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Different sensorimotor mechanism in fast and slow progression amyotrophic lateral sclerosis

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Abstract

The huge heterogeneity of the disease progression rate may cause inconsistent findings between local activity and functional connectivity of the primary sensorimotor area (PSMA) in amyotrophic lateral sclerosis (ALS). For illustration of this hypothesis, resting-state fMRI (RS-fMRI) data were collected and analyzed on 38 "definite" or "probable" ALS patients (19 fast and 19 slow, cut off median = 0.41) and 37 matched healthy controls. Amplitude of low frequency fluctuations (ALFFs) and functional connectivity strength (FCS) were analyzed within the PSMA. There was a decreased ALFF (p_{FDR} <.05) and FCS ($p = .022$) in all ALS patients. The two metrics shared about 50% of variance ($R = .7$) and both showed significant positive correlation with ALS Functional Rating Scale-Revised (ALSFRS-R) in the fast (p values <.034) but not in the slow progression groups. Interestingly, when regressing out the ALFF, the PSMA network FCS, especially the inter-hemisphere FCS, showed negative correlation with the ALSFRS-R score in the slow ($R = -.54$, $p = .026$) but not the fast progression group. In summary, the current results suggest that RS-fMRI local activity and network functional connectivity accounts for the severity differently in the slow and fast progression ALS patients.

KEYWORDS
amplitude of low frequency fluctuations, amyotrophic lateral sclerosis, functional connectivity, resting state fMRI, slow and fast progression rates

1 | INTRODUCTION

As one of the most fatal neurodegenerative disease, patients with amyotrophic lateral sclerosis (ALS) have a median survival duration of 3 years after onset of the symptoms (Kiernan et al., 2011). One pronounced characteristic of the disease is the huge heterogeneity of disease progression rate (PR; Brown & Al-Chalabi, 2017; Chiò et al., 2009), causing significant differences in survival duration. Patients with rapid PR may past away within several months from symptom onset while 10%–20% of patients can live up to decades.

The huge heterogeneity in disease progression is probably one of the critical factor that brings uncertainty to in vivo ALS studies, especially for resting-state fMRI (RS-fMRI) that detects the

Abbreviations: ALFF, amplitude of low frequency fluctuations; ALS, amyotrophic lateral sclerosis; ALSFRS-R, ALS functional rating scale-revised; FCS, functional connectivity strength; PSMA, primary sensorimotor area; UMN, upper motor neuron.

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neuropathological spontaneous brain activity (Greicius, 2008). While some studies have found consistent reduction of RS-fMRI local activity (Luo et al., 2012; Ma et al., 2020; Sako et al., 2017) which were highly in line with hypo-glucose metabolism (Pagani et al., 2014) as well as decreased neural oscillation (Dukic et al., 2019) in the primary sensorimotor area (PSMA), many other studies have reported inconsistent or even contrary results of resting-state functional connectivity (FC) in the PSMA of ALS patients. For example, a number of studies have reported decreased FC (Fekete, Zach, Mujica-Parodi, & Turner, 2013; Jelsone-Swain et al., 2010; Mohammadi et al., 2009; Tedeschi et al., 2012) in ALS patients, yet almost equal number of studies showed increased FC (Basaia et al., 2020; Douaud, Filippini, Knight, Talbot, & Turner, 2011; Menke, Proudfoot, Talbot, & Turner, 2018). The increased FC has been interpreted as a compensatory effect (for review, refer to [Chiò et al., 2014]). The RS-fMRI local activity and FC possibly underlie distinct neuroimaging mechanisms of ALS. The distinct roles of local activity and FC may be associated with the heterogeneity of the disease PR, yet, no neuroimaging study has taken PR of ALS into account for the different mechanism.

Therefore, the current study divided ALS patients into two subgroups in light of their PR for RS-fMRI scanning. We measured both the local activity and network FC in the PSMA for two aims. First, we aimed to replicate the reduction of PSMA local activity and alteration of PSMA network connectivity. Second, we hypothesized that the local activity and network connectivity account differently for patients with different PRs.

2 | MATERIALS AND METHODS

2.1 | Participants

Forty-four clinically "definite" or "probable" ALS patients and 40 healthy controls (HCs) were recruited. Data were acquired at Xuanwu Hospital, Capital Medical University from 2018 to 2020. All ALS patients were diagnosed according to the EI Escorial revised criteria of the World Federation of Neurology (Brooks, Miller, Swash, & Munsat, 2000) and had no history of cerebral vascular disease, dementia, Parkinson's disease, epilepsy or multiple sclerosis. ALS patients were right-handed, free of psychiatric disease and psychotropic medications and were considered cognitively normal via the neurologists during interview. The right-handed HCs were recruited according to the following criteria: (1) reported no history of substance drug abuse, traumatic brain injury, cerebrovascular events, neuroinflammations, neurological and psychiatric conditions, (2) age between 30 and 70, and (3) did not show signs of movement problem during the interview with the neurologists. After recruitment, we excluded subject if: (1) conditions such as claustrophobia so that the participant did not finish the whole MRI measurement; (2) head motion exceeded 2 mm or 2° during the RS-fMRI scanning; (3) incidental findings of space-occupying lesions. One ALS patient was excluded due to claustrophobia. Five ALS patients and three HCs were removed due to large head motion.

2.2 | Protocol approvals and patient consents

All participants have provided written informed consent before the measurement. The current study was approved by the ethics committee of Xuanwu Hospital.

2.3 | Clinical measurements

The disease severity was evaluated by the ALS Functional Rating Scale-Revised (ALSFRS-R) (lower score means severer symptom) (Cedarbaum et al., 1999). We also collected upper motor neuron (UMN) score for evaluation of UMN impairment. The duration of the disease in months was measured from the onset of the first ALS-associated symptom to the scan date. The disease progression rate (PR) was calculated based on the ALSFRS-R score and the course of disease as [PR = (48-ALSFRS-R/disease duration)]. The median PR (0.41) was used to assign ALS patients into two subgroups, 19 in fast progression subgroup and 19 in slow progression group after exclusion for patients with excessive head motion. Detailed information of the participants was provided in Table 1.

2.4 | Image acquisition

RS-fMRI was performed using an echo-planar imaging (EPI) sequence on GE 3 T scanner (GE MR750) with the following parameters: TR = 2,000 ms, TE = 30 ms, 36 axial slices per volume, voxel size = 3 × 3 × 3 mm, 1 mm slice gap, matrix = 64 × 64, and flip angle = 90°, and 180 volumes. During the RS-fMRI scanning, we instructed participants to close their eyes, relax, and not engage in any particular mental activity. After RS-fMRI scanning, we confirmed with the subjects that they had not fallen asleep in the scanner. In addition, we acquired high-resolution T1 structure images (3D BRAVO) using the following parameters: TR = 6.66 ms, TE = 2.93 ms, TI = 450 ms, flip angel = 12°, FOV = 256 × 256 mm, slice thickness = 1 mm, matrix = 256 × 256.

2.5 | fMRI data preprocessing

Data preprocessing procedure were carried out by using the DPABI (http://rfmri.org/dpabi/; Yan, Wang, Zuo, & Zang, 2016) and SPM8 (https://www.fil.ion.ucl.ac.uk/spm/) toolboxes in MATLAB-R2018b (Mathworks, Sherborn, MA). For each subject, the first 5 volumes of RS-fMRI data were removed, leaving 175 volumes. The middle slice was used as the reference slice for slice timing correction. Then, fMRI data were realigned to correct the head motion and the six head motion parameters were obtained. The Diffeomorphic Anatomical Registration Through Exponentiated Lie algebra (DARTEL) (Ashburner, 2007) function in DAPBI was used to transform 3D T1 images from the individual native space to the Montreal Neurological Institute space. Then the RS-fMRI data were transformed to the MNI

TABLE 1 Demographic information of enrolled participants and fast and slow progression subgroups

	ALS patients (range)		Healthy controls	Statistics	*p*
N (after exclusion)	38 (44 enrolled)		37 (40 enrolled)		
Age	50.60 ± 8.64 (*SD*)		51.89 ± 10.35	$T = 0.58$	.56
Sex	15 (*f*)/23		23 (*f*)/14	$X^2 = 2.99$	.08
ALSFRS-R	40.89 ± 4.63 (*SD*), [29–47]		NA		
Disease duration[a]	12 (median), 24 (75% percentile), [2–204]		NA		
Progression rate[a]	0.41 (median), 1.03 (75% percentile), [0.1–3.75]		NA		
UMN score	8.94 ± 6.29 (*SD*), [0–16]		NA		
Disease onset	5 bulbar/33 limb		NA		
Subgroups	Slow progression ALS	Fast progression ALS	NA		
N	19	19	NA		
Age	47.43 ± 9.79 (*SD*)	53.83 ± 10.26 (*SD*)	NA	$T = -1.93$	.06
Sex (female)	7 (*f*)/12	8 (*f*)/11	NA	$X^2 = .11$	.74
ALSFRS-R	43.32 ± 3.25 (*SD*)	38.47 ± 4.60 (*SD*)	NA	$T = 3.75$	.001*
Disease duration[a]	22, 36 (75% percentile)	7, 11 (75% percentile)	NA	$T = 2.22$	.033*
Progression rate[a]	0.25, 0.33 (75% percentile)	1, 1.83 (75% percentile)	NA	NA	NA
UMN score	8.33 ± 6.55 (*SD*)	9.63 ± 6.12 (*SD*)	NA	$T = .59$	.56

Abbreviation: ALSFRS-R, ALS Functional Rating Scale-Revised.
[a]We reported median with 75% percentile for disease duration and progression rate.
*p values <.05.

space via the parameters of 3D T1 and resampled to a $3 \times 3 \times 3$ mm^3 voxel size, and smoothed with a 6 mm FWHM Gaussian kernel. We further regressed out the time series from the white matter and cerebrospinal fluid (99% possibility map from SPM) in addition to the global mean time series and six head motion parameters as nuisance variables to reduce the effects of head motion and non-neuronal BOLD fluctuations. Thirty-eight ALS patients and age- (p >.5) and sex- (p >.08) matched 37 controls were used for group analyses. Detailed demographic information was provided in Table 1.

2.6 | Amplitude of low frequency fluctuations calculation

After image preprocessing, we calculated amplitude of low frequency fluctuations (ALFF; Zang et al., 2007) in a low frequency band between 0.01 and 0.1 Hz to estimate the resting state local spontaneous activity. We then divided ALFF by global mean ALFF for standardization purpose (Zang et al., 2007).

2.7 | Network functional connectivity strength

FC was computed using the coherence method which was based on the matlab "mscohere.m" function as described in previous study (Salami, Avelar-Pereira, Garzón, Sitnikov, & Kalpouzos, 2018). We took the averaged coherence between 0.01 and 0.1 Hz as the FCFC.

We calculated ROI FC between the left and right sphere ROIs that located at the peak voxel in each hemisphere. Further, to calculate network functional connectivity strength (FCS) of the PSMA, we parcellated the PSMA in light of the automated anatomical labeling (Rolls, Huang, Lin, Feng, & Joliot, 2020; precentral gyrus and postcentral gyrus combined) into 102 nodes using the compact parcellation approach by Zalesky et al. (2010). The 102 nodes were spatially randomly distributed and the largest node (1,856 mm^3) were smaller than twice of the smallest node (939 mm^3; Zalesky et al., 2010). We calculated the averaged FC of all pairs of 102 nodes as the network FCS. We did not calculate the coherence of pair of voxels because it is extremely time consuming.

2.8 | Group level analyses

Our first goal was to replicate previous findings regarding impaired local activity and FC in ALS patients. Therefore, we applied voxel-wise two-sample *T*-test in SPM12 (https://www.fil.ion.ucl.ac.uk/spm/software/spm12/) for comparisons of ALFF images and applied false discovery rate (FDR) correction within the PSMA mask (corrected p value <.05). The network FCS comparisons as well as clinical associations with RS-fMRI metrics were done in SPSS (https://www.ibm.com/analytics/spss-statistics-software).

To further test our hypothesis, comparisons of ALFF and FCS as well as the associations with clinical measurements in slow, fast progression ALS patients and HCs and were done in a post-hoc manner in SPSS. Specifically, after comparing the voxel-wise ALFF between the whole ALS group and the HCs, we extracted the mean ALFF values from the sphere ROIs that locate at the peak voxel in each hemisphere. Comparisons of mean ALFF values and mean network

FCS between fast ALS and HCs, slow ALS and HCs as well as fast ALS and slow ALS were done in SPSS. Similarly, we examined the Pearson's correlation coefficient of the mean ALFF, network FCS and the clinical measurements (ALSFRS-R, UMN score, PR and disease duration) in the whole ALS group and the fast, slow ALS sub-group separately. In addition, correlations between mean ALFF and mean network FCS were investigated in the HCs and whole ALS group separately. Results with p <.05 were considered as significance.

3 | RESULTS

3.1 | Demographic information

We found no significant difference of age (p >.5) and sex (p >.08) between HC and ALS group (Table 1). The average age of the ALS patients was 50.6 years old, which is younger than the study reported by Ingre and colleagues (Ingre, Roos, Piehl, Kamel, & Fang, 2015), highly similar with the previous study reporting sporadic ALS in China (Chen et al., 2015). Among the ALS patients, five of them are bulbar-onset and the rest are limb-onset. Since the genetic examination was not free of charge, only five of the ALS patients underwent gene test. We found one ALS patient with SOD1 and one ALS patient with VAPB mutation. We assigned ALS patients into slow and fast progression subgroups based on the median of PR (0.41). Each subgroup contains 19 patients. No significant difference of age (p >.06) and sex (p >.7) between the two subgroups were found. The slow progression group showed less severe symptoms (higher ALSFRS-R score) than the fast progression patients ($T_{(36)} = 3.75$, $p = .001$). Disease duration was significantly longer in slow progression patients ($T_{(36)} = 2.22$, $p = .033$). There was no group difference of age and sex between the HCs and ALS patients in the slow and fast group (p values >.11, Table S1).

3.2 | Decreased ALFF and network FCS in the PSMA

Voxel-wise two-sample T-test on the ALFF maps showed significantly decreased ALFF in the bilateral PSMA (Figure 1a). Further ROI analysis revealed that both the slow and fast progression groups showed significantly decreased ALFF in both the left and right PSMA (5 mm sphere ROI around peak voxels), while the difference of ALFF between the two ALS subgroups was not significant (Figure 1b,c). The whole brain exploratory analysis revealed that only PSMA ALFF showed significant reduction (T <−3.24) while the posterior cingulate cortex showed increased ALFF at an uncorrected threshold (T >3.24). To provide a view of the whole brain for any potential difference, the whole brain p < 0.05 uncorrected result was provided in Figure S1. ANOVA analysis revealed similar distribution of the group differences in the bilateral PSMA at p <.001 uncorrected threshold. However, no voxels survived FDR correction (Figure S2).

T-test revealed that there was a significant reduction of network FCS in the ALS patients ($T_{(73)} = -2.35$, $p = .022$). Specifically, the

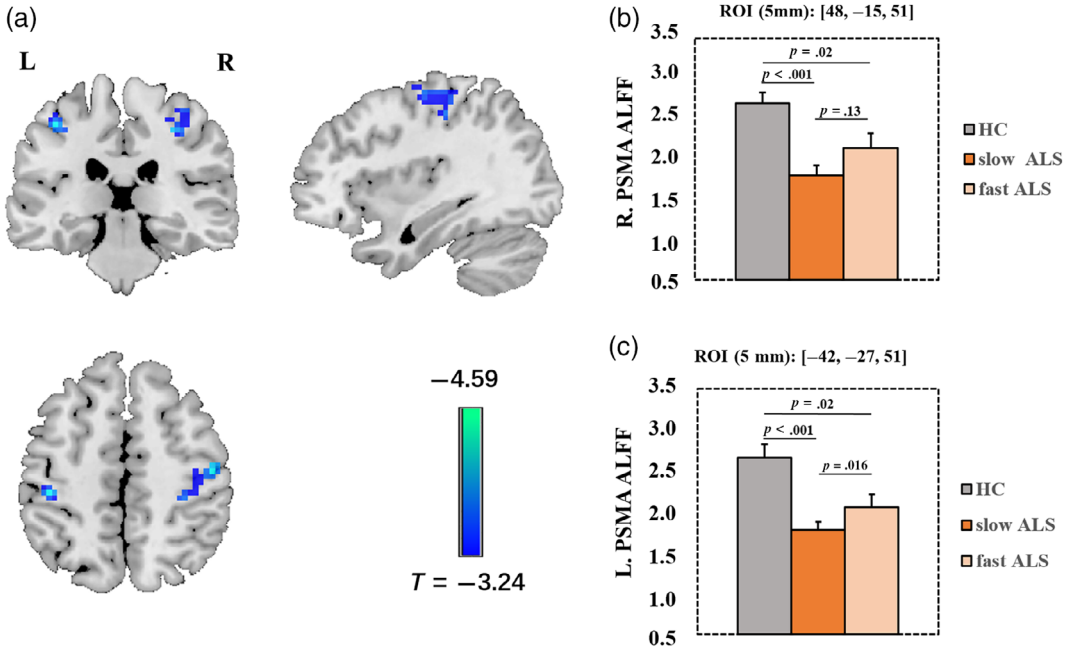

FIGURE 1 Reduced primary sensorimotor area (PSMA) amplitude of low frequency fluctuation (ALFF) in amyotrophic lateral sclerosis (ALS) patients. Panel a: two-sample T-tests showed decreased ALFF in ALS patients (p <.05 FDR corrected in the PSMA). The averaged ALFF extracted from spherical ROIs centered at the left and right peak voxels of reduced ALFF showed significantly reduced ALFF for both fast and right progression ALS patients in both the left and right PSMA, while the two subgroups showed no significant difference (panels b and c). Error bars represent standard error

network FCS was significantly reduced in the slow progression patients ($T_{(54)} = -2.80$, $p = .007$) compared to HCs while no significant difference was found in the fast progression patients ($p = .25$, Figure 2).

It should be noted that the network FCS was to measure the functional integration of the whole PSMA. To further investigate whether the part showing significantly reduced ALFF also show impaired FC, we calculated the FC between the sphere ROIs (Figure 1b,c) located at the peak voxel in each hemisphere. Unlike the network FCS which measures the overall connectivity within the PSMA, the ROI FC measures only the connectivity between the area that showed most significant reduction of brain activity. We found that both the fast ($T_{(54)} = -2.43$, $p = .018$) and slow ($T_{(54)} = -3.10$, $p = .003$) progression groups showed significant reduced ROI FC compared with HCs. However, there was no significant difference between the fast and slow subgroups ($p = .49$). Whole brain p <.05 uncorrected results of the seed FC maps are provided in Figures S3 and S4. ANOVA model also revealed significant group effect ($F_{(2,72)} = 3.46$, $p = .037$).

3.3 | Correlation between RS-fMRI metrics and clinical features in the slow and fast progression groups

When taking all ALS patients together, no significant correlations were detected between the RS-fMRI metrics and clinical measurements including ALSFRS-R score (p values ≥.1), disease duration (p values ≥.08, one subject with a 204-month duration was excluded) and UMN score (p values ≥.62). Detailed information was provided in Table S2.

We then performed correlation analyses for the slow and fast progression groups separately. There were no significant correlations of the ALSFRS-R score with either the bilateral ALFF or the network FCS (p values >.2, Figure 3a,b) in the slow progression patients. But in the fast progression patients, we found significant positive correlations of the ALSFRS-R score with both the bilateral ALFF ($R = .62$, $p = .005$) and the network FCS ($R = .49$, $p = .034$) (Figure 3c,d). No significant correlations were found between the ROI FC and the clinical measurements in any ALS groups (p values >.053).

Since there was a significant correlation between the PSMA local activity (ALFF) and network FCS in the ALS group ($R = .7$, p <.001, Figure S5) but not in the healthy group ($R = .26$, $p = .13$), we further performed partial correlation analyses between the clinical features and RS-fMRI metrics in the slow and fast progression groups separately. In the fast progression ALS group, while regressing out the ALFF or network FCS, the network FCS or ALFF had no longer significant correlation with the ASLFRS-R (Figure 4c,d). But in the slow progression ALS group, regressing out the network FCS yielded no significant correlation between ALFF and ALSFRS-R ($p = .19$, Figure 4a), however, regressing out the ALFF yielded a significant negative correlation between the network FCS and ALSFRS-R ($R = -.54$, $p = .026$. Figure 4b). Partial correlation analyses for the slow progression patients were based on 18 ALS patients since one patient (disease duration = 48, ALSFRS-R = 33) was detected as significant outlier (partial regression model's Cook's distance = 1.25).

Despite its reduction in the slow progression group compared to HCs, the network FCS may play a compensatory role as revealed by the negative correlation with ALSFRS-R when the ALFF effect was controlled. An interesting question is that which component of the network FCS in the whole PSMA contributes more to this potential compensatory effect. We thus calculated the FCS between the left and right hemisphere (namely inter-hemisphere FCS) and within the left and right hemisphere (average of the left and right PSMA FCS, namely intra-hemisphere FCS). Both the inter-hemisphere FCS ($T_{(73)} = -2.20$, $p = .031$) and intra-hemisphere FCS ($T_{(73)} = -2.34$, $p = .022$) were reduced in all ALS groups. Specifically, inter- ($T_{(54)} = -2.52$, $p = .015$) and intra-hemisphere ($T_{(54)} = -2.87$, $p = .006$) FCS in the slow progression patients were reduced while the comparisons between the two subgroups as well as for fast progression patients versus HCs were not significant (p values >.19, Figure 5a,b). While regressing out the ALFF in the slow progression group, the inter-hemisphere FCS showed relatively more significant negative correlation with the ALSFRS-R ($R = -.58$, $p = .014$) (Figure 5c) than the intra-hemisphere FCS ($R = -.45$, $p = .071$) (Figure 5d). The same outlier was excluded in the partial correlation analyses as we mentioned in the previous paragraph.

We further decomposed the network FCS into FCS within/outside the area that showed reduced ALFF and replicated the partial correlation analyses in the slow progression group. Both the FCS

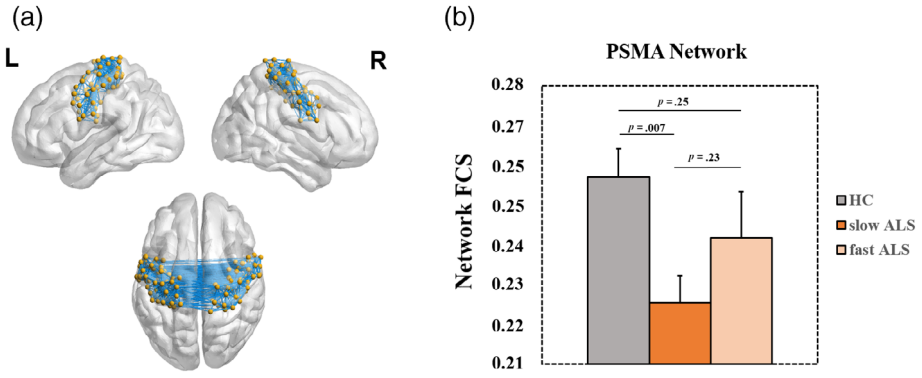

FIGURE 2 Reduced primary sensorimotor area (PSMA) network functional connectivity strength (FCS) in amyotrophic lateral sclerosis (ALS) patients. Panel a illustrates the parcellated 102 nodes and their connections within the entire PSMA. Panel b shows the significant reduced FCS of the PSMA in slow progression patients, while there was no significant difference between the two ALS groups, nor between the HC and fast progression group. Error bars represent standard error

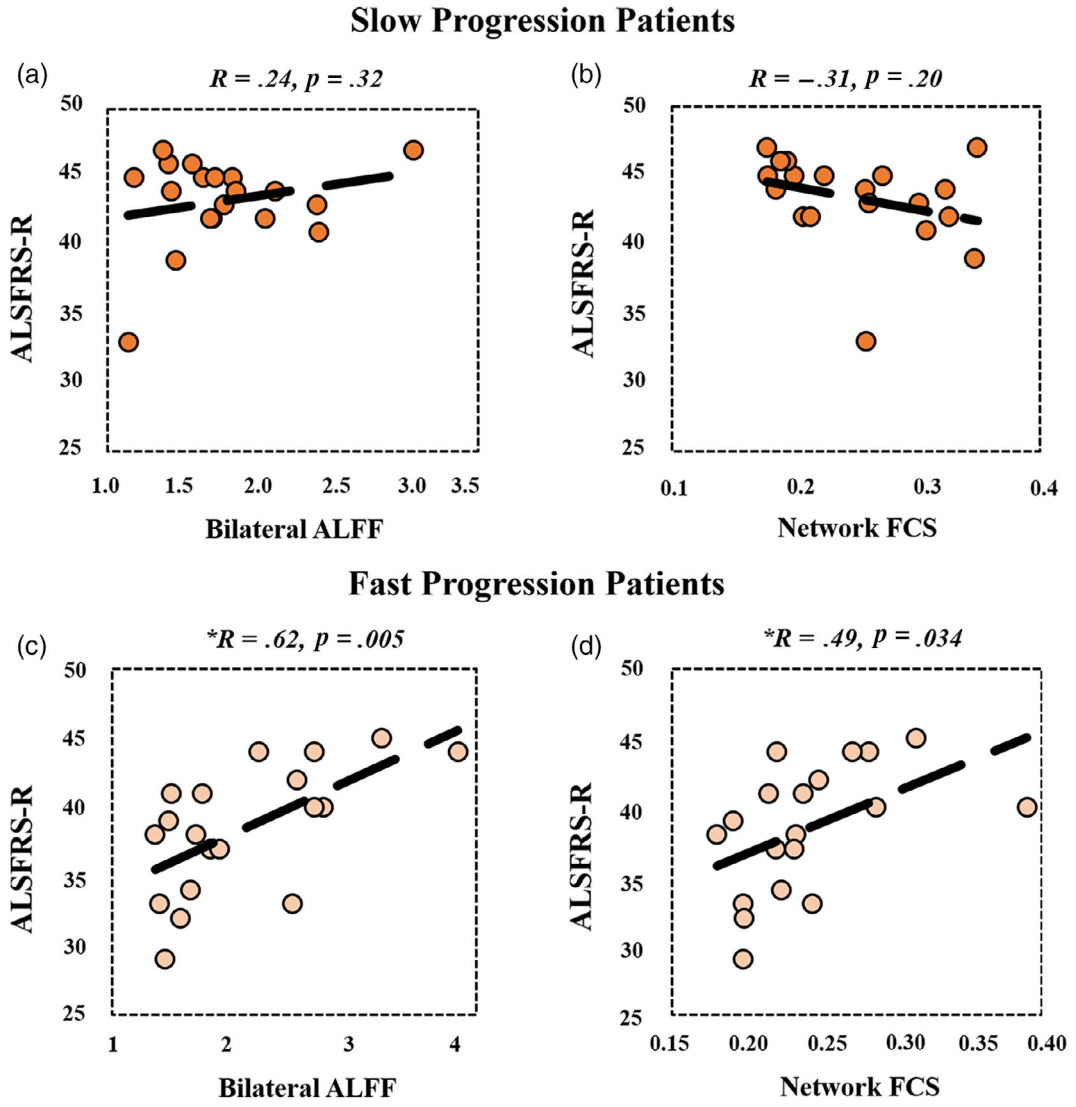

FIGURE 3 Correlations of PSMA amplitude of low frequency fluctuation (ALFF) and network functional connectivity strength (FCS) with ALFRS-R. Correlations of ALSFRS-R score with ALFF and network FCS in the slow progression group (Panels A and B) and fast progression group (Panels C and D). *: p <.05. ALSFRS-R: ALS Functional Rating Scale-Revised

within and outside the area showing reduced ALFF were correlated negatively with the ALSFRS-R, yet the correlation between within-FCS and the ALSFRS-R was more significant ($R = -.61$, $p = .004$) than that of the outside-FCS ($R = -.50$, $p = .035$).

4 | DISCUSSION

In the current study, by applying ALFF and network FCS analyses on RS-fMRI data, we demonstrated that the ALS patients showed reduced brain local activity as well as network FCS within the PSMA. The reduced ALFF and network FCS was highly correlated with each other in the ALS patients. Patients with fast PR exhibited significant positive correlation of the ALSFRS-R score and ALFF and network FCS. After controlling the ALFF, the inter-hemisphere FCS showed significant negative correlation with the ALSFRS-R score in the slow progression patients but not the fast progression group, suggesting a different mechanism for the fast and slow progression patients as discussed in details below.

4.1 | Decreased local activity in the PSMA accounts for severity in fast but not slow progression patients

In the current study, the decreased ALFF in the PSMA was highly consistent with the results from previous observations, including decreased glucose metabolism in ^{18}F-FDG PET studies (Claassen, Josephs, & Peller, 2010; Pagani et al., 2014), decreased activity of α, β, and θ frequency bands of EEG study (Dukic et al., 2019), as well as

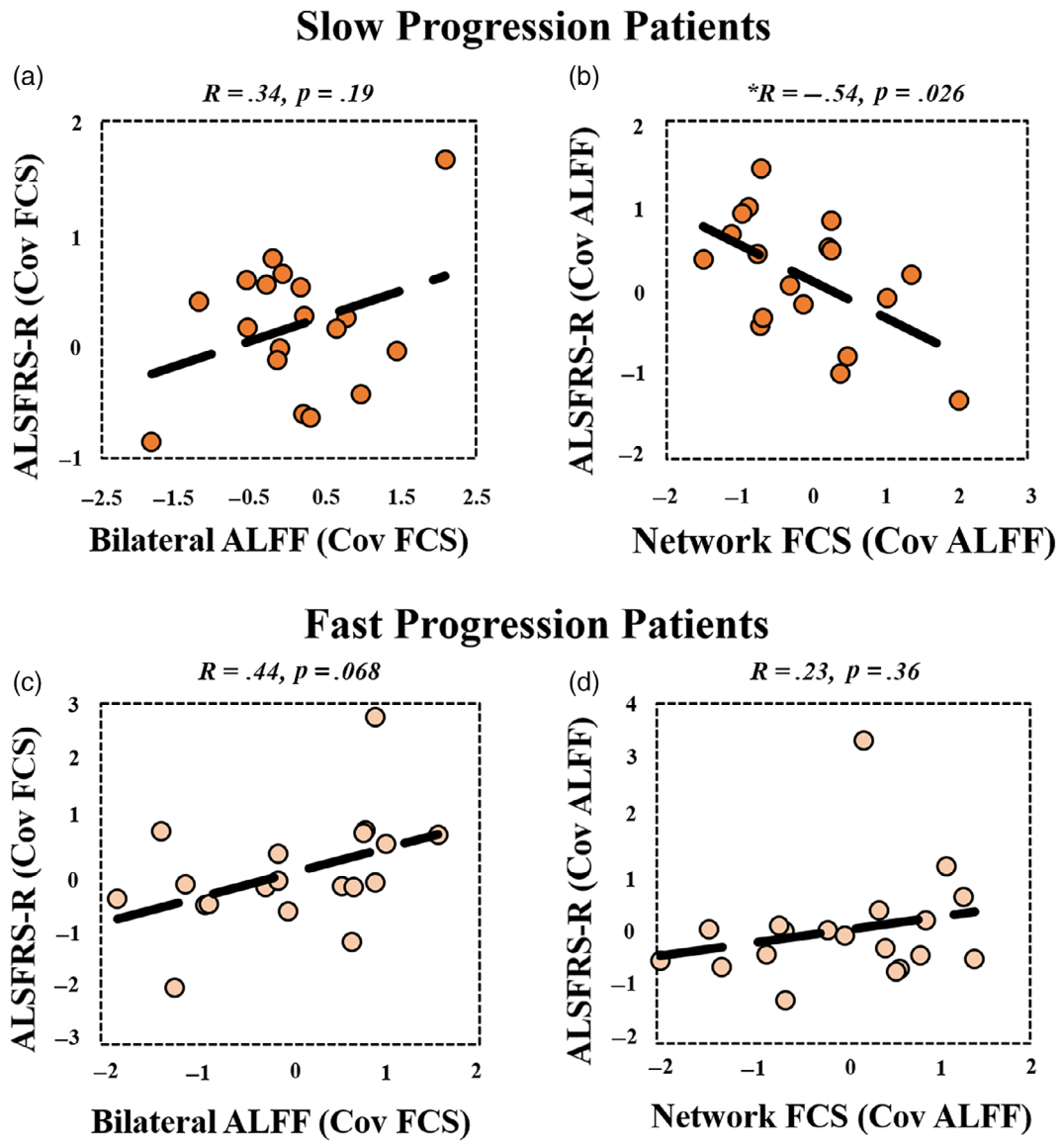

FIGURE 4 Partial correlations of PSMA amplitude of low frequency fluctuation (ALFF) and network functional connectivity strength (FCS) with ALFRS-R. Partial correlation analysis of ALSFRS-R with ALFF (network FCS as covariate of noninterest. Panels a and c) or with the network FCS (ALFF as covariate of noninterest. Panels b and d) in the slow progression group (Panels a and b) and fast progression group (Panels b and d). Cov: regressing out the covariate

decreased ALFF in RS-fMRI studies (Luo et al., 2012; Ma et al., 2020; Sako et al., 2017). The consistent cross-modality finding regarding decreased PSMA activity in ALS patients demonstrated that sensorimotor activity reduction is a robust feature.

However, neither previous nor the current study found correlations between the local activity and ALSFRS-R in ALS patients, probably due to the heterogeneity of disease PR. Although group comparison did not show difference of local activity between ALS subgroups, we demonstrated that reduced ALFF in the PSMA was positively correlated with ALSFRS-R only in the fast progression patients. These observations indicated that the PSMA local activity could reflect pathological mechanism in all ALS patients while it may further explain disease severity in the fast progression patients.

4.2 | Decreased and compensatory FC co-exist in slow but not fast progression patients

In the current study, both the network FCS and the FC between the two ROIs that showed decreased local activity were significantly reduced in the slow progression patients, yet only the ROI FC reached significance in the fast progression patients, demonstrating location-dependent magnitude of FC reduction in the slow and fast progression patients. While the RS-fMRI studies have consistently reported decreased local activity in the PSMA, the FC studies were not consistent or even contrary (Basaia et al., 2020; Douaud et al., 2011; Jelsone-Swain et al., 2010; Mohammadi et al., 2009). For example, our result was consistent with the study by Mohammadi that showed decreased FC (Mohammadi et al., 2009) using independent

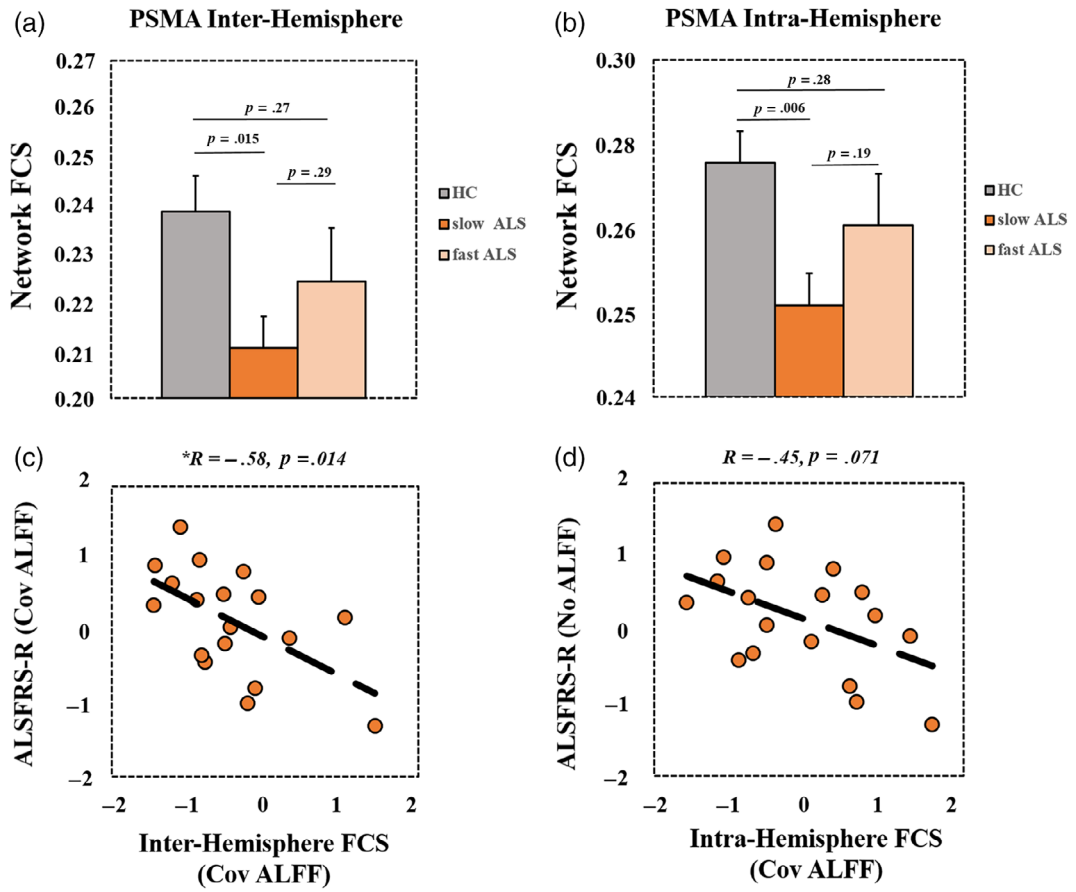

FIGURE 5 Inter- and intra-hemisphere network functional connectivity strength (FCS). Inter- (panel a) and intra-hemisphere (panel b) FCS in the amyotrophic lateral sclerosis (ALS) patients. Panel c shows, in the slow progression group, the ALSFRS-R score showed significant negative correlation with the inter-hemisphere FCS ($p = .014$) but not significant with intra-hemisphere FCS was as shown in panel D ($p = .071$) when amplitude of low frequency fluctuation (ALFF) was controlled as covariate of noninterest to remove the shared variance with network FCS

component analysis but opposite to the study by Basaia where increased network connectivity was detected (Basaia et al., 2020). Although the analytic methods are not the same for these studies, the contrary results, that is, increased FC vs. decreased FC, are not likely due the dissimilar analytic methods.

In the current study, regarding that about 50% of shared variance was obtained between the reduced FCS and the reduced ALFF in ALS patients, we further explored the "net" association between FCS and the disease severity by regressing out the ALFF in fast and slow progression patients. Interestingly, the FCS no longer showed significant correlation with disease severity in the fast progression group, but was significantly negatively correlated with disease severity in the slow progression group. Vice versa, ALFF showed no significant correlation with the symptoms in either fast or slow groups when the FCS was regressed out. Results from these partial correlation yield that the "net" FCS is an independent variable accounting for the symptom opposite to the ALFF in slow progression patients: the higher the "net" FCS is, the more severe the symptom is. Even though the current study identified decreased FC, the negative correlation was seemingly in line with the compensatory mechanism which was raised as a potential explanation regarding the increased PSMA FC in ALS patients (Chiò et al., 2014; Qiu et al., 2019). Researchers considered that patients with different stages of disease development may have different level of compensatory effect for neural impairments (Qiu et al., 2019).

One plausible explanation for the seemingly opposite results of the correlation between the network FCS and the disease severity with/without the shared variance of ALFF in the slow progression group may be due to the co-existence of both pathological (i.e., decreased network FCS) and compensatory (i.e., association of higher network FCS with more severity) components of the network FCS to the disease. The negative correlation means that better performance as revealed by ALSFRS-R required less "net" FCS while lower ALSFRS-R required more "net" FCS. This observation was only found in patients with slow PR, which probably indicates that patients who progress slowly may still preserve the compensation effect of the "net" FCS. As a result, higher "net" FCS can compensate lower performance. However, such compensation effect may exceed the limit in fast progression patients. By further decomposing the network FCS into inter- versus intra-hemisphere FCS, we found that the inter-hemisphere FCS showed relatively more significant negative correlation with severity than the intra-hemisphere FCS when the ALFF was regressed out, demonstrating that the inter-hemisphere FCS may

contribute more to the compensatory effect than the intra-hemisphere FCS in the slow progression ALS patients. However, in the fast progression group, the positive correlation between the network FCS and disease severity became not significant when the ALFF was regressed out, indicating that both the ALFF and network FCS showed pathophysiological decrease yet apparently compensatory FCS was not pronounced in the fast deterioration of the disease. The different correlation results of ALFF and FCS revealed different PSMA mechanisms between slow and fast ALS patients, which further indicates that different clinical treatments may be considered according to the progression speed of the disease.

The small sample size of the current study which may influence the cut-off median PR to divide the ALS patients constrained us to further investigate the PSMA mechanisms in other phenotypes of the disease. Future studies with large sample size are needed to validate the current findings.

4.3 | Limitations

One limitation of the current study was the arbitrary threshold for ALS subgroup classification. However, to the best of our knowledge, there is currently no golden standard role for group separation based on their PR. In addition, we recruited five mild bulbar-onset patients which may also influence the PR cut-off. Only five patients agreed for genetic examination and one was SOD1 and one was VAPB mutation. The lack of genetic investigation also limits the strength of the current study. Another limitation is the small sample size for each subgroup. Studies with large sample size are needed in the future for clarification of the current results. The third limitation was that we did not include cognitive measurements, which was closely associated with disease progression. Therefore, the current study focused on sensorimotor area which was considered not to be highly associated with cognitive functions.

5 | CONCLUSIONS

Taken together, the current RS-fMRI study showed different pathophysiological mechanisms of the local activity and FC in the PSMA for fast and slow progression ALS patients. The decreased ALFF could account for the severity in the fast progression group but not for slow progression group. The network FCS, especially the inter-hemisphere FCS, showed both pathophysiological effect (i.e., decreased FCS) and a compensatory effect (i.e., negative correlation with severity when the covariate ALFF was regressed out). We hope that our study may not only highlight the importance of consideration of the heterogeneity of disease PR in future studies of ALS, but also provide reference for the application of different clinical interferences according to the disease PR of the patient.

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CONFLICT OF INTEREST

All authors declare no conflict of interests.

AUTHOR CONTRIBUTIONS

Qianwen Li: subjects recruitment, experimental design, data collection, statistics, and manuscript preparation. **Wenjia Zhu**: subjects recruitment, experimental design, data collection and manuscript preparation. **Xinmei Wen**: subjects recruitment and data collection. **Zhenxiang Zang**: data analysis and statistics. **Yuwei Da**: experimental design, data collection, statistics and conception. **Jie Lu**: conception, experimental design, supervision, and manuscript preparation.

DATA AVAILABILITY STATEMENT

The data that support the findings of this study are available from the corresponding author upon reasonable request.

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SUPPORTING INFORMATION

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