Sensorimotor Functional Connectivity Changes in Amyotrophic Lateral Sclerosis

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We investigated whether the functional connections to the primary sensorimotor cortex (SMC) at rest are abnormal in 26 patients with amyotrophic lateral sclerosis (ALS) and whether such changes are related to the corticospinal tract (CST) damage, measured using diffusion tensor magnetic resonance imaging (DT MRI). ALS patients versus controls showed a significantly increased functional connectivity between the left SMC and the right cingulate cortex, parahippocampal gyrus, and cerebellum-crus II. No right SMC connectivity changes were found. The pattern of increased functional connectivity to the left SMC was more widespread when considering only patients with no CST DT MRI abnormalities than the whole group of patients. In this patient group, functional connectivity was also increased between the right SMC and the right parahippocampal gyrus. On the contrary, in ALS patients with CST damage (as assessed using DT MRI) versus controls, functional connectivity was increased between the left SMC and the right cingulate cortex only, while it was decreased between the right SMC and the right cerebellum-lobule VI. In ALS patients, disease severity correlated with reduced SMC functional connectivity. Functional brain changes do occur in ALS with mild disability. These changes might have a role in compensating for (limited) structural damage and might exhaust with increasing burden of disease pathology.

Keywords: amyotrophic lateral sclerosis, corticospinal tract, diffusion tensor MRI, functional connectivity, sensorimotor network

Introduction

Amyotrophic lateral sclerosis (ALS) is a fatal neurodegenerative disorder characterized by a progressive degeneration of lower motor neurons in the spinal cord and brainstem and upper motor neurons (UMNs) in the motor cortex, leading to limb paralysis, dysphagia, dystonia, and respiratory failure (Rowland and Shneider 2001). The cause of the disease is unknown and there is no effective cure. Although it is generally reported that the mean survival of patients from symptom onset is 3–5 years, ALS has a considerable variability in outcome and prognostic factors are not satisfactorily defined yet (Chio et al. 2009).

The use of functional magnetic resonance imaging (fMRI) has provided evidence for cortical reorganization in ALS. In comparison to healthy subjects, motor fMRI investigations in these patients have demonstrated an enhanced activity of regions of the sensorimotor network and the recruitment of additional areas involved in motor planning and control, such as the cerebellum and basal ganglia (Konrad et al. 2002, 2006; Schoenfeld et al. 2005; Tessitore et al. 2006; Stanton et al. 2007). However, functional abnormalities that might be found in clinically impaired patients could be a reflection of task difficulty due to motor disability rather than being related to an actual brain rewiring. Furthermore, assuming that interacting regions are an important prerequisite for normal brain function, changes in the interaction among regions of a given brain network could even precede their altered recruitment. To date, little is known regarding the functional interaction among the different regions of the sensorimotor neural network in ALS patients.

fMRI studies have shown that spontaneous fluctuations of the blood oxygen level-dependent signal occur continuously in the resting state (RS, i.e., in the absence of external stimuli) in the human brain (Fox and Raichle 2007). Recent studies have suggested that coherent spontaneous fluctuations in distinct brain systems at rest may have functional implications in normal aging (Damoiseaux et al. 2008), psychiatric disorders (Kennedy et al. 2006), Alzheimer’s disease (Greicius et al. 2004), and multiple sclerosis (Rocca et al. 2010). Only one study investigated RS fMRI in ALS and found a decreased connectivity in the sensorimotor network, which was restricted to the premotor cortex (Mohammadi et al. 2009). The structural substrates of such functional abnormalities have not been investigated yet.

In this study, our primary aim was to determine whether the RS functional connections to the primary sensorimotor cortex (SMC) bilaterally are altered in patients with ALS and whether such changes are related to the corticospinal tract (CST) damage, assessed using diffusion tensor (DT) MRI tractography. We also explored the clinical relevance of functional connectivity changes by evaluating their correlation with the clinical status of ALS patients. We hypothesized that measures of SMC functional connectivity may already be altered when patients still have a limited CST damage and mild disability, and that such a different pattern of functional connectivity might have the potential to contribute in limiting the clinical consequences of tissue injury.

Materials and Methods

Subjects

Patients with sporadic ALS were recruited consecutively. To be included, patients had to have: a diagnosis of probable laboratory supported, probable, or definite ALS according to the El Escorial revised criteria (Brooks 1994); no family history of ALS; ALS Functional Rating Scale-revised (ALSFRS-r) score ≥ 20 (Cedarbaum et al. 1999); and right handedness (Oldfield 1971). Patients were excluded if they had: frontotemporal dementia (FTD) (Neary et al. 1998); cerebrovascular disorders, history of traumatic brain injury, hydrocephalus, or intracranial mass; other neurological and medical diseases; psychotropic
medication; and history of substance abuse. Within 48 h from MRI, ALS disease severity was assessed by the ALSFRS-r questionnaire (Cedarbaum et al. 1999). Muscle strength was scored using the Medical Research Council (MRC) scale from 0 to 5 (de Carvalho et al. 2003). UMN involvement was assessed by totaling the number of pathological UMN signs on examination (maximum total score = 16) (Turner et al. 2004).

Twenty-six sporadic ALS patients were included (11 women, 15 men, mean age = 62, range = 40–77 years, 14 definite, 8 probable, and 4 probable laboratory supported) (Table 1). Twenty had a limb-onset, 3 a bulbar-onset, and 3 a limb + bulbar-onset disease. Among patients with limb onset, the onset was symmetric in 7 patients, right lateralized in 8 patients (1 upper limb, 7 lower limb) and left lateralized (3 upper limb, 5 lower limb) in the remaining 8 patients. At the time MRI was performed, 17 patients showed a symmetric involvement, 6 patients had a right-lateralized involvement, and 3 patients a left-lateralized involvement. All patients were taking therapy with riluzole. Fifteen sex- and age-matched healthy individuals (7 women, 8 men, mean age = 63, range = 43–77 years), with no history of neurological or psychiatric disorders and a normal neurological examination, served as healthy controls. None of the controls received psychotropic medication.

**Standard Protocol Approvals and Patient Consents**

Approval was received from local ethical standards committee on human experimentation and written informed consent was obtained from all subjects participating into the study.

**MRI Acquisition**

MRI study was performed on a 1.5 T system (Avanto, Siemens). RS MRI scans were acquired using a T2*-weighted single-shot echo-planar imaging (EPI) sequence (time repetition/time echo = 3500/60 ms, flip angle = 90°, matrix size = 64 × 64, field of view = 200 mm²; 36, 4 mm thick, contiguous, axial slices with in-plane resolution = 3 × 3 mm², number of volumes = 200, acquisition time = 10 min). During MRI scanning, subjects were instructed to keep their eyes closed, not to think of anything in particular, and not to fall asleep. After MRI acquisition, participants were asked about being able to keep their eyes closed, to refrain from moving, and to stay alert during fMRI scanning. All subjects confirmed that they remained awake with their eyes closed during fMRI. During the same session, the following MRI sequences were also included: 1) dual-echo turbo spin-echo and 2) pulsed-gradient spin-echo echo-planar sequence (for further details, see Supplementary Appendix e-1).

**MRI Analysis**

RS functional connectivity analysis is reported in Supplementary Appendix e-1. Briefly, the left and right primary SMC were selected as seed regions to compute functional connectivity with the REST software (http://resting-fmri.sourceforge.net/). DT MRI tractography analysis was carried out as described previously (Agosta, Pagani, Petrolini, Caputo, et al. 2010) (for further details, see Supplementary Appendix c-1). CST average fractional anisotropy (FA) values were measured bilaterally.

**Statistical Analysis**

Subject’s gender was reported as frequencies and between-group comparisons were performed using a Fisher Exact test. Skewed nonnormal distributed continuous variables (i.e., age, time from symptom onset, ALSFRS-r, MRC scores, UMN score, and mean SMC connectivity) were reported as medians (ranges), and between-group comparisons were performed using the nonparametric Mann–Whitney U test. Normal continuous variables (i.e., CST average FA values) were reported as means (standard deviations, SDs), and between-group comparisons were performed using analysis of covariance models adjusting for subject’s age. The normality of continuous variables was checked by means of Kolmogorov–Smirnov and Shapiro–Wilks tests and by graphical inspection. A receiver operating characteristic (ROC) curve analysis was performed to discriminate patients from controls using mean CST FA values. The optimal cutoff level was considered the value giving the highest sum of specificity and sensitivity. Specificity and specificity, computed at the optimal cutoff, were reported along with their 95% confidence intervals (CIs). Patients with mean CST FA value below the optimal cutoff value were classified as "patients with CST damage," while patients with mean CST FA value above such a cutoff were classified as "patients with undetectable CST damage." A P value <0.05 was considered as significant. These analyses were performed using the SAS Statistical Package Release 9.1 (SAS Institute).

Individual functional connectivity maps of z-scores were entered into the Statistical Parametric Mapping (SPM5) random-effect analysis to assess the main functional connectivity to the left and right SMC in controls and ALS patients (one-sample t-test), as well as to test between-group differences (analysis of variance, ANOVA). In ALS patients, SPM5 multiple regression models were run to assess correlations between functional connectivity changes and clinical variables.

To investigate whether functional connectivity changes were associated with structural CST damage, an index of average functional connectivity for the left SMC was obtained in patients and controls by averaging the z-scores of all voxels significantly different between groups at the ANOVA test. The correlation between this index and CST FA values was assessed using the Spearman coefficient. In addition, analysis of functional connectivity was performed for the 2 patient subgroups separately, defined by the degree of CST damage (see above).

To assess functional connectivity only within the grey matter (GM), all random-effect statistics were masked explicitly with a GM probability map derived from the SPM A priori templates, thresholded in order to retain only pixels having a probability > 60% of belonging to GM. All analyses were adjusted for subject’s age. Results were

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**Table 1**

Demographic, clinical, and DT MRI findings from healthy controls and patients with ALS

<table>
<thead>
<tr>
<th></th>
<th>Controls</th>
<th>ALS patients</th>
<th>ALS patients with CST damage</th>
<th>ALS patients with undetectable CST damage</th>
<th>P**</th>
</tr>
</thead>
<tbody>
<tr>
<td>N</td>
<td>15</td>
<td>26</td>
<td>16</td>
<td>10</td>
<td></td>
</tr>
<tr>
<td>Age (years)</td>
<td>66 (43–77)</td>
<td>63 (40–77)</td>
<td>0.46</td>
<td>64 (40–74)</td>
<td>0.62</td>
</tr>
<tr>
<td>Women, men (N)</td>
<td>7, 8</td>
<td>11, 15</td>
<td>0.99</td>
<td>8, 8</td>
<td>0.43</td>
</tr>
<tr>
<td>Time from symptom onset (months)</td>
<td>—</td>
<td>20 (3-84)</td>
<td>23 (6–72)</td>
<td>20 (3-84)</td>
<td>0.92</td>
</tr>
<tr>
<td>ALSFRS-r</td>
<td>—</td>
<td>36 (22-46)</td>
<td>31 (24-46)</td>
<td>36 (22-44)</td>
<td>0.43</td>
</tr>
<tr>
<td>UL-MRC score (0–70)</td>
<td>—</td>
<td>60 (39–70)</td>
<td>60 (39-68)</td>
<td>58 (39-70)</td>
<td>0.94</td>
</tr>
<tr>
<td>LL-MRC score (0–50)</td>
<td>—</td>
<td>42 (2-50)</td>
<td>38 (2-48)</td>
<td>46 (7-50)</td>
<td>0.32</td>
</tr>
<tr>
<td>Total MRC score (0–120)</td>
<td>—</td>
<td>97 (41–120)</td>
<td>94 (41-110)</td>
<td>104 (49-120)</td>
<td>0.36</td>
</tr>
<tr>
<td>UMN score (0–16)</td>
<td>—</td>
<td>15 (3-16)</td>
<td>15 (6-16)</td>
<td>14 (3-16)</td>
<td>0.21</td>
</tr>
<tr>
<td>CST average FA</td>
<td>—</td>
<td>0.67 (0.29)</td>
<td>0.64 (0.37)</td>
<td>0.62 (0.02)</td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td>Right</td>
<td>0.67 (0.29)</td>
<td>0.64 (0.37)</td>
<td>0.003</td>
<td>0.62 (0.02)</td>
<td>0.68 (0.02)</td>
</tr>
<tr>
<td>Left</td>
<td>0.67 (0.30)</td>
<td>0.63 (0.36)</td>
<td>0.004</td>
<td>0.61 (0.03)</td>
<td>0.67 (0.01)</td>
</tr>
<tr>
<td>Mean</td>
<td>0.67 (0.29)</td>
<td>0.63 (0.36)</td>
<td>0.003</td>
<td>0.61 (0.02)</td>
<td>0.67 (0.01)</td>
</tr>
</tbody>
</table>

Note: Skewed nonnormal distributed continuous variables (i.e., age, time from symptom onset, ALSFRS-r, MRC scores, and UMN score) were reported as medians (ranges). Normal continuous variables (i.e., CST average FA values) were reported as means (SDs). P values refer to *ALS patients versus healthy controls and **ALS patients with detectable versus those with undetectable CST damage. See text for further details. Abbreviations: UL-MRC = upper limb-MRC, LL-MRC = lower limb-MRC.
thresholded at $P < 0.05$ (family-wise error corrected) for within-group analysis and $P < 0.001$ (uncorrected for multiple comparisons, cluster extent = 10 voxels) for between-group comparisons and correlation analyses.

Results

No difference was found in terms of age and gender between ALS patients and controls (Table 1). Compared with controls, ALS patients showed a significantly decreased average FA of the CST, bilaterally (Table 1).

Regions functionally connected to the right and left primary SMC were obtained in controls and ALS patients, and the within-group maps were similar at visual inspection in terms of brain regions included in the network. Figure 1 shows the functional connectivity maps for the right and left SMC in all subjects studied. In both groups, right and left SMC functional connectivity was found with bilateral prefrontal cortex, supplementary motor area (SMA), midcingulate cortex, basal ganglia, thalami, bilateral postcentral gyrus, bilateral parahippocampal and fusiform gyri, and bilateral cerebellum. Voxel-based between-group comparisons demonstrated that ALS patients relative to controls had a significantly increased functional connectivity between the left primary SMC and several regions in the right hemisphere, namely the cingulate cortex, parahippocampal gyrus, and cerebellum-crus II ($P < 0.001$; Table 2 and Fig. 2). The mean left SMC connectivity in these regions was 0.15 (SD = 0.13) in controls and 0.46 (SD = 0.36) in ALS patients ($P = 0.006$). No regions of decreased functional connectivity to the left primary SMC was found in ALS patients compared with controls. In ALS patients relative to controls, no changes were found in the connectivity of the right primary SMC. When the analyses were repeated excluding patients with bulbar and limb + bulbar onset, the results were similar (data not shown).

ROC curve analysis showed that mean CST FA allowed to differentiate ALS patients from controls with an optimal cutoff of 0.64 (sensitivity: 0.80, 95% CI 0.55–0.93; specificity 0.65, 95% CI 0.45–0.81). Sixteen (61%) ALS patients were classified as patients with CST damage and 10 ALS patients were classified as subjects with “undetectable CST damage.” No difference was found in terms of demographic and clinical variables between the 2 groups of patients (Table 1). When compared with controls, patients with undetectable CST damage showed a widespread voxel-based pattern of increased functional connectivity to the left primary SMC, including the right midcingulate cortex, right parahippocampal gyrus, right putamen, right superior temporal pole, bilateral cerebellum (right crus II and left lobule IX), and right fusiform gyrus ($P < 0.001$; Table 2 and Fig. 3A). In these patients as compared with controls, functional connectivity was also increased between the right SMC and the right parahippocampal gyrus ($P < 0.001$; Table 2 and Fig. 3B). In patients with CST damage compared with controls, functional connectivity was increased between the left SMC and the right midcingulate cortex, only ($P < 0.001$; Table 2 and Fig. 3A). In addition, in these patients when compared with controls, functional connectivity was decreased between the right SMC and the right cerebellum-lobule VI ($P < 0.001$; Table 2 and Fig. 3B).

In the entire sample of ALS patients, significant voxel-based positive correlations ($P < 0.001$) were found between ALSFRS-r score and increased functional connectivity between the left SMC and the right parahippocampal gyrus ($r = 0.69, t$ value: 4.73, Montreal Neurological Institute [MNI] coordinates: 30, –32, –8; and $r = 0.67, t$ value: 4.49, MNI coordinates: 20, 4, –28) and right cerebellum-lobule VI ($r = 0.78, t$ value: 6.20, MNI coordinates: 38, –40, –26) (Fig. 4). No correlation was found between the functional connectivity abnormalities and the other clinical variables. The mean left SMC connectivity index in those areas, which were significantly increased in ALS patients compared with controls at the voxel level, correlated positively with the left CST FA ($r = 0.41, P = 0.049$).

Discussion

In ALS, disease severity may relate to focal disruptions of RS sensorimotor circuits. We found that RS functional connectivity between the left primary SMC and several brain areas is increased in patients with ALS and mild disability relative to healthy controls. Such an increased functional connectivity was driven by a subgroup of patients with a preserved diffusivity along the CST. ALS patients with undetectable CST damage also demonstrated an increased functional connectivity to the right SMC. Congruently, an increased ALS severity correlated with a reduced SMC functional connectivity. These results support the notion that functional brain changes do occur in ALS with mild disability. These changes might have a role in compensate for (limited) structural damage and might exhaust with an increasing burden of disease pathology.
A previous RS fMRI study in ALS showed that the sensorimotor network connectivity is altered in ALS patients (Mohammadi et al. 2009). Using an independent component analysis (ICA) approach, this study demonstrated that such a change was limited to the premotor cortex (Mohammadi et al. 2009). Some methodological issues related to RS fMRI data analysis might explain the differences between our and previous (Mohammadi et al. 2009) findings. ICA is a model-free multivariate approach that decomposes, by grouping brain activity into regions sharing the same response pattern, a set of fMRI data into several components with no a priori spatial hypothesis. Despite ICA is a powerful method, since it is able to find multiple networks of functionally connected brain regions on the same data set, it has some major drawbacks. First, the number of components into which fMRI time series can be decomposed is usually estimated on the data set itself, by means of minimum description length (Calhoun et al. 2001); however, the high dimensionality and noise level of fMRI data might lead to overfitting or underfitting of the estimated networks. Secondly, such a decomposition might be inaccurate for small brain areas, which are likely to be affected by the spatial distortions and suboptimal resolution associated with EPI acquisitions. Since the seed correlation approach is based on the choice of reference time series serving as a template for correlation (Biswal et al. 1995), it may be less sensitive to noise and variance in the data; therefore, it is a simple but optimal exploratory technique to detect connections in a condition where a clear a priori hypothesis can be formulated, even when small regions located in the deep GM are considered.

Although there is little prior information concerning functional connectivity in ALS, compensatory functional changes in cortical and subcortical motor areas have been previously suggested with fMRI experiments during active motor tasks (Konrad et al. 2002, 2006; Schoenfeld et al. 2005; Tessitore et al. 2006; Stanton et al. 2007). Motor fMRI studies have shown consistently an increased activation of the contralateral primary SMC, SMA, and cerebellum in ALS relative to controls (Konrad et al. 2002, 2006; Schoenfeld et al. 2005; Stanton et al. 2007). An increased recruitment was also described in the sensorimotor network ipsilateral to the movement (Schoenfeld et al. 2005) and inferior parietal cortex bilaterally (Konrad et al. 2002; Stanton et al. 2007). Conversely, one study demonstrated movement-associated decreased cortical responses of the contralateral SMC, premotor area, SMA, and posterior parietal cortex in ALS compared with healthy controls, associated with a relatively increased response of the basal ganglia (Tessitore et al. 2006). The difficulty to control task performance in disabled patients may be responsible for the variable and sometimes contradictory results obtained by motor fMRI studies in ALS. RS fMRI is a promising new tool for the investigation of the intrinsic connectivity of brain networks in patient populations. Although task-related and RS fMRI techniques do investigate 2 completely different states of the brain, RS fMRI makes no demands on subject other than holding still and therefore can be acquired in patients that cannot perform a task.

In the entire sample of ALS patients, we found an increased functional interaction between the left primary SMC and the cingulate cortex, parahippocampal cortex, and cerebellum-crus II, in the right hemisphere. The cingulum has a central role in the integration of attention, motor modulation, and response selection (Corbetta et al. 1991). Activation of this region has also been found to be related to the presentation of new motor tasks and its recruitment is likely to reflect relative task difficulty (Corbetta et al. 1991). The parahippocampal cortex, which is mainly involved in memory, is also considered to be a site of heteromodal neurons, where modality-specific sensory inputs are bound into a multimodal representation (Calvert et al. 2000). The cerebellum integrates sensory information and motor programs to coordinate fine movements. Several imaging studies have reported a cerebellar recruitment associated with timing of rhythmic movements (Ramnani and Passingham 2001) or increasing movement frequency (Sadato et al. 1997; Jancke et al. 2000). The cerebellum has also been involved in the “automatization” (i.e., improvement of motor performance) of learned skills, the establishment of movement strategies, and the consolidation of motor knowledge (Doyon et al. 1998). In ALS patients, an enhanced recruitment of the cerebellum has been previously reported during an active motor task and a relationship with task difficulty have been suggested (Schoenfeld et al. 2005). The abnormal connectivity we found between the left SMC and cortical and cerebellar areas can therefore be interpreted as a reflection of an enhanced modulatory response in diseased patients relative to the normal control subjects. Our findings also suggest that the limited resources in the motor cortex of ALS patients may be paralleled by continuous—albeit finally ineffective—modulation and motor learning.

It is noteworthy that in ALS patients, SMC functional connectivity abnormalities were asymmetric. Previous data suggest that exercise may be involved in the pathogenesis of the disease (Harwood et al. 2009). A recent study demonstrated a high concordance for handedness and side of upper limb-onset ALS, which was not found between footedness and side of lower limb onset (Turner et al. 2010). This might be explained by the fact that routine physical demands on the upper limb are heavily influenced by limb dominance, while the commonest functions for the lower limbs are standing and locomotion, which use both legs equally (Turner et al. 2010). In our study, all patients were
right handers. If right handedness had influenced the side of onset in our patients, at least in those with upper limb onset, the left hemisphere might have expected to be more vulnerable. However, when we controlled for the side of onset among patients with limb-onset disease, we did not find a right-lateralized prevalence. In addition, there was no more severe...
damage to the left CST than to the right one in ALS patients. Another potential reason for a difference in the results between left and right SMC functional connectivity may be the more profuse connections in the dominant than in the nondominant hemisphere (Hammond 2002). Although the relatively small sample of patients does not allow us to obtain firm conclusions on this issue, we believe that our study offers an interesting a priori hypothesis to be tested in future larger studies.

Once established that sensorimotor functional connectivity changes do occur in ALS patients, we wished to gain some insight into the structural abnormalities associated with such changes. In ALS, CST pathology can be detected in vivo using DT MRI (Agosta, Chio, et al. 2010). DT MRI studies reported consistently decreased FA values along the CST in these patients (Ellis et al. 1999; Agosta, Pagani, Petrolini, Caputo, et al. 2010). Loss of pyramidal motor neurons in the primary motor cortex and axonal degeneration of the CST, together with the proliferation of glial cells, extracellular matrix expansion, and intraneuron abnormalities (Hughes 1982), are all likely to contribute to CST FA changes in ALS. In this study, CST FA has been chosen as a marker of ALS-related brain structural damage in order to further explore the nature of functional connectivity changes. The pattern of increased functional connectivity to the left primary SMC was more widespread when considering only patients with undetectable CST damage (i.e., ALS patients with no CST DT MRI abnormalities) than the whole group of patients. These patients showed regions of increased functional connectivity involving the right cingulate cortex, parahippocampal gyrus, putamen, superior temporal pole, fusiform gyrus, and bilateral cerebellum (right crus II and left lobule IX). They also had an increased connectivity between the right SMC and the right parahippocampal gyrus. In ALS patients, an enhanced recruitment of subcortical motor structures has been described during the performance of active motor tasks (Konrad et al. 2006; Tessitore et al. 2006). Basal ganglia have extensive connections to the motor and somatosensory cortices and are involved in motor programming, execution, and control (Alexander 1994). In particular, basal ganglia activity has been associated with motor program selection and control of movement simulation (Kessler et al. 2006). In addition, the relearning of simple motor tasks is likely to engage basal ganglia and cerebellar networks (Ward et al. 2003). All these changes seem to be lost in ALS patients with CST damage, who also showed a decreased functional connectivity between the right SMC and the right cerebellum-lobule VI. These findings are likely to indicate that heightened sensorimotor network connectivity occurs in ALS patients who harbor subtle CST structural changes and that such an enhanced connectivity might have a compensatory role. They also suggest that with an increased damage to the CST, there is a "pseudonormalization" of brain functional connectivity, which might yet be an additional factor contributing to a worse patient clinical status.

Patients with and without CST DT MRI abnormalities did not differ with regards to clinical parameters. Although this finding is disappointing, it is not surprising in light of previous literature.
Decreased FA was found to be related to disease severity (Ellis et al. 1999; Graham et al. 2004; Cosottini et al. 2005; Wang et al. 2006), as well as to clinical (Ellis et al. 1999; Abe et al. 2004), and electrophysiological (Iwata et al. 2008) measures of UMN degeneration in ALS patients. However, these findings were not confirmed by other authors (Toosy et al. 2003; Mitsumoto et al. 2007; Schinnrig et al. 2007). Furthermore, an association between increased mean diffusivity along the CST and disease duration was reported by some studies (Ellis et al. 1999; Toosy et al. 2003; Abe et al. 2004), but not all (Graham et al. 2004). We recently found that more severe CST DT MRI abnormalities at baseline predict a poorer long-term clinical evolution in ALS patients with mild disability (Agosta, Pagani, Petronelli, Sormani, et al. 2010). As a consequence, we speculate that patients with CST damage may have a poorer clinical outcome compared with patients with undetectable CST damage.

To explore further the “compensatory hypothesis,” we investigated the relationships between disability and functional connectivity measures. A positive correlation was found between ALSFRS-r and increased connectivity between the left primary SMC and the right parahippocampal gyrus and cerebellum (i.e., an increased disease severity correlated with a decreased functional connectivity). This finding emphasizes that the observed functional abnormalities might have a compensatory role in limiting the clinical consequences of ALS-related pathological changes, at least for limited structural damage.

This study is not without limitations. First, it may have been informative to study patients with possible ALS. However, the present study is the first investigating sensorimotor functional connectivity in ALS and we preferred to include patients with a probable or definite disease in order to decrease clinicopathological heterogeneity. In addition, the small number of patients with bulbar onset did not allow us to assess the pattern of SMC functional connectivity changes in these patients separately. Second, the existence of a correlation of SMC functional connectivity abnormalities with UMN score and symptom duration would have strengthened the compensatory hypothesis. Third, although ALS patients with a concurrent dementia meeting the criteria for a FTD were excluded, our study did not include a formal neuropsychological testing and, as a consequence, we cannot exclude that some patients had a subtle cognitive impairment (Strong et al. 2009) that might have, at least partially, influenced connectivity results. Finally, there was a partial overlap between CST FA values in controls and patients with CST damage. In particular, there were 2 healthy subjects (age > 70 years old) with a CST FA value lower than 0.64. This finding fits with several pathological (Meier-Ruge et al. 1992; Aboitiz et al. 1996) and neuroimaging (Sullivan et al. 2010; Sala et al. 2010) studies showing a decline in white matter integrity with aging. As a consequence, a FA value lower than 0.64 should not be seen as diagnostic for ALS.

Based on these considerations, as well as on data of previous motor fMRI studies (Konrad et al. 2002, 2006; Schoenfeld et al. 2005; Tessitore et al. 2006; Stanton et al. 2007), it is tempting to speculate that fMRI changes observed in ALS patients at rest might reflect a more general impairment of their sensorimotor network function, which might be characterized by an initial phase of overinteraction of movement-associated areas (Konrad et al. 2002, 2006; Schoenfeld et al. 2005; Tessitore et al. 2006; Stanton et al. 2007) and recruitment of additional neural resources involved in task planning and control, as observed in patients with undetectable CST damage. This phase might be followed by a one where the extent of tissue injury might lead to an exhaustion of the functional properties of the brain plastic reservoir. Obviously, we cannot exclude that other, not mutually exclusive, processes may be at work, including a secondary effect due to movement restriction, a reduced sensory inflow to the SMC, or excitotoxicity-related mechanisms. Future longitudinal studies, possibly in patients at the earliest phase of the disease, are now warranted to confirm our hypothesis and to investigate whether a window of opportunity exists during which an increased activity of the RS networks is adaptive in ALS and can be possibly enhanced by pharmacotherapy or rehabilitative programs.

Supplementary Material
Supplementary material can be found at: http://www.cercor.oxfordjournals.org/

Notes
Conflict of Interest: None declared.

References