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Biba R. Stanton
V.C. Williams
P.N. Leigh
Steven C.R. Williams
C.R.V. Blain
J.M. Jarosz
Andrew Simmons

Altered cortical activation during a motor task in ALS

Evidence for involvement of central pathways

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B.R. Stanton, MRCP
V.C. Williams, MRCP
P.N. Leigh, FRCP (✉)
S.C.R. Williams, PhD
C.R.V. Blain, MRCP
Dept. of Clinical Neuroscience
MRC Centre for Neurodegeneration Research, Institute of Psychiatry
King's College London
De Crespigny Park
London SE5 8AF, UK

A. Simmons, PhD · S.C.R. Williams, PhD
Centre for Neuroimaging Sciences
Institute of Psychiatry
King's College London
London, UK

J. M. Jarosz, FRCR
Dept. of Neuroradiology
King's College Hospital
London, UK

Abstract *Objective* To test the hypothesis that patients with amyotrophic lateral sclerosis (ALS) show increased cortical activation during a motor task compared to both healthy controls and patients with muscle weakness due to peripheral lesions. *Methods* Functional magnetic resonance imaging (fMRI) was used to measure activation during a block design paradigm contrasting right hand movements against rest in sixteen patients with ALS, seventeen healthy controls and nine patients with peripheral lesions. The groups were matched for age and gender and the two patient groups were matched for their degree of upper limb weakness. Analysis used a non-parametric approach to perform a 3 way hypothesis-driven comparison between the groups. *Results* During the motor task, patients with ALS showed increased cortical activation bilaterally, extending from the sensorimotor cortex [Brodmann areas (BA) 1, 2, 4] posteriorly into the inferior parietal lobule (BA 40) and inferiorly to the superior temporal gyrus (BA 22) when compared to peripheral lesion patients and controls. In addition, ALS patients showed reduced activation in the dorsolateral prefrontal cortex (DLPFC) extending to anterior and medial frontal cortex (BA 8, 9, 10, 32). *Conclusions* We conclude that alterations in cortical function in ALS differ in sensorimotor and prefrontal regions. Importantly, we have shown that these changes do not reflect confounding by weakness or task difficulty, but are likely to be related to upper motor neuron pathology in ALS.

Key words ALS · MRI · functional imaging · motor system

Introduction

Amyotrophic lateral sclerosis (ALS) is characterised by degeneration of corticospinal tract motor neurons and by lower motor neurons of the brain stem and spinal cord [1–3]. Previous functional imaging studies have found altered patterns of cortical activation during motor tasks in patients with ALS compared to controls [4–8]. For example, using positron emission tomography to measure cerebral blood flow (rCBF) during a motor task showed an increased area of activation extending beyond the primary sensorimotor cortex (SMC) compared to controls. This 'boundary shift' effect was not seen in subjects with pure lower motor neuron (LMN) syndromes. However, the ALS patients had slower response times, suggesting that they may have found the task more difficult. Subsequently, functional magnetic resonance imaging (fMRI) has been used to investigate cortical

activation in ALS, with attempts to minimise the confounding effect of task complexity and difficulty. In one such set of experiments [7] ALS patients showed more extensive cortical activation than controls when performing an 'easy' version of a motor task, but controls performing a more difficult task showed a similar pattern of activation to the ALS patients. The authors hypothesised that changes in cortical activation reflected the difficulty of the task for subjects with impaired motor function rather than cortical reorganisation or adaptation.

If increased activation of the primary motor cortex is directly related to corticospinal tract pathology rather than to the way patients with weakness perform the task, fMRI might provide a method to investigate mechanisms of neuronal damage and adaptation. In this study, we used fMRI to clarify this issue by including a group of subjects with weakness due to peripheral lesions. We conclude that abnormalities of cortical activation in ALS most likely do reflect cortical adaptation as a result of corticospinal tract damage.

Methods

Subjects

The study involved 16 patients with ALS, 9 patients with peripheral lesions (LMN and muscle) and 17 healthy controls. All subjects were right-handed and were able to hold and move a joystick. No subject studied had a history of cerebrovascular disease, hypertension or diabetes. The study was approved by the Institute of Psychiatry local research ethics committee and all subjects gave written informed consent prior to their inclusion in the study.

Patients with ALS and peripheral disorders were recruited from the motor disorders clinic at King's College Hospital. ALS patients were diagnosed following clinical examination by a consultant neurologist supported by electrophysiological evidence of denervation. Other conditions were excluded by appropriate blood tests and neuroimaging [9]. Patients were categorised according to the revised El Escorial criteria [10] (definite $n = 3$, probable $n = 10$, possible $n = 3$). The peripheral lesion group (PL) included 7 patients with multifocal motor neuropathy, 1 with scapular-peroneal muscular dystrophy and 1 with Welander's myopathy. Healthy controls, with no history of neurological disorder, were recruited from the spouses and friends of patients and from members of a local voluntary organisation.

All subjects underwent a clinical assessment including full neurological examination. The MRC sum score for upper limb muscle groups was used as a measure of upper limb power [11]. This is the MRC grades (0–5) for shoulder abduction, elbow flexion, elbow extension, wrist flexion, wrist extension, finger flexion and finger extension on each side, summated to give a maximum total score of 70. Grip and pinch strength in the right hand were measured with a Jamar dynamometer (Jackson, MI, USA) and B&L Engineering pinch gauge (Santa Fe Springs, CA, USA). ALS patients were assessed with the revised ALS functional rating scale (ALSFRS-R) [12]. Patients and controls all performed a short version of the motor task for practice before MRI scanning.

MRI procedures

Experimental design and fMRI paradigm

A block design paradigm was used to contrast right hand movements against rest. During scanning, subjects moved a joystick with their right hand. The joystick had low friction and could be moved approximately 6 cm in one of four possible directions (left, right, forward, back). Subjects were instructed to make joystick movements in a freely selected random sequence. Before scanning, subjects were trained in using the joystick and observed to ensure that they were able to do so fluently. In each condition a command was presented on a screen every three seconds to pace the task. During the rest condition, the command "REST" was used and subjects were asked not to make any movement. During the motor condition, subjects were asked to make freely selected joystick movements in response to the command "MOVE". The two conditions alternated in 30 s blocks, with the order counter-balanced between subjects. 5 blocks of each condition were performed.

Subjects' response times (time from prompt to moving joystick though its full range of movement) and errors (failure to move the joystick through its full range of movements in any of the four directions) were recorded. In addition, the pattern of joystick movements was recorded in order to determine the degree of randomness with which movements were selected. Evans' random number generation score (RNG) [13] was calculated using the RGCalc programme [14] as a measure of randomness. This method uses the distribution of pairs of adjacent responses to calculate a score between 0 (perfectly random responses) and 1 (completely predictable responses).

Data acquisition

Functional MRI data were acquired on a GE Signa NV/*i* 1.5 Tesla MRI scanner (General Electric, Milwaukee, WI, USA). 100 T2* weighted EPI volumes depicting BOLD (Blood Oxygenation Level Dependent) contrast were acquired in each of 16 non-contiguous near-axial planes (7.0 mm thick with 0.7 mm interval, in-plane resolution 3 mm) parallel to the Anterior Commissure-Posterior Commissure line (TE 40 ms, TR 3000 ms, flip angle 90°, number of signal averages = 1). Data acquisition from patients and controls was interleaved to ensure that a shift in scanner performance would not lead to spurious results.

T2-weighted fast spin echo images were also acquired for each subject from 60 contiguous 3mm slices (echo train length = 8, field of view = 220 × 220 mm matrix size 256 × 256) and were reviewed by an experienced neuroradiologist.

Data analysis

All fMRI data analysis was undertaken using locally written software, which has been extensively validated [15–19]. All of the analysis up to the group stage was made blinded to the subjects' identity.

Time-series analysis

Prior to time-series analysis, data were corrected for the effects of head motion in 3D as previously described [18]. The data were analysed using a general linear model in which the task design was convolved with a mixture of two one-parameter gamma variate functions (peak responses at 4 and 8 s) to account for haemodynamic delay and dispersion. The time series at each voxel was regressed on the convolved design. The parameters obtained from the regression were used to calculate a "goodness of fit" statistic [the ratio of the sum of squares of the model fit and the residual

sum of squares (SSQ ratio)] at every voxel. The significance of the statistic was then assessed by a data-driven permutation approach [16, 17].

Group activation maps

In order to calculate group activation maps, data for each individual were transformed into the standard space of Talairach and Tournoux [15, 20]. The median value of the goodness of fit statistic was calculated at every voxel in standard space (medians were used to minimise outlier effects). The significance of these median values were then assessed using non-parametric data-driven, non-permutation-based procedures [15] and then extended to cluster level [19].

Between group comparisons

Differences in activation between groups were tested for significance using an Analysis of Variance (ANOVA), at each voxel in standard space [15] A similar cluster-wise testing procedure to group mapping was adopted to test for significant differences between the groups. A three-way hypothesis-driven approach was used, to test the hypothesis that ALS patients showed increased activation compared to both controls and peripheral lesion patients. In addition, we performed individual comparisons of activation in the ALS patients compared with the two control groups.

Correlations

To examine neural regions whose magnitude of response correlated with upper limb power (MRC upper limb score) mean response time and disease duration, overlap maps were produced combining regions activated by performance of each condition, and regions correlating ($P < 0.0001$, fewer than one false-activated voxel expected over the whole brain) with these measures.

Results

Subject characteristics

The demographic and clinical data for the three subject groups are presented in Table 1. The three groups were comparable with respect to age and gender. The two patient groups were well matched for MRC upper limb score (independent samples t test: $t = -0.64$, d.f. 22, $P = 0.949$) and pinch and grip strength ($t = -0.779$, d.f. 19, $P = 0.446$; $t = -0.054$, d.f. 19, $P = 0.958$). Disease duration was significantly shorter in the ALS patients ($t = -3.502$, d.f. 23, $P = 0.002$). None of the patients showed abnormal high signal in the corticospinal tract on T2-weighted images.

Performance on fMRI motor task

All subjects performed the paradigm successfully. The median error score was 0 in each group (range 0–3). The response times and stereotypy of responses for each group of subjects are shown in Table 1. There was no statistically significant difference between the three groups in response times (one way ANOVA $F = 0.395$; d.f. = 2,36; $P = 0.670$) or randomness of movement (one way ANOVA $F = 0.06$; d.f. = 2,35; $P = 0.942$). The proportion of joystick movements in each direction did not differ significantly between the groups.

fMRI group maps

As expected, in all three groups the largest significant cluster of activation during the right motor task involved the left sensorimotor cortex. In controls, this cluster was centred on the left sensorimotor cortex (SMC) and extended posteriorly into the inferior parietal lobule (LPi) and inferiorly to the superior temporal gyrus (STG), inferior frontal gyrus (IFG) and insula. In addition, controls showed a cluster of activation centred on the right STG extending into IFG and insula and a third cluster involving the anterior cingulate cortex (ACC) and medial pre-frontal cortex. In ALS patients, there was a large cluster of activation extending from the left SMC posteriorly into the LPi and inferiorly to the STG. ALS patients also showed a slightly smaller cluster of activation involving these areas on the right side, but showed no activation in the frontal lobes. In peripheral lesion patients, the largest cluster of activation was centred on the left LPi but extended anteriorly into the SMC and inferiorly to the STG. Peripheral lesion patients also showed a cluster of activation involving the right LPI, SMC and STG and another significant cluster in the ACC and medial frontal lobe. The size of each cluster and Talairach coordinates of the most activated voxel are given in Table 2.

The group maps also demonstrated significant areas of deactivation associated with the motor task in all three groups. The controls showed a cluster of deactivation involving the right posterior cingulate cortex, precuneus and retrosplenial cortex. The ALS patients showed a large cluster of deactivation involving the dorsolateral pre-frontal cortex (DLPFC) and ACC bilaterally as well as the left frontal pole and PMC. The peripheral lesion patients showed a very large area of deactivation involving the ACC, medial frontal lobe, PCC, precuneus and paracentral lobule bilaterally. The size and Talairach coordinates of the significant clusters of deactivation are shown in Table 2.

fMRI group comparisons: areas of increased activation in ALS patients

In the three-way comparison, patients with ALS showed a single large cluster of increased activation bilaterally compared to both controls and patients with peripheral lesions (Fig. 1). On both sides, the cluster of increased activation was centred on the

Table 1 Subject characteristics and functional magnetic resonance imaging (fMRI) task performance

	Amyotrophic lateral sclerosis (ALS) patients	PL patients	Controls
n	16	9	17
Age, *y*	55.1 ± 8.5	51.9 ± 10.6	53.3 ± 16.4
Gender (M/F)	12/4	7/2	11/6
MRC upper limb score[a] (max 70)	63.3 ± 6.55	63.5 ± 7.27	b
Pinch strength[a], kg	4.73 ± 2.56	5.61 ± 2.58	b
Grip strength[a], kg	28.3 ± 13.5	28.7 ± 14.8	b
Disease duration, *y*	2.16 ± 1.55*	7.76 ± 6.15*	b
ALSFRS-R score (max 48)	41.1 ± 4.1	b	b
Mean response time[a] (s)	0.51 ± 0.16	0.52 ± 0.12	0.56 ± 0.19
RNG[a]	0.54 ± 0.04	0.55 ± 0.06	0.55 ± 0.06

Values represent mean ± SD
*$P < 0.05$
[a]Data for MRC upper limb score was missing for 1 PL patient. Data for pinch and grip strength were missing for 4 ALS subjects. Response time data was missing in 3 subjects (2 ALS patients, 1 control) and randomness data in 4 subjects (2 ALS patients, 2 controls)
[b]Data not collected for this group

primary sensorimotor cortex (BA 1, 2, 4) and extended posteriorly into the inferior parietal lobule (BA 40) and inferiorly into the superior temporal gyrus (BA 22). These results were confirmed in the individual comparisons of ALS patients with controls and patients with peripheral lesions. The Talairach coordinates of the most activated voxel of all significant clusters are given in Table 3.

fMRI group comparisons: areas of reduced activation in ALS patients

In the three-way comparison, patients with ALS showed a single large cluster of reduced activation in the left prefrontal cortex compared to both controls and patients with peripheral lesions during the task (Fig. 2). This cluster was centred on the left dorsolateral pre-frontal cortex (DLPFC; BA 9) and extended into the anterior and medial prefrontal cortex and supplementary motor area (BA 8, 10, 32, 6). However, in the individual comparisons of ALS patients with controls and PL patients there were no areas where activation was significantly reduced in ALS patients. The Talairach coordinates of the most activated voxel of this cluster are given in Table 3.

fMRI data: correlations

There were no significant correlations between weakness (as measured by MRC upper limb score), reaction time or disease duration and activation in any of the regions identified in the group comparisons.

Discussion

Our findings demonstrate that patients with ALS show an altered pattern of cortical activation during a motor task compared to controls and to patients with the same degree of upper limb weakness due to peripheral lesions including lower motor neuron syndromes and muscle disorders.

Increased activation around the motor cortex

Increased activation extending beyond the primary sensorimotor cortex in ALS patients has been shown consistently in previous studies using both PET and fMRI [4–8]. Comparisons between the results of these studies are complicated by their different approaches to analysis and presentation of data. Most studies have reported increased activation in the contralateral sensorimotor cortex [4, 5, 7]. In the study of Konrad et al. [6] the volume of activation in this area was not increased, but its centre of mass was shifted anteriorly [6]. All studies have reported increased activation in premotor areas [4–8], and most studies have reported increased activation in the inferior parietal lobule (area 40) [4–6] and anterior cingulate cortex [4, 7, 8]. Areas less consistently showing increased activation include ipsilateral regions (sensorimotor cortex [5, 7], premotor cortex [7, 8] and inferior parietal lobule [6]), contralateral anterior insula [4], and contralateral cerebellum [6, 8] and brainstem [8]. Thus, our findings are consistent with previous observations, although the centre of increased activation in our sample was rather more posterior than has previously been reported. We found clear evidence of increased activation in ipsilateral regions, but did not confirm the recent finding of altered subcortical activation in ALS [8].

Despite these consistent findings of increased cortical activation in ALS, their interpretation has remained controversial. If the motor tasks used in fMRI experiments are more difficult for people with ALS they may activate additional motor areas by

Table 2 Significant 3 dimensional clusters of activation (A) and deactivation (D) in controls, amyotrophic lateral sclerosis (ALS) patients and PL patients

Group	Effect	No of voxels	Talairach coordinates (most activated voxel)			*P* value	Position of most activated voxel
			x	*y*	*z*		
Control	A	469	−36.1	−33.3	47.9	0.001	L post-central gyrus (BA40)
Control	A	144	50.6	14.8	−1.7	0.006	R superior temporal gyrus (BA22)
Control	A	126	0.0	−3.7	42.2	0.005	Cingulate gyrus (BA31)
Control	D	321	14.4	−44.4	42.4	0.003	R posterior cingulate (BA31)
ALS	A	375	−39.8	−33.3	47.9	0.002	L post-central gyrus (BA 40)
ALS	A	249	57.8	−18.5	14.9	0.007	R post-central gyrus (BA 40)
ALS	D	511	−18.1	33.3	42.4	0.004	L middle frontal gyrus (BA8)
PL	A	190	−39.7	−44.4	47.9	0.001	L inferior parietal lobule (BA40)
PL	A	154	43.3	−37.0	36.9	0.006	R inferior parietal lobule (BA 40)
PL	A	103	0.0	0.0	47.9	0.008	Anterior cingulate gyrus (BA 24)
PL	D	838	−14.4	−40.7	47.9	0.001	L precuneus (BA 7)

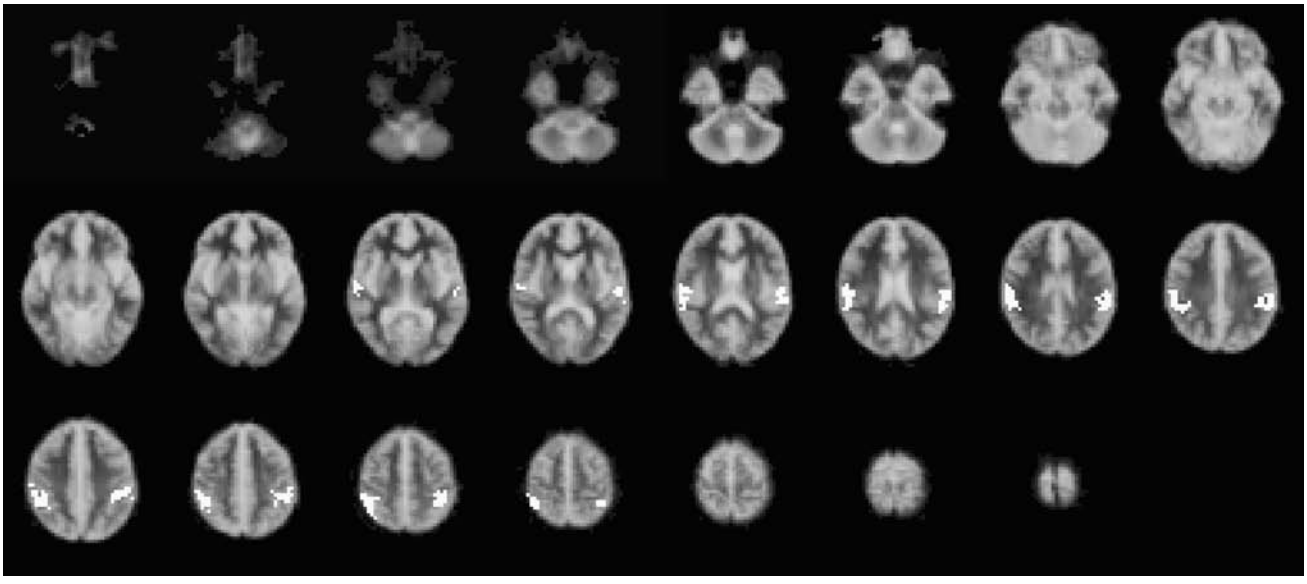

Fig. 1 Group comparison map: areas of increased activation in amyotrophic lateral sclerosis (ALS) patients. White areas show clusters of significant greater activation in ALS patients compared to both controls and PL patients

using existing pathways that control subjects only recruit in a more difficult task [7]. Our data argue against this explanation, by showing increased activation in a task which was designed to be easy for both patients and controls and also by demonstrating this in comparison to a group of patients with peripheral neuromuscular syndromes who were well matched for upper limb weakness. Our performance data shows that response times, error scores, randomness and direction of movements did not differ between the two patient groups, supporting the assumption that task difficulty and strategy were equivalent. Thus, altered cortical activation in the region of the motor cortex in ALS is unlikely to result from confounding by task difficulty. Furthermore, the degree of weakness was not correlated with activation in these regions.

We therefore propose that these changes reflect damage to central motor pathways. Interestingly, Kew et al. [5] describe more extensive changes in a subset of their original patients Kew et al. [4] who had been selected for prominent spasticity. An alternative approach to controlling for weakness is to use a paradigm in which patients and controls each exert a specific proportion of their own maximum force [6, 8], ideally in a parametric design. Findings from a study using this methodology are very similar to our own [6], providing further evidence that these changes in cortical function are specifically related to ALS pathology.

Table 3 Three-dimensional clusters of difference in group activation in the three-way hypothesis driven comparison between amyotrophic lateral sclerosis (ALS) patients, PL patients and controls

Comparison	No of voxels	Talairach coordinates (most activated voxel)			*P* value	Position of most activated voxel
		x	*y*	*z*		
Three-way hypothesis driven comparison						
PL < ALS > CON	159	54.2	−25.9	20.4	0.005	Left post central gyrus
PL < ALS > CON	137	−39.7	−29.6	47.9	0.002	Right post central gyrus
PL > ALS < CON	161	−18.1	33.3	42.4	0.002	Left dorsolateral pre-frontal cortex (DLPFC)
Individual two-way comparisons						
ALS > CON	151	54.2	−29.6	25.9	0.003	Right inferior parietal lobule
ALS > CON	66	−39.7	−33.3	47.9	0.008	Left post central gyrus/inferior parietal lobule
ALS > PL	190	−43.3	−29.6	47.9	0.001	Left post central gyrus/inferior parietal lobule

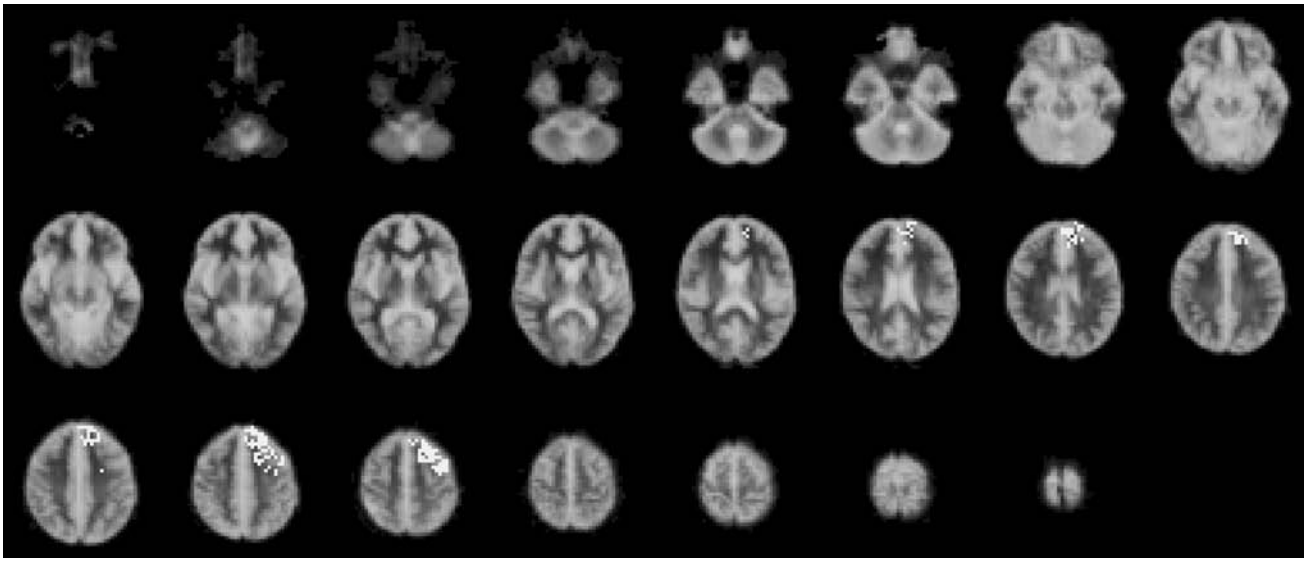

Fig. 2 Group comparison map: areas of reduced activation in amyotrophic lateral sclerosis (ALS) patients. White areas show clusters of significantly reduced activation in ALS patients compared to both controls and PL patients

The mechanism underlying altered cortical activation in ALS is not understood. The neuropathology of ALS is characterised by the loss of motor neurons in the cerebral cortex as well as in the anterior horn cells and brainstem motor nuclei [21, 22]. The cardinal feature is loss of giant pyramidal (Betz) cells from cortical layer V in the pre-central gyrus [1], but it is recognised that Betz cell degeneration may extend beyond primary motor cortex [23] and that other pyramidal projection neurons may also be involved [24]. Pyramidal cell loss has been described in the post-central gyrus, pre-motor and pre-frontal areas [24, 25]. In addition to the loss of pyramidal neurons, there is evidence of loss of inhibitory inter-neurons in ALS. [1, 23, 26]. Loss of inhibitory GABAergic neurons in ALS could account for the greater extent of cortical activation around the motor cortex observed in our patients.

Alternatively, it has been proposed that these changes may represent cortical plasticity, as new synapses and pathways are developed to compensate for the selective loss of pyramidal cells in the motor cortex [7]. The motor system shows parallel as well as hierarchical organisation, and reorganisation within the motor system is known to occur in patients with vascular, traumatic and neoplastic lesions [27–30]. PET studies of patients recovering from striatocapsular motor strokes have shown a strikingly similar pattern of change to that observed in our ALS patients, with increased activation in ipsilateral premotor cortex and in BA 40 [27]. However, the capacity for functional reorganisation in neurodegenerative disorders such as ALS (where neuronal loss is progressive, bilateral and less restricted to one anatomical region) is unknown.

Reduced activation in pre-frontal cortex

Accumulating evidence of cognitive impairment in ALS has challenged the traditional view of the disease as solely affecting the motor system. In addition to the recognised association of ALS with frontotemporal dementia in a small proportion of cases [31, 32], cognitive deficits, particularly in executive functions, have been identified in ALS patients without dementia [33–37]. Abrahams et al. [38], using a letter fluency paradigm, showed reduced activation in extensive regions of the pre-frontal cortex including the DLPFC in patients with ALS compared with healthy controls.

Motor tasks requiring freely selected (rather than stereotyped or externally specified) movements are analogous to verbal fluency tests in their requirement for self-initiated responses. Functional imaging studies in normal subjects contrasting freely selected against specified movements consistently demonstrate activation in the DLPFC [39], as seen in verbal fluency tasks [40, 41]. In this study, the motor paradigm used was chosen as a sensitive and reliable probe of sensorimotor cortical function. However, as the task required subjects to make freely selected joystick movements it does have an executive as well as motor component. As expected, our control subjects showed activation in pre-frontal as well as motor regions during the paradigm. As in Abrahams' verbal fluency paradigm [38], ALS patients showed markedly reduced activation in pre-frontal regions, particularly the DLPFC, despite generating random movement sequences as successfully as controls. This provides further support for the existence of deficits of frontal lobe functions in ALS patients.

These findings are in keeping with increasing evidence that ALS pathology involves extra-motor areas, especially frontal and temporal cortex. Automated voxel based MRI morphometry has shown localised reductions in frontal grey matter volume in patients with ALS [42]. In addition, there is reduced white matter volume underlying frontal, temporal and anterior parietal regions in ALS subjects with impaired verbal fluency [43] compared to those who are not thus impaired. MRS findings of reduced *N*-acetylaspartate/Creatine + Phosphocreatine ratio in the frontal lobe of ALS patients provide further evidence of neuronal loss in this region [44]. Maekawa et al. [26] showed loss of pyramidal and GABAergic cells in DLPFC and anterior cingulate cortex, as well as in the primary motor cortex [26]. It is intriguing that a similar pattern of neuronal loss occurs in areas showing increased activation (e.g. primary motor cortex) or decreased activation (e.g. DLPFC). This argues against a simplistic explanation of altered cortical activation based on a notional imbalance between inhibitory and excitatory circuits.

Conclusions

This study shows that cortical activation in motor areas is increased in ALS compared to patients with equivalent weakness due to peripheral lesions as well as healthy controls. Although we cannot absolutely exclude the possibility the two groups of patients may have differed in their approach to the task (e.g. because of spasticity in ALS patients, or subtly differing patterns of weakness), the performance data supports the suggestion that task difficulty was equivalent for ALS and PL patients.

Our results show that increased activation in motor areas and reduced activation in pre-frontal regions previously described in ALS subjects can be demonstrated through a single paradigm. Thus, altered cortical function in ALS is complex and differs in sensorimotor and pre-frontal regions. Further research should aim to address the relationship between cellular pathology, the neural pathways involved in motor planning and execution and functional changes in different brain regions. ALS may provide a useful model to explore the mechanism of cortical adaptation in neurodegenerative disorders.

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