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Altered cortical activation during action observation in amyotrophic lateral sclerosis patients: a parametric functional MRI study

Haiqing Li · Yan Chen · Yuxin Li · Bo Yin · Weijun Tang · Xiangrong Yu · Weiyuan Huang · Daoying Geng · Biyun Zhang

Abstract

Objectives To investigate functional cerebral abnormalities in patients with amyotrophic lateral sclerosis (ALS) using functional magnetic resonance imaging (fMRI) during action observation.

Methods Thirty patients with ALS and 30 matched healthy controls underwent fMRI with an experimental paradigm while observing a video of repetitive flexion-extension of the fingers at three frequency levels or three complexity levels, alternated with periods of a static hand. A parametric analysis was applied to determine the effects of each of the two factors.

Results Action observation activated similar neural networks as the research on execution of action in the ALS patients and healthy subjects in several brain regions related to the mirror-neuron system (MNS). In the ALS patients, in particular, the dorsal lateral premotor cortex (dPMC), inferior parietal gyrus (IPG), and SMA, were more activated compared with the activation in the controls. Increased activation within the primary motor cortex (M1), dPMC, inferior frontal gyrus (IFG), and superior parietal gyrus (SPG) mainly correlated with hand movement frequency/complexity in the videos in the patients compared with controls.

Conclusions The findings indicated an ongoing compensatory process occurring within the higher order motor-processing system of ALS patients, likely to overcome the loss of function.

Key Points
• *Action observation activated similar core nodes of MNS in ALS and controls.*
• *Increased activation within M1, dPMC, IFG and SPG mainly correlated with hand movement frequency/complexity.*
• *Differences in patients and controls may be due to compensatory processes in ALS.*

H. Li · Y. Li · B. Yin · W. Tang · X. Yu · D. Geng (✉)
Department of Radiology, Fudan University, Huashan Hospital, Shanghai, China
e-mail: gengdaoying2245@163.com

Y. Chen
Department of Neurology, Huashan Hospital, Fudan University, Shanghai, China

W. Huang
Department of Radiology, People's Hospital of Hainan Province, Haikou, Hainan Province, China

B. Zhang (✉)
Department of radiotherapy, Affiliated Jiangsu Province Hospital of Traditional Chinese Medicine, Nanjing University of Traditional Chinese Medicine, Nanjing, China
e-mail: bianka0830@126.com

Abbreviations

AAL	Automated anatomical labeling
ALS	Amyotrophic lateral sclerosis
ALSFRS-R	Revised ALS functional rating scale
BCI	Brain–computer interface
dPMC	Dorsal lateral premotor cortex
EPI	Echo-planar imaging
FLAIR	Fluid-attenuated inversion recovery
fMRI	Functional magnetic resonance imaging
IFG	Inferior frontal gyrus
M1	primary motor cortex
MNS	Mirror neuron system
MPRAGE	Magnetization prepared rapid acquisition of gradient echo

SMA   Supplementary motor area
SPM8   Statistical Parametric Mapping 8
SPG   Superior parietal gyrus

Introduction

Amyotrophic lateral sclerosis (ALS) is a progressive neurodegenerative disease that presents with a selective pattern of degeneration of motor neurons in the cerebral cortex, brain stem, and spinal cord; the pattern is not well understood [1]. Studying the functional consequences of such degeneration on the activity of brain regions that are responsible for motor behaviour in patients with ALS is an important step in understanding the basic mechanisms that underlie recovery and plasticity of the motor cortex.

Studies using functional magnetic resonance imaging (fMRI) have verified aberrant brain activation in ALS patients in response to tasks. The majority of ALS studies have found increased activation around the motor cortex in patients with ALS compared with controls during motor tasks [2–4]. In contrast, some studies have reported reduced activation of several cortical regions in ALS patients, including the sensory–motor cortex and contralateral pre-frontal cortex, in response to hand movement [5, 6]. However, the interpretation of the relationship between functional activation and impaired preservation of function in ALS remains controversial.

Action observation, the internal reactivation of the representation of specific motor action without motor output [7], allows patients with movement disorders to be investigated for the internal dynamics of motor control, while avoiding the sensory and motor problems related to motor execution. There are increasing experiments verifying that motor areas are recruited when actions are actually executed and when similar or identical actions are passively observed [8, 9]. The mirror neuron system (MNS) was first described in the macaque monkey [10, 11]. These neurons were discovered during single-cell recordings in areas of the ventral premotor cortex (F5), parietal areas and the anterior intraparietal area when the monkeys performed motor acts as well as when the animals observed another individual performing the same action or a similar action. It has been hypothesized that a similar parieto-frontal "mirror" mechanism is present in the human brain [12, 13].

This study was to investigate motor plasticity in ALS for action observation with parametric fMRI. We hypothesized that ALS patients would show increased activation around the motor cortex, as has been observed in motor execution studies. To test this hypothesis, we used a block paradigm fMRI design to compare cortical activation while participants watched video clips depicting hand movements in ALS patients and healthy controls. To specify further how the rate/complexity correlated to the brain structures, fMRI measurements were performed during the observation of hand activation at three frequency levels and three complexity levels.

Materials and methods

Subjects

Thirty probable or definite (n=23) sporadic ALS patients were recruited consecutively from the neurology department of Huashan Hospital of Fudan University. The ALS patients were diagnosed according to the revised El Escorial criteria [14]. Sporadic ALS was defined as ALS without a family history of ALS. All of the ALS patients were right-handed. The patients were excluded if they had other neurological diseases, psychiatric problems, or visual impairment. The severity of the disease was assessed by the revised ALS functional rating scale (ALSFRS-R) questionnaire [15]. The disease duration was calculated from symptom onset to the scan date, in months. The control group consisted of 30 age, gender, and education-matched healthy volunteers with no history of psychiatric or neurological disorders and with normal MRIs. The study was approved by the local ethics committee of Huashan Hospital of Fudan University, and all of the subjects provided written informed consent.

MRI data acquisition

The subjects underwent one MRI examination on a 3.0 T Siemens Trio with an 8-channel head coil (Erlangen, Germany). The structural MRIs included a 3D high-resolution T1-weighted magnetization-prepared rapid acquisition of a gradient echo (MPRAGE) sequence (TE 2.98 ms, TR 2300 ms, 1.0 mm isotropic resolution and FOV of 256 mm*256 mm) and a fluid-attenuated inversion recovery (FLAIR) sequence (TE 102 ms, TR 9000 ms and FOV of 230 mm*230 mm).

The functional MRI data included two sessions of T2*-weighted gradient-echo echo-planar imaging (EPI TE 35 ms, TR 2000 ms, 4.0 mm*33 slices, matrix 64*64, FOV of 200 mm*200 mm, 90° flip angle, contiguous axial slices) obtained while the subjects performed visual tasks. The slices covered the entire brain and were positioned parallel to the plane intersecting the anterior and posterior commissure.

fMRI stimuli and design

During imaging, the subjects were asked to observe carefully different videotaped actions being performed by another individual. Stimuli for each task were programmed using the E-Prime software (Psychology Software Tools, Inc. Pennsylvania, USA). The subjects saw the stimuli projected via a video

projected onto a screen through a mirror mounted onto the head coil in the scanner. The subjects underwent two consecutive fMRI examinations using a block design, each 4 min and 8 sec in length, consisting of 12 pseudo-randomly presented blocks of 20 seconds (Fig. 1). The first four TR periods from each functional run were removed to allow for steady-state tissue magnetization. In the first run, the subjects were instructed to watch a videotape showing the right hand of another subject performing repetitive flexion-extension of the fingers at three different speeds (0.5, 1, and 2Hz frequencies, respectively), alternating with periods of a static picture of the same hand. The second run consisted of an observation of a movie showing the right hand performing three tasks of different complexities (repetitive flexion-extension of the fingers, four fingers all-to-thumb opposition, and sequential finger-to-thumb opposition) at a rate of 1 Hz, alternating with periods of an image of a static hand. Each of the experimental conditions was presented twice per run, and the order of the runs was counter-balanced across the subjects. Prior to scanning, the subjects were familiarized with the stimulus and with the instructions. During the practice session, the subject was instructed not to perform any movement while observing the actions. Additionally, they were monitored visually during imaging by an observer inside the scanner room to assess accurate task performance and to ensure that the subjects did not move. After each run, the subjects were asked to report what actions they were presented with and whether they had any problems during the task.

fMRI processing and analysis

Preprocessing and analysis of the fMRI data were conducted using the Statistical Parametric Mapping 8 (SPM8) software (Wellcome Trust Centre for Neuroimaging, University College London, UK) implemented in Matlab R2011a (Mathworks, Massachusetts, USA). The subjects with head motion greater than 3.0 mm in translation or 3.0° in rotation (absolute measures) were eliminated. No differences were found in these measures (six parameters obtained from realignment) between ALS patients and healthy controls ($P>0.05$). Normalization to the MNI (Montreal Neurological Institute) standard space was conducted to facilitate the group analysis. Subsequently, the fMRI data underwent resampling with a 2-mm isotropic resolution. The normalized images were spatially smoothed using an 8-mm full-width at-half-maximum isotropic Gaussian kernel and temporal filtering with a high pass filter (t=128 s) prior to conducting the statistical analysis.

The first analysis of each participant used the simple boxcar approach, modelling the difference between the action, irrespective of the rate or difficulty, and the static baseline condition. The confounding factors from head movement (six parameters obtained from realignment) were included in the model as multiple regressors. We then used a parametric approach to allow for a linear or nonlinear relationship between either the rate or complexity (three levels each) and the BOLD signal changes. The second stage random effect analysis was then performed using one-sample (healthy control and ALS groups) and two-sample (comparisons between the groups) t-tests on contrast images obtained from each subject for each comparison of interest. The age and gender of each subject were entered as additional covariates of no interest. The relationship between the BOLD signal changes (response to three kinds of different rates and complexities) and ALSFRS-R in the patient group was examined as a covariate of interest during a within-group analysis of all of the conditions of interest. The contrasts were performed across the entire brain using standard threshold criteria [16], with significant activation at a voxel-level of $p<0.001$ (uncorrected) and a cluster-wise correction (p value of cluster <0.05) for the within-group analysis. The full-extent clusters showing significant activation were reported below a voxel-level of $p<0.001$ (uncorrected) between the group analyses. Automated anatomical labelling (AAL) [17] was used because it consistently labels clusters with reference to a standard atlas.

Results

Two patients and two controls were excluded from the analyses because of head motion. The final analysis consisted of 28
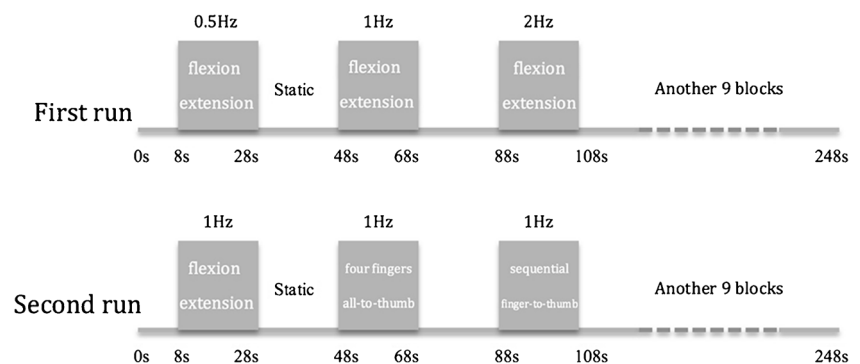
Fig. 1 fMRI design and stimuli

Table 1 Demographic and clinical characteristics of the subjects

	ALS	controls	P*
No.	30	30	
Mean age±SD (range)	53.5±11.1 (30–75)	51.7±10.9 (30–68)	0.52
Gender (male: female)	15:15	10:20	0.19
ALSFRS –R score	36.5±7.9 (17–47)		
Disease duration (months)±SD	24.5±18.7 (3–107)		
Rate of disease progression±SD	0.57±0.4 (0.1-1.7)		

Data in the table are displayed as the mean±SD (range);

*t test or X^2 test was carried out between the two groups;

and Rate of disease progression was calculated as (48-revised ALS Functional Rating Scale)/disease duration

patients and 28 controls. The demographic and clinical characteristics of the subjects are presented in Table 1. The groups did not differ in the mean age and gender. The coordinates of the maximum voxel t value, its approximate anatomical location, and the numbers of voxels are shown for each significant cluster in Table 2.

Table 2 Brain regions demonstrating the main effects of the observation of hand action in the ALS and control groups

		voxel	Anatomic regions	Brodmann area	Z	MNI Coordinates		
						x	y	z
ALS								
	Cluster 1	3972	left inferior parietal lobule	39/40	7.08	−45	−78	3
			left primary motor area	4				
			left somatosensory area	1/2				
			left superior parietal lobule	7				
			left supplementary motor area	6				
			left dorsal premotor gyrus	6/9				
			left inferior frontal gyrus	44/45				
	Cluster 2	4884	right somatosensory area	1/2	6.50	33	−48	60
			right superior parietal lobule	7				
			right primary motor area	4				
			right dorsal premotor gyrus	6/9				
			right inferior frontal gyrus	44/45				
			right inferior parietal lobule	39/40				
			right supplementary motor area	6				
Control								
	Cluster 1	3249	left inferior parietal lobule	39/40	6.878	−45	78	3
			left primary motor area	4				
			left somatosensory area	1/2				
			left superior parietal lobule	7				
			left supplementary motor area	6				
			left inferior frontal gyrus	44/45				
			left dorsal premotor gyrus	6/9				
	Cluster 2	4371	right primary motor area	4	6.60	42	−72	9
			right somatosensory area	1/2				
			right inferior parietal lobule	39/40				
			right superior parietal lobule	7				
			right supplementary motor area	6				
			right dorsal premotor gyrus	6/9				
			right inferior frontal gyrus	44/45				

Main effects of the observation of hand action

In comparing the observations of hand action and the static baseline condition, no difference in the main effect was observed between the rate-related task and complexity-related task in a within-group analysis ($P>0.05$). The brain regions showing consistent activation were observed in both groups symmetrically across the bilateral hemispheres in two large clusters (Fig. 2). These clusters involved the inferior frontal gyrus (IFG, BA 44/45), dorsal parts of the superior frontal gyrus and middle frontal gyrus (dorsal premotor cortex, dPMC, BA 6/9), precentral gyrus (primary motor area, M1, BA 4), supplementary motor area (SMA, BA 6), inferior parietal gyrus (supramarginal gyrus, IPG, BA40), postcentral area (primary somatosensory cortex, SI, BA1/2) and superior parietal gyrus (SPG, BA 7). The between-group comparison of observations versus rest conditions demonstrated greater activation of the bilateral dPMC, IPG, and SMA in the ALS group compared with the control group (Fig. 3, Table 3). The healthy controls failed to present greater activation compared with the ALS patients under any of the conditions.

Parametric BOLD responses to increasing movement frequency of observation

Applying the first-order term, the group analysis demonstrated the BOLD response magnitude correlating with the finger movement rate of observation, with signal increases observed in the bilateral M1 (linear correlation, Pearson correlation, $R=0.73$) around the central sulcus hand region and the dPMC. In contrast with the control group, the ALS group showed greater activation in the M1 and dPMC areas related to the rate (Fig. 3). These results are summarized in Table 3.

Parametric BOLD responses to increasing spatiotemporal complexity of observation

A significant positive linear correlation ($R=0.82$, Pearson correlation coefficient) was found in terms of increases in the BOLD response with spatiotemporal complexity in several regions, including the bilateral SPG, corresponding to BA 7, areas of the IFG, with an activation peak in the intraparietal sulcus, and the dPMC, with an activation peak around the superior precentral sulcus. Applying the second-order term, the ALS patients showed greater complexity-related activation than the controls in the bilateral SPG and right IFG (Fig. 3, Table 3).

Correlation between fMRI and ALSFRS-R score

There were no significant correlations between functional impairments in the ALS patients, measured by ALSFRS-R, and activation caused by action observation in any of the regions ($P>0.05$).

Discussion

Network for exploratory hand movement observation (main effect)

During the observation activity, brain regions showing consistent activation were observed in both groups across both hemispheres in the IFG, dPMC, SMA, M1, IPG, SPG and, more significantly, SI. These areas are established to be related to the MNS, as if they were performing the same actions [18]. In a recent study, the SI was explicitly shown to address this issue during action observation [19]. Furthermore, regions of the SI have been reported to respond to the sight of touch in other
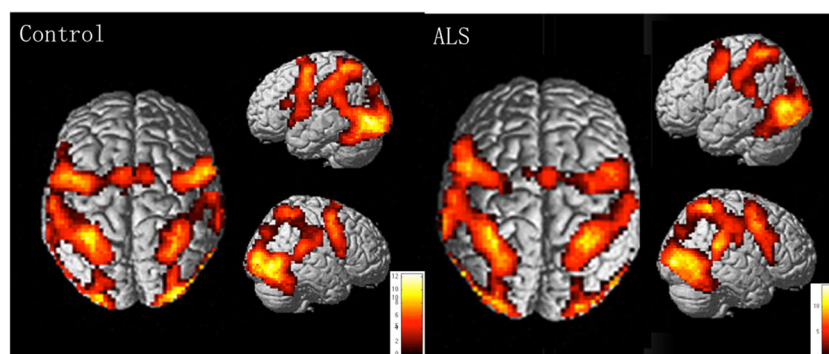

Fig. 2 The brain regions showing consistent activation were observed symmetrically across bilateral hemispheres in two large clusters in both groups. These clusters included the inferior frontal gyrus (IFG, BA 44/45), dorsal parts of the superior frontal gyrus and middle frontal gyrus (dorsal premotor cortex, dPMC, BA 6/9), precentral gyrus (primary motor area, M1, BA 4), supplementary motor area (SMA, BA 6), inferior parietal gyrus (supramarginal gyrus, IPG, BA40), postcentral area (primary somatosensory cortex, SI, BA1/2), and superior parietal gyrus (SPG, BA 7). (one-sample t test, $P<0.05$, FDR correction) the bars stands for the degree of activation

Fig. 3 **a** The between-group comparison of observation versus rest conditions demonstrated greater activation of the bilateral dPMC, IPG, and SMA in the ALS group compared with the control group. (two-sample *t* test, *P*<0.001) **b** The ALS group showed greater activation in areas of the M1 and dPMC relative to the rate. (unpaired *t* test, *P*<0.001) **c** The ALS patients showed greater complexity-related activation than controls in the bilateral SPG and right IFG. (unpaired *t* test, *P*<0.001) the bars stands for the degree of activation
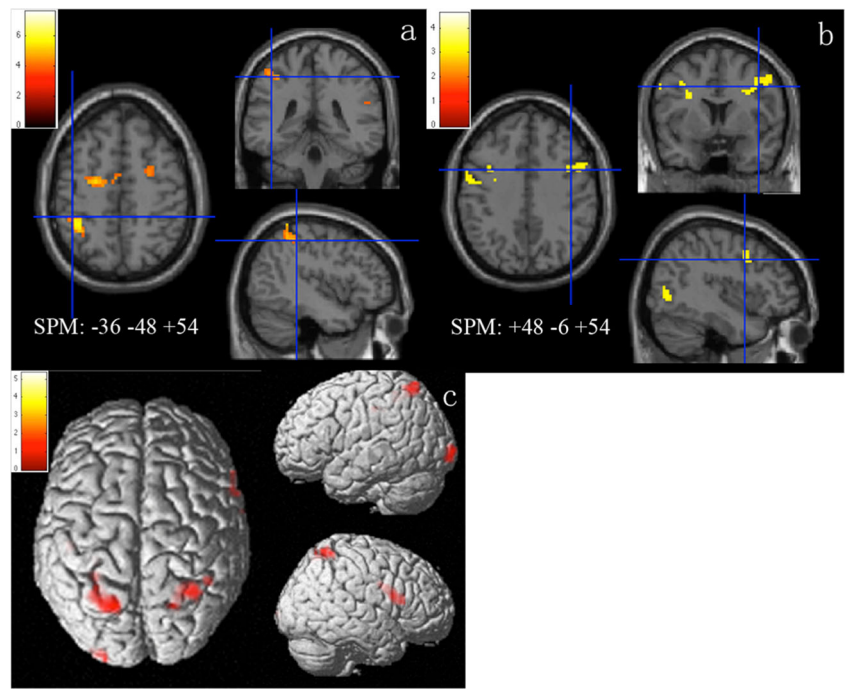
studies [20, 21]. However, the neurobiology of SI activation during action observation remains elusive. One interpretation for this phenomenon is that this region might act as a simulator of "what it could feel like to act as seen." The other interpretation is that an action needs to be mapped onto one's own sensorimotor system for complete understanding of the motor components of the observed action [19]. The most striking result of this study was the contrast between the groups for action observation versus rest. In agreement with previous studies [4, 6], this comparison demonstrated that some of these regions, in particular the dPMC, IPG, and SMA, were more activated in patients with ALS than in controls. Some studies proposed that the dPMC was involved in learning appropriate action responses, action planning, and action preparation based on arbitrary cues [22, 23]. In addition, the dPMC has been suggested to integrate different pieces of sensorimotor information to formulate the appropriate motor program [24]. Given this current knowledge regarding the dPMC, we

Table 3 Distribution of significant brain regions of main effects, rate-and complexity-related of the observation of hand action in the ALS patients compared with controls

	Voxel	Anatomic regions	Brodmann area	Z	MNI Coordinates		
					x	y	z
Main effects							
	116	left dorsal premotor gyrus	6/9	4.06	−21	−9	48
	123	right inferior parietal lobule	39/40	4.54	57	−27	39
	92	left inferior parietal lobule	39/40	4.38	−36	−48	54
	21	left supplementary motor area	6	3.12	−6	−9	45
	34	right dorsal premotor gyrus	6/9	3.41	27	0	13
rate-related	106	left primary motor area /dorsal premotor gyrus	4 6	5.68	−48	−6	57
	29	right dorsal premotor gyrus / primary motor area	6/9	3.87	48	−6	54
complexity-related							
	132	left superior parietal lobule	7	5.05	−24	−63	60
	81	right superior parietal lobule	7	4.50	33	−57	66
	60	right inferior frontal gyrus	44/45	4.73	63	21	15

suggest that the dPMC might provide the composition of the appropriate motor program during movement preparation within the action observation networks. The IPG region is thought to be the human homologue of the macaque rostral inferior parietal areas, i.e., the PFG and PF. In this area, mirror neurons were discovered using invasive recordings [25]. This area is concerned with hand movements, visuomotor space and shape representation [26]; therefore, its increased activation in patients might relate to the need to convey all sensory information regarding the motor act to the frontal and motor cortices. The SMA is related to movement preparation, coordination, and execution [27] and might influence finger movements either via direct action on the cord motor neurons [28] or through connections to the primary sensorimotor cortex. Hyperactivation of the previously mentioned areas in ALS subjects during the observation of human motion suggests that compensatory processes exist to overcome neuronal and functional loss and provides strong support for the hypothesis of "atypical" activity of the MNS, which might be at the core of the motor disorders in ALS. In agreement with our study, one study reported increased activation in some regions (e.g., the pre-motor cortex) during motor imagery in ALS patients compared with controls [29]. In contrast, a study examining mirror neuron abnormalities in patients with ALS demonstrated reduced activation during motor imagery in the left IPG as well as in the anterior cingulate gyrus and medial prefrontal cortex compared with controls [30]. It could be assumed that for motor imagery, it is extremely difficult to control for the actual performance between subjects.

Activation of associated brain regions via observations of hand action with sequential rate increases

A dominant frequency effect was observed for areas of the bilateral M1, together with smaller effects within the dPMC during hand action observation in our study. Our findings regarding the speed were in agreement with previous studies on the relationship between velocity and cortical activation during motor execution. Primate studies described a speed–velocity modulation of neurons in the M1 [31] and dPMC [32]. Similarly, numerous neuroimaging studies in humans have observed increasing activation in the M1 as the movement frequency increased [33–35], whereas frequency effects were only sporadically reported for the dPMC, as shown in the ALS patients in this study. This result confirms that dPMC activity plays some role in movement execution, although the dPMC likely has more pronounced involvement in the control of other aspects of movement. Additionally, in this study, ALS patients exhibited stronger activity correlated with the speed of action observation than the controls in areas of the M1 and dPMC in both hemispheres, suggesting that ALS patients might present a compensatory activity in the frontal network to obtain control during movement observation. The higher order motor control

structures in ALS patients are involved in compensatory processes to overcome neuronal and functional losses.

Activation of associated brain regions with sequential complexity in hand action observation

Activation correlating with the complexity of action observation was found for the IFG, SPG and dPMC of both cerebral hemispheres. The rostral part of the IFG is in Broca's region (BA 44 and BA45). In contrast to the concept of Broca's area as a mere representation centre for speech or orofacial movements, a wider range of complex motor functions has recently been attributed to this area. Various functional imaging studies have reported the activation of Broca's area during finger movements [36], motor imagination [37], and motor observation [38]. According to those investigations, a clear representation of finger movements exists in BA44. Broca's region is most likely involved in the context of specific stimuli recognition [39]. To further differentiate the results, activation within BA44 was ascribed to the initiation and termination of simple actions, whereas activation within BA45 was more likely responsible for the supraordinate aspect of the action [39]. The superior parietal gyrus is anatomically linked to the dPMC, which constitutes the fronto-parietal circuit. Various functional imaging studies have previously indicated that increased activation in the dPMC, with the SPG, correlated with the complexity of externally cued finger movements [40, 41]. Consistent with these studies, a parametric fMRI study supported a functional interaction between the SPG and dPMC in the control of complex finger sequencing [42]. The dPMC is hypothesized to play a role in the programming of sequential movements under sensory guidance as well as in the "retrieval of abstract action plans that are stored in the parietal lobe" [43]. Accordingly, the parietal-premotor circuit likely serves as the sensorimotor transformation unit. In agreement with these studies, patients with parietal lobe damage have demonstrated an impairment of these control processes during bimanual coordination, resulting in a decoupling of the limb trajectories [44]. The activation of the fronto-parietal areas observed in this study might be related to higher order visuomotor processing, a view that is consistent with previous findings [45]. In addition, the patients with ALS in our study demonstrated increased cortical activation in the IFG and SPG related to sequential complexity in hand action observation compared with the controls. The enhanced activity in these areas for the ALS patients might indicate that the functional loss in the motor areas of ALS patients leads to an increased request for high-level control in motor tasks.

Limitations

Although we enrolled patients with no clinical involvement of the cognitive system or visual impairment, and we assessed

MNS activity elicited by action observation, rigorous cognitive and visual assessments were not performed in this study.

Conclusion

Although the findings of this study should be replicated in another group of patients, they have several fundamental implications. First, the increased recruitment of pre-existing latent pathways, as well as of cross-modal regions, might play a role in the adaptation to CNS damage in ALS. Second, the higher order motor control structures in ALS patients may be involved in compensatory processes to overcome neuronal and functional loss. Finally, action observation offers some advantages for studying the motor system with fMRI to avoid possible biases related to different task performances between patients and controls. This makes the assessment of more disabled patients feasible.

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