template. The volumes were re-sampled, resulting in 3 × 3 × 3 mm^3 voxels, and were spatially smoothed with a 3D Gaussian kernel of 8 mm full-width at half-maximum (FWHM).

According to the EMG, swallowing activity was recorded when the first stimulation-time signal was acquired; then, the canonical haemodynamic response function (HRF) was 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 modelled using a general linear model (GLM) (23).

For patients and controls, contrast images were created for each subject and processed with one-sample *t*-test, for analysing random effects. Additionally, the two-sample *t*-test was used to compare findings between each ALS patient group and control group and between two ALS patient groups. A statistical threshold was set at $p < 0.05$ (false discovery rate, FDR corrected) with a cluster size > 30 voxels.

Regions of interest for DTI data

After image acquisition, DTI data pre-processing was also performed using SPM2 software. First, all of the non-diffusion weighted (b = 0) images were normalized to the MNI template for estimating normalization parameters. Secondly, these derived parameters were applied to the MD and FA maps calculated for each voxel from the diffusion-weighted images in order to normalize them to the MNI template. Finally, the normalized MD and FA maps were spatially smoothed with a Gaussian kernel of 6 mm FWHM.

Age and sex were used as confounding variables in all statistical analyses. Three spatially-normalized masks, with the same spatial size as the normalized FA and MD maps, were built according to the corresponding functional maps of 1) ALS patient group without dysphagia versus control; 2) ALS patient group with dysphagia versus control; and 3) ALS patient group with dysphagia versus without dysphagia, respectively. Subsequently, voxel-based analysis was performed on each paired group using two-sample *t*-test within this mask. Significant differences were defined by a threshold of $p < 0.05$ (FDR corrected) and size clusters > 30 voxels between the patients and controls.

Results

Clinical features and dysphagia examination

The patients' clinical features and lesions are summarized in Table I. Dysphagia data collected were analysed using penetration-aspiration (P-A) scale

scores (22). Based on the results of the initial VFSS, there was no significant difference in the severity of dysphagia among patients.

Verification of fMRI task

All subjects tolerated the scanning well, without excess body movements, and succeeded in swallowing at a consistent rate during fMRI. Head movement was restricted to avoid contamination of the signal by motion artifacts. The laryngeal movement of the EMG indicated that all subjects swallowed once in response to each of the "do swallow" cues. According to the EMGs, swallowing response latencies at baseline showed no significance difference between patients and controls for "do swallow" cues (one-sample t-test, $t=0.69$, $p=0.25$).

fMRI activation group maps

Figure 1A shows the distribution of activation in cortical and subcortical sites (designated in Brodmann areas, BA) of group analysis for controls during the voluntary swallowing. 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 precentral and postcentral gyri, corresponding to the primary motor (MI) and primary somatosensory (SI) associated cortices.

Figure 1B shows cerebral activation associated with voluntary saliva swallowing in ALS patients without dysphagia for group analysis. The voluntary swallowing evoked significant activation ($p<0.05$, FDR corrected) in a number of discrete cerebral regions. During swallowing, the MI cortex (BA 4 and 6), SI cortex (BA 3, 2, 1 and 43), insula, thalamus, and basal ganglia (putamen and lateral globus pallidus) were activated.

Figure 1C shows that prominent activation foci corresponded to the SM cortex and inferior frontal gyrus of group analysis for ALS patients with dysphagia. The activation of the SM cortex was decreased, compared to the controls. No activation was observed in the basal ganglia, insula or thalamus.

In the intergroup comparison, ALS patients without dysphagia showed increased activation in the postcentral gyrus bilaterally, compared to controls (Figure 2A). The group comparison of ALS patients without dysphagia versus with dysphagia revealed activation located in precentral and postcentral gyri in both cerebral hemispheres. Additional activity was also observed in the left thalamus (Figure 2C). ALS patients with dysphagia showed a multifocal, large cluster of reduced activation in the bilateral postcentral gyrus compared to control subjects during the task (Figure 2B). The Talairach coordinates of the most activated voxel of these clusters are given in Table II.

DTI abnormalities maps

In the voxel-by-voxel comparison of FA and MD maps of ALS patients and controls, a distinct pattern of significant changes occurred in the regions of interest. A significant decrease in FA was found bilaterally in the thalamus and the left anterior cingulate gyrus of ALS patients without dysphagia, compared to controls ($p<0.05$; Figure 3A). Significant clusters of reduced FA were found bilaterally in the posterior limb of the internal capsule of ALS patients with dysphagia

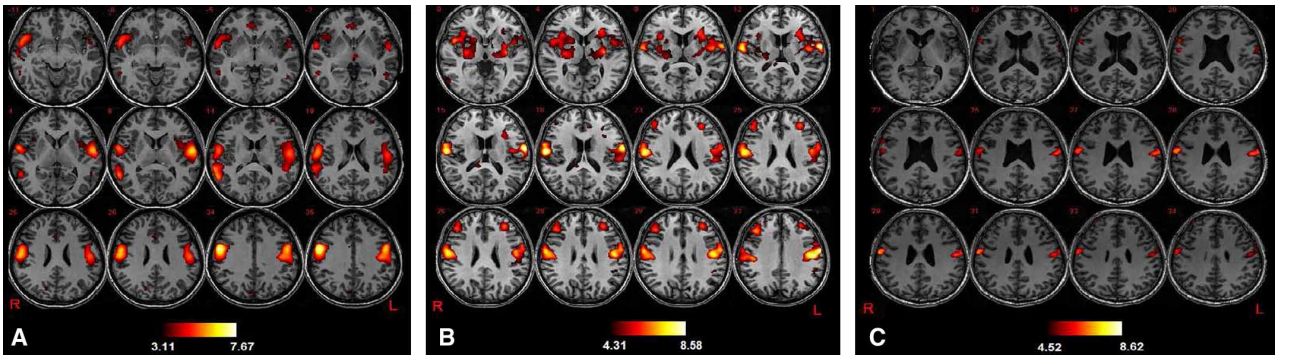

Figure 1. (A) Cerebral activation associated with voluntary saliva swallowing for group analysis of control. Coloured bar represents t-value ($p<0.05$, FDR corrected). Regions of significant activation are displayed on normalized axial brain slices using the Talairach-Tournoux coordinate system. The results showed a significant increase ($p<0.05$, FDR corrected) in fMRI signal intensity in the primary motor cortex (M1, the precentral gyrus, BA 4 and 6), the primary somatosensory cortex (S1, postcentral gyrus, BA 3 and 43), the superior temporal gyrus and middle temporal gyrus (BA 20 and 21), the anterior cingulate gyrus and insular cortex (BA 33 and 13), as well as in the areas of the pallidum, thalamus and cerebellum. The total volume of the activated brain regions in the group map was 9820 mm^3 ($p<0.05$, FDR corrected). (B) Cerebral activation associated with voluntary saliva swallowing in ALS patients without dysphagia for group analysis. The primary motor cortex, the primary somatosensory cortex, middle frontal gyrus, insula, thalamus, and basal ganglia were activated. The maximal activation regions were observed in the SM cortex and basal ganglia. Coloured bar represents t-value ($p<0.05$, FDR corrected). The total volume of the activated cortex and subcortex was 29,200 mm^3. This was three times the mean value of the control group. (C) Cerebral activation associated with voluntary saliva swallow task in ALS patients with dysphagia group analysis. Prominent activation foci corresponded to the SM cortex, inferior frontal gyrus. No activation was observed in the basal ganglia, insula and thalamus. Coloured bar represents t-value ($p<0.05$, FDR corrected).

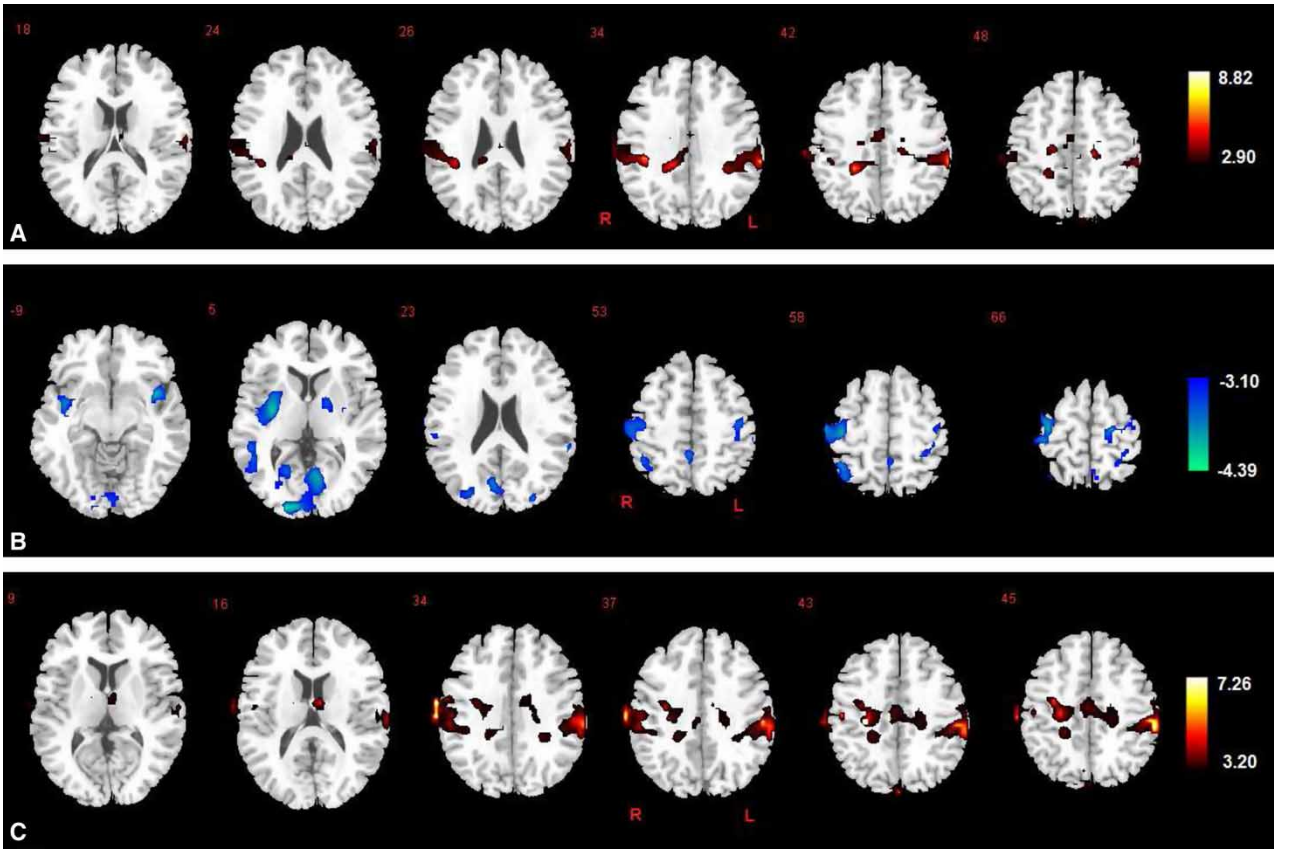

Figure 2. Statistical parametric maps of intergroup comparison were shown in ALS patients compared to 10 controls. (A) ALS patients without dysphagia versus controls. The cluster of increased activation was centred on the primary somatosensory cortex (BA 1, 2, 3) and extended posteriorly into the inferior parietal lobule (BA 40). Additional activity was also observed in the middle cingulate gyrus. (B) ALS patients with dysphagia versus controls. A multifocal large cluster of reduced activation in the bilateral postcentral cortex compared to control subjects. This cluster was centred on the dorsolateral postcentral cortex (BA 1, 2, 3) and extended into the anterior and medial prefrontal cortex and supplementary motor area (BA 6). The insula and basal ganglia underwent reduced activation compared to controls. (C) ALS patients without dysphagia versus ALS patients with dysphagia. The increased activation was located in the primary motor and somatosensory areas (precentral and postcentral cortex) in both hemispheres. Additional activity was also observed in the left thalamus. The activity in those regions was higher and the cluster size was larger ($p < 0.05$, FDR corrected).

compared to controls ($p < 0.05$, FDR corrected; Figure 3B). In addition, a significant reduction in FA was observed in the putamen, as well as in the right and left insula and left posterior cingulate gyrus. Compared to ALS patients without dysphagia, ALS patients with dysphagia had significant clusters of local decreased FA in the left thalamus ($p < 0.05$, FDR corrected; Figure 3C).

The MD had a tendency to increase in ALS patients compared to controls. Furthermore, the MD maps showed features similar to FA maps when comparing abnormalities in regions with functional changes ($p < 0.05$, FDR corrected; Figure 3D, E, F).

Discussion

To our knowledge, this is the first report where a combination of DTI and fMRI was used to produce structural and functional maps of the brains of ALS patients with or without dysphagia. The results of our study show that diffusion abnormalities and cerebral activation maps may identify mechanisms involved in swallowing dysfunction and predict disease prognosis in patients with ALS. Hence, these findings support the theoretical background for the application of DTI and fMRI in patients, especially for patients whose findings were normal by traditional MRI techniques.

This study has three significant implications. First, these data demonstrate a different functional activation mode in ALS patients during swallowing in contrast to healthy controls. These findings indicate that swallowing in ALS patients, like healthy controls, is processed within multiple regions of the cerebral cortex and subcortex regions, corresponding to Brodmann's areas 2, 3, 4, 6, 13, 33 and 43. The prominent swallow-related activation of the precentral and postcentral gyri in a bilateral and asymmetrical manner is consistent with previous event-related task paradigms studies in healthy subjects (26–28). Interestingly, the key finding was that ALS patients without dysphagia showed an over-activation in their SM cortex compared with controls and dysphagic ALS patients. However, ALS patients with dysphagia showed reduced activation in contrast to healthy controls, particularly in the SI

Table II. Brain regions exhibiting changes in activation during dry swallowing.

Cerebral region	Side	Brodmann area	Talairach coordinate (x, y, z) Local maxima of cluster			Cluster volume (voxels)	*t*-value	*p*-value
Group comparison: increased activation (ALS patients without dysphagia vs. controls).								
Postcentral gyrus	R	1,2,3,40	50	−21	37	1003	7.11	0.0000*
	L	2,3	−53	−29	54	815	7.26	0.0000*
Supramarginal gyrus	R	40	65	−24	40	549	7.49	0.0000*
	L	40	−62	−18	40	272	8.77	0.0000*
Middle cingulate gyrus	R	23,24	15	2	36	280	4.93	0.0000*
	L	24	−12	−2	36	203	8.82	0.0000*
Group comparison: decreased activation (ALS patients with dysphagia vs. controls).								
Postcentral gyrus	R	2,3	42	−23	59	270	−3.86	0.0009
	L	2,3	−45	−15	50	148	−3.41	0.0021
Precentral gyrus	R	4,6	39	−18	56	154	−4.13	0.0005
	L	4,6	−24	−8	69	87	−4.1	0.0005
Lingual gyrus	R	17,18,19	9	−43	5	81	−3.92	0.0008
	L	17,18,19	−9	−64	6	147	−3.88	0.0008
Posterior cingulate gyrus	R	30	6	−46	8	39	−3.38	0.0022
	L	30	0	−41	52	80	−3.52	0.0017
Cuneus	R	17,18	18	−90	13	90	−4.39	0.0003
	L	17,18	3	−69	23	112	−3.68	0.0012
Insula	R	13	39	−1	−8	93	−3.61	0.0014
	L	13	−42	6	−5	67	−4.11	0.0005
Putamen	R		30	−8	6	126	−4.33	0.0003
	L		−21	0	8	33	−3.40	0.0022
Lentiform nucleus	L		−20	1	5	88	−4.12	0.0005
Calcarine	R	19,23	15	−96	5	272	−4.23	0.0004
	L	19,23	3	−66	20	289	−3.91	0.0008
Group comparison: increased activation (ALS patients without dysphagia vs. ALS patients with dysphagia).								
Precentral gyrus	R	4,6	48	−16	39	34	7.26	0.0000*
	L	4,6	−50	11	44	35	6.59	0.0001
Postcentral gyrus	R	3,2,1	65	−10	28	262	6.84	0.0000*
	L	3,2,1	−62	−19	26	217	6.13	0.0001
Supramarginal gyrus	R	40,43	65	−19	31	251	6.42	0.0001
	L	40,43	−56	−21	37	165	6.53	0.0001
Superior temporal gyrus	R	21,22	68	−11	12	44	3.99	0.0016
	L	22,42	−65	−14	9	34	3.82	0.0020
Middle cingulate gyrus	R	23	18	−18	42	91	3.33	0.0044
	L	23	0	−12	42	93	3.35	0.0043
Thalamus	L		6	−26	42	35	4.34	0.0009

The MNI coordinates were transformed to Talairach coordinates using mni2tal (http://imaging.mrc-cbu.cam.acuk/download/MNI2tal). The locations of activated areas in each subject were determined by identifying the location of activation in Brodmann areas using established neuroanatomical landmarks (24,25); *p*-values (*) indicated as 0.0000 refer *to* $p < 10^{-4}$.

cortex. Due to the presence of significantly different activation modes from intergroup comparisons, it could be postulated that the cerebral cortex is involved in execution or sensory feedback processing for voluntary swallowing. Considering the brain's plasticity, and based on the changes of these functional maps, our results add novel insights in that reduced activation in the bilateral hemisphere may indicate a poor prognosis, while improvement in dysphagia may be associated with cerebral activation related to a cortical swallowing representation in compensating or recruited areas of the bilateral hemisphere in ALS patients. Therefore, a prospective, longitudinal study with a larger sample is needed to confirm these preliminary findings.

Secondly, in the voxel based analysis of the regions of interest, a distinct pattern of changes in diffusion parameters within the fMRI mask was revealed in ALS patients. We only focused on the DTI abnormalities in regions that showed functional changes by fMRI results. From this first study, we determined the following: in ALS patients with dysphagia, FA and MD were more sensitive and specific for detecting these changes than ALS patients without dysphagia and showed abnormal diffusion in the white matter, bilateral insula, thalamus and the left cingulate gyrus. The abnormalities could be explained by the reduced cortical activation in ALS patients with dysphagia. The DTI abnormalities in the insula, thalamus and cingulate gyrus during voluntary swallowing are related specifically to the act of swallowing and can be explained in terms of dysphagia or prognosis in ALS patients with bulbar onset (26–30). Our findings support the notion that the DTI abnormalities in

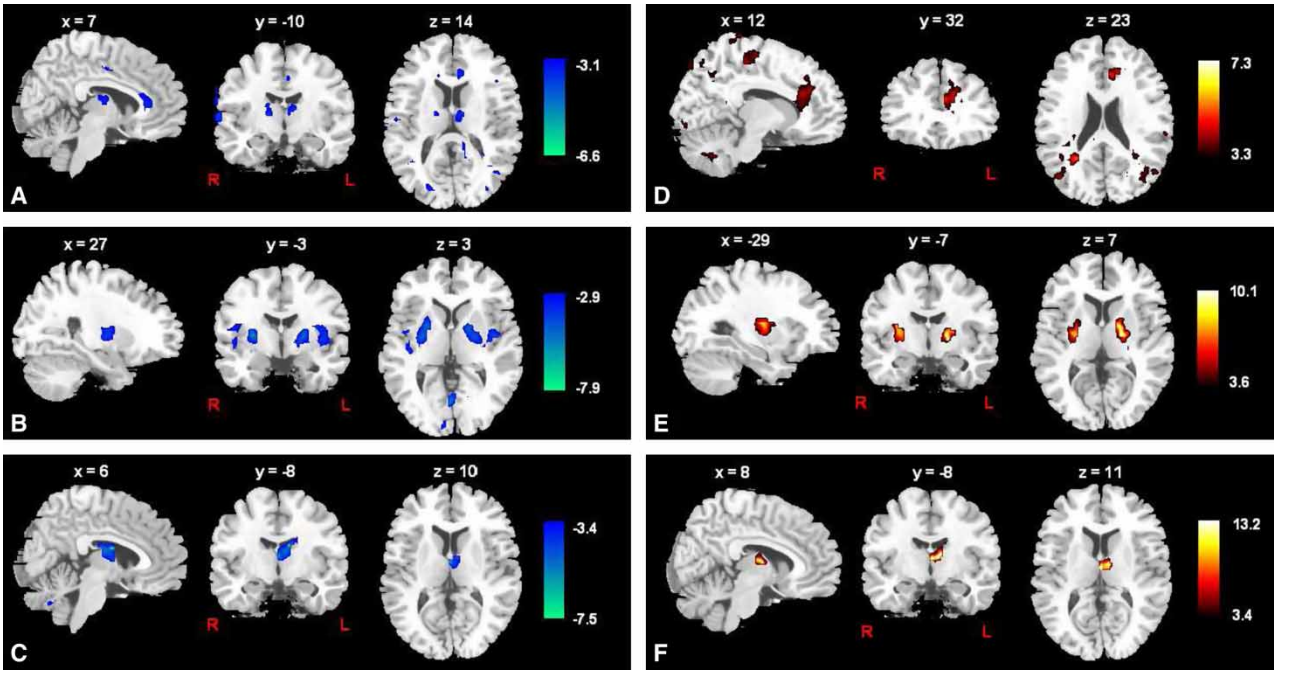

Figure 3. The significantly decreased fractional anisotropy (A, B, C) and increased mean diffusivity (D, E, F) maps were displayed on normalized sagittal (left panel), coronal (middle panel), and axial (right panel) brain slices, respectively. A significant decrease of FA was found bilaterally in the thalamus and the left anterior cingulate when comparing ALS patients without dysphagia to controls ($p < 0.05$, FDR corrected; see A). Significant clusters of reduced FA were found bilaterally in the posterior limb of the internal capsule when comparing ALS patients with dysphagia to controls ($p < 0.05$, FDR corrected; see B). A significant reduction of FA was observed in the putamen, as well as in the right and left insula and left posterior cingulate. Compared to ALS patients without dysphagia, ALS patients with dysphagia had significant clusters of locally decreased FA in the left thalamus ($p < 0.05$, FDR corrected; see C). The MD maps showed similar features to FA maps when comparing the abnormalities in the regions with functional changes ($p < 0.05$, see D, E, F).

these regions may reflect their importance in planning sequential movements associated with swallowing.

Thirdly, DTI and functional MRI together have provided new insights into brain reorganization and the impact of rehabilitation. Our study sheds light on the relationship between changes in brain structure and function and dysphagia in ALS patients. The findings indicate that during swallowing, ALS patients with dysphagia had a more significant reduction in FA and increase in MD, i.e. their cerebral activation was decreased compared to ALS patients without dysphagia. Prominent changes also were observed in the putamen and globus pallidus. The basal ganglia functionally connect the cerebral cortex and the thalamus, with one likely function being gating of sensory input to achieve motor control (31). These data are consistent with the view that voluntary swallowing is represented within distributed networks of functionally distinct cortical foci that participate in the control of swallowing (28). Our results support the hypothesis that cortical or subcortical dysfunction may result in swallowing impairment, due to interruption of corticobulbar output pathways, such as those from the precentral gyrus, or to possible interference with the neural circuitry mediating afferent input processing from the oral cavity and oesophagus. Understanding these mechanisms may provide a means to improve functional outcomes for dysphagic ALS patients.

Conclusions

Our study highlights the potential of DTI and fMRI to detect and monitor structural degeneration and functional changes in the ALS brain. The results obtained for structural and functional mapping show a clear impairment and cerebral activation of multifocal regions in ALS. Furthermore, ALS patients without dysphagia showed cerebral activation in the compensating or recruited areas of the cortex that was related to the cortical swallowing representation. This emphasizes the in vivo neurophsyiological role of intact regions in ALS. In ALS patients with dysphagia, FA and MD were more sensitive markers for detecting diffusion abnormalities than ALS without dysphagia; thus, cerebral activation related to the cortical swallowing representation was decreased. Our results provide support for future efforts to combine non-invasive, neuroimaging techniques to assess prognosis of ALS and to study the effect of therapeutic intervention of ALS bulbar onset.

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