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Early cortical alterations and neuropsychological mechanisms in amyotrophic lateral sclerosis

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ABSTRACT

Objective: This study investigates the characteristics of cortical structural and functional alterations in amyotrophic lateral sclerosis (ALS) patients and their modulation of emotional and cognitive functions, as well as to discuss their diagnostic value in early-stage ALS.

Methods: Fifty-nine ALS patients (28 in ALS 1 and 31 in ALS 2, categorized using King's College Staging) and 31 healthy controls were evaluated using multiparametric MRI, motor and neuropsychological assessments, and serum neurofilament light chain (NfL) levels. Mediation analyses were performed to examine how cortical alterations influence the relationship between emotional and cognitive functions. Support vector machine (SVM) classification models were constructed to assess the diagnostic utility of differential cortical parameters.

Results: ALS 1 patients exhibited increased cortical thickness (CT) and functional activity in the cingulate and frontotemporal regions, correlating with neuropsychological performance and NfL levels. Mediation analysis revealed that perigenual and frontotemporal functional activity significantly modulated the relationship between depressive symptoms and cognitive function. SVM classification showed that the combined altered regions with Amplitude of Low Frequency Fluctuations (ALFF) model achieved slightly better performance (AUC = 0.853, 95 %CI: 0.687–1.000, $p < 0.001$) compared to CT (AUC = 0.779, 95 %CI: 0.587–0.972, $p < 0.001$), although both models showed limited efficacy in differentiating between ALS 1 and ALS 2 groups.

Conclusions: Cortical structural and functional alterations in ALS mediate the impact of depression on cognitive function, offering insights into the neuropsychological mechanisms of the disease and potential biomarkers for early-stage diagnosis.

1. Introduction

Amyotrophic lateral sclerosis (ALS) is a fatal neurodegenerative disease that primarily affects motor neurons, resulting in progressive weakness of skeletal and respiratory muscles, with a median survival of 3 to 5 years (Vidovic et al., 2023; Cappella et al., 2021). Currently, no cure exists for ALS, though early diagnosis and intervention can slow disease progression (Carmona et al., 2017). However, due to the clinical, genetic, and neuropathological heterogeneity of ALS and the lack of reliable biomarkers for diagnosis and disease monitoring (Bendotti et al., 2020), the average time from the onset of symptoms to the diagnosis of ALS is often delayed by 9 to 13 months (Chiò, 1999; Rocchetti et al., 2012). In addition to motor symptoms, approximately 50 % of ALS patients present non-motor symptoms, including cognitive and behavioral changes, which can occur before motor impairments (Hardiman et al., 2017). These changes involve apathy (Kutlubaev et al., 2023), executive functions (Phukan et al., 2012), decision-making and theory of mind (ToM) (Lulé et al., 2019). These changes are primarily associated with the pathological changes observed in frontotemporal dementia (FTD) (Phukan et al., 2007), as ALS and FTD are considered to be part of the same disease spectrum (Burrell et al., 2011; Abramzon et al., 2020; Karch et al., 2018).

Depression and anxiety commonly occur in the early stages of ALS and are not correlated with disease duration or presentation (Prado et al., 2017; Poletti et al., 2018). Epidemiological studies report that depression affects up to 44 % of ALS patients, while anxiety prevalence

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may reach 30 % (Sathasivam, 2009). These conditions have been suggested to contribute to early cognitive decline in ALS patients (Jellinger, 2025; De Marchi et al., 2019). Moreover, studies have shown that the relationship between depression, anxiety, and cognitive performance in ALS patients may be influenced by specific brain regions, such as the amygdala and hippocampus, which are crucial for emotion regulation and memory (Jellinger, 2023). However, some studies argue that depression and anxiety have no significant impact on cognitive outcomes (Beeldman et al., 2016). Thus, the connection between depression, anxiety, and cognitive decline in ALS may be complex, involving various brain regions and neurobiological mechanisms. Further studies are needed to clarify these relationships, improve understanding of ALS pathogenesis, and develop targeted interventions to enhance cognitive function and mitigate the disease's negative effects.

With the advancement of neuroimaging techniques, Magnetic Resonance Imaging (MRI) has become increasingly valuable in studying pathological changes and objectively assessing treatment effects in ALS (Turner et al., 2009). Previous studies have reported differences in gray matter and cortical thickness (CT) between ALS patients and controls, with particular thinning observed in the right frontotemporal insular cortex in patients with cognitive-behavioral disorders, correlating with more severe cognitive deficits (Grosskreutz et al., 2006; Agosta et al., 2007; Benbrika et al., 2021; Consonni et al., 2020). Additionally, a recent study found that ALS patients with more depressive and anxiety symptoms exhibited poorer executive function, greater prefrontal dysfunction, and thinning of the frontal gyri and orbitofrontal cortex (Benbrika et al., 2021). However, most functional imaging studies primarily focus on alterations in gray and white matter, often reflecting late-stage changes due to the strict inclusion criteria for ALS patients. There is a notable lack of research on the correlations between these alterations and depression, anxiety, and other extrapyramidal manifestations. Importantly, analyses of cortical structure and function have shown significant diagnostic value for the early detection of various diseases (Qin et al., 2022; Ming et al., 2015; Li et al., 2024). This technology can sensitively detect subtle alterations in cortical structure and function, providing critical imaging evidence for the early identification of neurodegenerative diseases, mental disorders, and related conditions.

This study aimed to investigate the progression of cortical structural and functional alterations across different stages of ALS using multiparametric MRI and the associations between neuroimaging biomarkers and clinical parameters, including motor function, anxiety, depression, and cognitive performance, to elucidate potential neural modulatory mechanisms. Additionally, support vector machine (SVM) analysis was applied to differential cortical regions to construct receiver operating characteristic (ROC) curves, evaluating their potential as biomarkers for early diagnosis and disease staging in ALS.

2. Materials and methods

2.1. Participants

This study was conducted from 2022 to 2024 at a tertiary referral center in eastern China and included 59 ALS patients and 31 age- and sex-matched healthy controls. To explore the correlation between early cortical structure and function in ALS with cognitive and emotional abnormalities, ALS patients with involvement of two or fewer body regions were selected for the disease group, based on the Gold Coast diagnostic criteria, to minimize potential impacts from extensive motor region involvement. The ALS group was further divided into two subgroups based on King's College Staging System: ALS 1 (King's College Stage 1) and ALS 2 (King's College Stage 2A and 2B). Patients whose muscle weakness and motor dysfunction were attributed to other neurological diseases or metabolic disorders, as well as those unable to cooperate due to severe cognitive impairment or psychiatric disorders, were excluded.

All participants underwent baseline multiparametric MRI assessments, and detailed clinical data were collected, including age, sex, education level, age of onset, and the time from initial symptoms to diagnosis. This study was approved by the Ethics Committee, and all participants were informed of the purpose of the study prior to enrollment and provided written informed consent (Fig. 1).

2.2. Physical functional status and neuropsychological assessment

The ALS Functional Rating Scale-Revised (ALSFRS-R) was used to assess the physical functioning of ALS patients. This 12-item scale scored from 0 (worst) to 4 (best), evaluates bulbar, limb, and respiratory functions, with a total score ranging from 0 to 48. Higher scores indicate better physical condition and functioning (Cedarbaum et al., 1999).

Depression and anxiety were assessed using the 24-item Hamilton Depression Rating Scale (HAMD-24) and the Hamilton Anxiety Rating Scale (HAMA). Cognitive function was evaluated with the Mini-Mental State Examination (MMSE) and the Montreal Cognitive Assessment (MoCA). MoCA is a rapid cognitive screening tool with greater sensitivity than the MMSE in detecting mild cognitive impairment, covering visual-spatial/executive function, naming, attention, language, abstraction, memory, and orientation (Aiello et al., 2022). The Edinburgh Cognitive and Behavioral ALS Screen (ECAS) was not used in this study, as the focus was on assessing global cognitive function and emotional disturbances in the early stages of the disease. Furthermore, MoCA has shown comparable efficacy to ECAS in screening for early cognitive impairments (Aiello et al., 2022; Taule et al., 2020).

All assessments were conducted by two specially trained neuropsychologists in a quiet and comfortable environment, and detailed records of the evaluation outcomes were kept.

2.3. Serum NfL measurement

Fasting venous blood samples were collected from all ALS participants at 8 a.m. The samples were centrifuged at 2000 g for 15 min at 4 °C to separate the plasma. The plasma was aliquoted into 0.5 mL polypropylene tubes and stored at −80 °C. Serum neurofilament light chain (NfL) levels were measured using the single-molecule array (Simoa) method.

2.4. Imaging

2.4.1. Data acquisition of MRI

MRI data were acquired at the Department of Radiology, a tertiary referral center in eastern China, using a 3.0 T Prisma system (Siemens, Erlangen, Germany) with a 20-channel head coil. Scans were performed on the same day as neuropsychological assessments. During the scanning process, participants lay flat with their eyes closed and remained awake, with head movement minimized using sponges and noise reduced by earplugs. The scanning was conducted by two trained radiologists. High-resolution T1-weighted images were obtained using a magnetization-prepared rapid gradient echo sequence, with the following parameters: repetition time (TR) of 1900 ms, echo time (TE) of 2.45 ms, flip angle of 9°, field of view (FOV) of 256 × 256 mm^2, matrix of 256 × 256, slice thickness of 1.0 mm, total of 176 slices, and voxel size of 1 × 1 × 1 mm^3. Resting-state functional MRI (rs-fMRI) images were acquired using an axial gradient echo planar imaging sequence with the following parameters: TR of 2000 ms, TE of 30 ms, flip angle of 90°, FOV of 240 × 240 mm^2, matrix size of 64 × 64, slice thickness of 4.0 mm, a total of 35 slices, and voxel dimensions of 3.75 × 3.75 × 4 mm^3. The scanning lasted 12 min and 26 s.

2.4.2. Data pre-processing

Data preprocessing was conducted using DPABISurf (https://rfmri.org/DPABI) (Yan et al., 2021), a toolbox based on fMRIprep (version 20.2.1) (Esteban et al., 2019), for structural and functional MRI data. The preprocessing steps included discarding the initial 10-time points

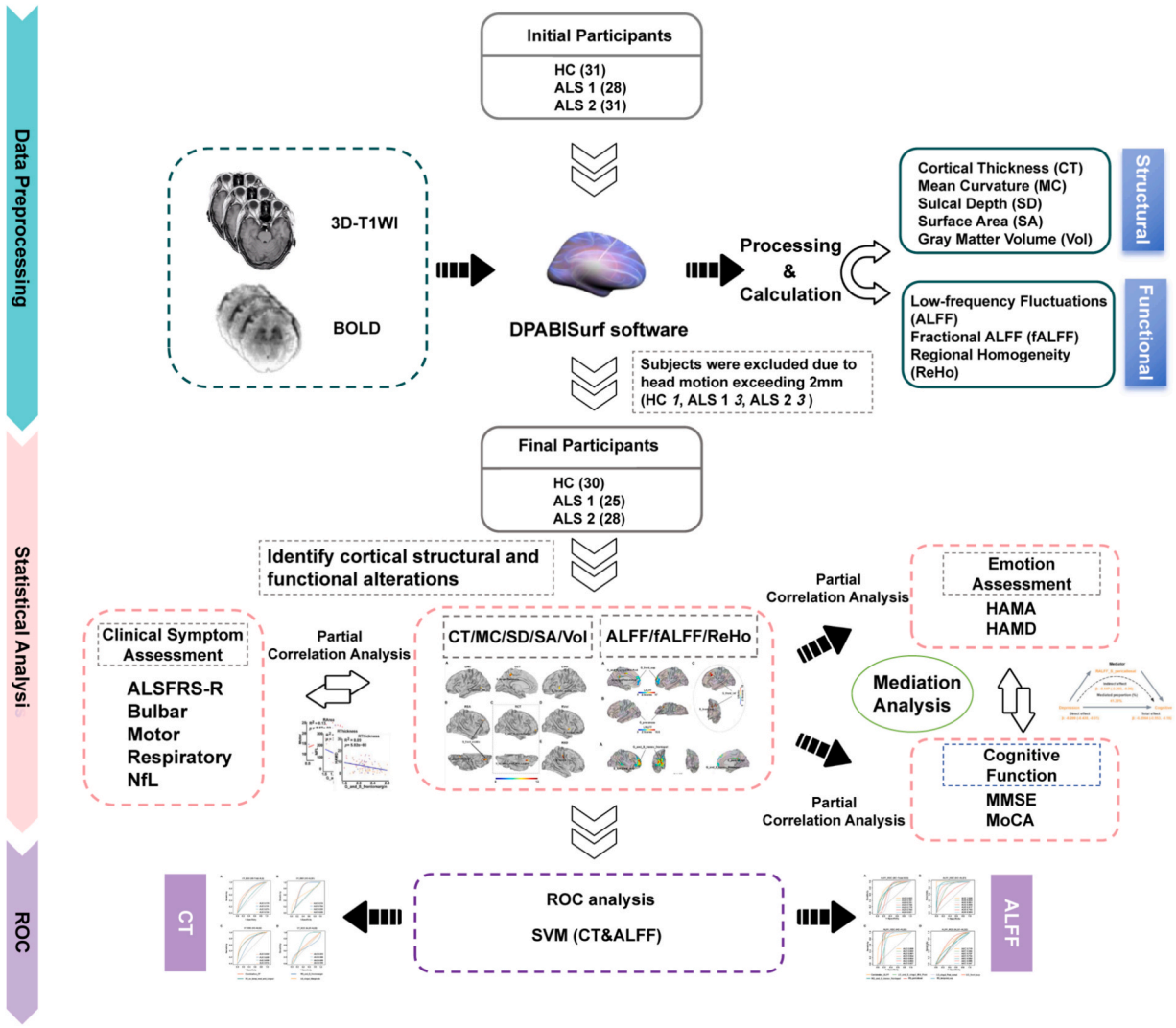

Fig. 1. The framework diagram of the study design. **Abbreviation:** HC, healthy controls; ALS 1: ALS Patients in King's College Stage 1; ALS 2: ALS Patients in King's College Stage 2A and 2B; 3D-T1WI, three-dimensional T1 weighted imaging; BOLD, Blood Oxygen Level Dependent; CT, cortical thickness; MC, mean curvature; SD, sulcal depth; SA, surface area; Vol, gray matter volume; ALFF, Amplitude of Low-Frequency Fluctuations; fALFF, fractional Amplitude of Low-Frequency Fluctuations; ReHo, Regional Homogeneity; ALSFRS-R, Amyotrophic Lateral Sclerosis Functional Rating Scale-Revised; NfL, Neurofilament light chain; HAMA, Hamilton Anxiety Rating Scale; HAMD, Hamilton Depression Rating Scale; MMSE, Mini-Mental State Examination; MoCA, Montreal Cognitive Assessment; ROC, Receiver Operating Characteristic; SVM, Support Vector Machine.

for signal stabilization, converting data into BIDS format (Gorgolewski and Poldrack, 2016), and initiating the fMRIprep docker. Anatomical preprocessing corrected T1-weighted images for intensity non-uniformity using N4BiasFieldCorrection, followed by skull stripping via the antsBrainExtraction workflow (Avants et al., 2008) with the OASIS30ANTs template. Brain tissue was segmented into cerebrospinal fluid (CSF), white matter (WM), and gray matter (GM) using the fast tool (Zhang et al., 2001), and brain surfaces were reconstructed with recon-all (Dale et al., 1999). Functional preprocessing involved generating and skull-stripping a BOLD reference volume, coregistering it to the T1 reference via bbregister (FreeSurfer) (Greve and Fischl, 2009), performing slice-time correction (3dTshift), and resampling to fsaverage5 space. Nuisance regression, using the Friston 24-parameter model (Friston et al., 1996), removed head motion, WM, and CSF signals, while also mitigating respiratory and cardiac effects. Linear trends were removed to correct for BOLD signal drift. The Destrieux Atlas (Destrieux et al., 2010) was used as the cortical region template in DPABISurf.

Finally, the data were filtered (0.01–0.1 Hz) and smoothed (6 mm FWHM) to extract cortical metrics, including cortical thickness (CT), mean curvature (MC), sulcal depth (SD), surface area (SA), gray matter volume (Vol), ALFF, fractional Amplitude of Low-Frequency Fluctuations (fALFF), and Regional Homogeneity (ReHo). Low-quality T1 images, blurred functional images, and data with head motion exceeding 2 mm or 2° were excluded. The remaining data proceeded to statistical analysis.

2.5. Statistical analysis

Statistical analyses were performed using SPSS 25.0. Data normality was assessed using the Shapiro-Wilk test, with results presented as mean ± standard deviation or median (interquartile range) as appropriate. Between-group comparisons were conducted using independent t-tests (for two groups) or ANCOVA with Bonferroni post hoc tests (for three groups). Gender differences were analyzed using chi-square tests ($p < 0.05$).

Cortical analyses were conducted using DPABISurf. Whole-brain ANOVA and post hoc analyses were performed, controlling for age, sex, and head motion. Multiple comparisons were corrected using Monte Carlo Null-Z simulation (10,000 permutations, two-tailed; cluster-wise $p < 0.025$ per hemisphere, vertex-wise $p = 0.001$). Bonferroni correction

was applied for post hoc pairwise comparisons.

Partial correlation analyses were then performed to examine the associations between cortical metrics and clinical measures (motor function, cognition, NfL, anxiety, and depression), with Bonferroni correction applied ($p < 0.0125$ for neuropsychological scores; $p < 0.01$ for motor assessments). Results were visualized using DPABISurf.

Mediation analyses were conducted using the R package mediation (v3.4.4) (Tingley et al., 2014) to explore the mediating role of cortical alterations between anxiety/depression (independent variables) and cognition (outcome variable). Effect sizes were estimated using 5,000 bootstrap samples with bias-corrected 95 % confidence intervals ($p < 0.05$).

Finally, SVM classification was performed using structural and functional imaging biomarkers from regions showing significant group differences. Both individual region-based and combined models were constructed using a 70/30 training–testing split. Model optimization was performed with 10-fold cross-validation using an RBF kernel (cost: 0.001–1000; gamma: 0.5–4). Performance was evaluated based on accuracy, sensitivity, specificity, and AUC, with significance assessed through 1,000 permutation tests. SVM analyses were implemented in R (v4.2.1) using the e1071 package (v1.7.13).

3. Results

3.1. Demographic, motor functional and neuropsychological tests

The clinical and demographic characteristics of the subjects are summarized in Table 1. After excluding data with head motion, the final analysis included *25* ALS 1, *28* ALS 2, and 30 HC participants. No significant differences in sex and age were observed among the three groups ($p > 0.05$). Compared to the HC group, both ALS 1 and ALS 2 participants scored significantly lower on the MoCA and higher on the HAMA and HAMD ($p < 0.001$). ALSFRS-R scores and sub-items showed no statistical differences between ALS 1 and ALS 2, though a downward trend was observed. This may be related to the fact that a higher proportion of patients in ALS 2 were in Stage 2A. Notably, a significant difference in NfL levels was found between the two ALS subgroups, with levels decreasing as the disease progressed ($p = 0.014$).

Table 1
Demographic Information and Behavioral Characteristics.

	HC (n = 30)	ALS 1 (n = 25)	ALS 2 (n = 28)	*p* Value
Age (y)	60.93 ± 6.51	56 ± 10.1	56.75 ± 10.83	0.101
Gender (F/M)	16/14	12/13	9/19	0.246[†]
NFL (pg/mL)	–	109.49 ± 79.62	66.12 ± 39.57	0.014[c]
Psychological Cognitive Assessment				
MMSE	28.47 ± 1.408	24.32 ± 5.51	26.61 ± 2.62	< 0.001[a]
MoCA	27.50 ± 1.68	20.40 ± 6.28	21.54 ± 3.90	< 0.001[ab]
HAMA	3.17 ± 2.47	8.80 ± 5.22	7.93 ± 5.72	< 0.001[ab]
HAMD	2.30 ± 2.67	8.72 ± 4.56	6.57 ± 4.61	< 0.001[ab]
ALSFRS-R	–	40.36 ± 5.05	38.61 ± 5.29	0.888
Bulbar	–	10.00 ± 2.58	10.57 ± 1.73	0.084
Motor	–	18.64 ± 4.54	16.11 ± 4.18	0.892
Respiratory	–	11.68 ± 0.75	11.57 ± 0.69	0.764

Note: The *p* values were obtained from the one-way ANOVA (age) and the ANCOVA (controlled for age, gender, and education) analysis, while the † *p*-value was derived from the χ^2 test. Data are presented as mean ± SD. Significant differences were observed in MMSE, MoCA, HAMA, and HAMD. Post hoc analysis (Bonferroni correction) further identified the source of ANCOVA differences: (a) HC vs. ALS 1, (b) HC vs. ALS 2, (c) ALS 1 vs. ALS 2.
Abbreviation: HC, Healthy Control; ALS 1: ALS Patients in King's College Stage 1; ALS 2: ALS Patients in King's College Stage 2A and 2B; F/M, Female/Male; MMSE, Mini-Mental State Examination; MoCA, Montreal Cognitive Assessment; HAMD, Hamilton Depression Scale; HAMA, Hamilton Anxiety Scale; NFL, Neurofilament Light Chain; ALSFRS-R, Amyotrophic Lateral Sclerosis Functional Rating Scale-Revised.

3.2. Differences of cortical structural among the three groups

After controlling for age, sex, and head motion, ANCOVA revealed significant cortical structural differences among the groups. Following Monte Carlo correction, alterations were observed in the left hemisphere, including the MC of inferior occipital sulcus and preoccipital notch [S_occipital_ant, 59], CT of marginal branch of the cingulate sulcus [S_cingul-Marginalis, 46], and Vol of superior segment of the circular sulcus of the insula [S_circular_insula_sup, 49]. In the right hemisphere, alterations were noted in the SA of middle frontal sulcus [S_front_middle, 53] and superior parietal lobule (lateral part of P1) [G_parietal_sup, 27], CT of gyrus and sulcus of the fronto-marginal [G_and_S_frontomargin, 1] and medial occipito-temporal sulcus (collateral sulcus) and lingual sulcus [S_oc-temp_med_and_Lingual, 61], Vol of short insular gyri [G_insular_short, 18] and SD of central sulcus (Rolando's fissure) [S_central, 45] (Table2 and Fig. 2). Post-hoc analysis revealed that the structural differences in the left hemisphere were primarily between the HC group and both the ALS 1 and ALS 2 groups rather than between the ALS 1 and ALS 2 groups (Fig. 3). The MC of S_occipital_ant and Vol of S_circular_insula_sup showed a downward trend associated with disease progression. While not statistically significant, the CT of the left S_cingul-Marginalis increased in ALS 1 but decreased in ALS 2. Similarly, in the right hemisphere, the SA of G_parietal_sup, CT of S_oc-temp_med_and_Lingual, and SD of S_central showed the largest reductions in the ALS 2 group (Figs. 4 and 5), while Vol of G_insular_short significantly declined in ALS 1 (Fig. 5). As in the left hemisphere, the CT of G_and_S_frontomargin in the right hemisphere also increased in the ALS 1 group (Fig. 4).

Partial correlation analyses revealed that only the MC of S_occipital_ant in the left hemisphere and the SA of G_parietal_sup in the right hemisphere were positively correlated with respiratory function ($p = 0.0124$) and motor function ($p = 0.00867$), respectively. Most of the other structurally distinct cortical regions were linked to cognitive and emotional functions. Specifically, the Vol of S_circular_insula_sup, CT of S_oc-temp_med_and_Lingual and Vol of G_insular_short were positively correlated with MoCA scores and negatively correlated with HAMA and HAMD scores ($p < 0.01$), while the alterations in the CT of S_cingul-Marginalis exhibited opposing results (Figs. 2, 3 and 4). Notably, the CT of G_and_S_frontomargin in the right hemisphere showed a significant negative correlation with NfL levels ($p < 0.001$) (Fig. 4).

3.3. Altered cortical brain functional activities among groups

After controlling for age, sex, and head motion, functional alterations

Table 2
Anatomical Abbreviations of Cortical Regions.

index	short name	Long name (TA nomenclature is **bold typed**)
1	G_and_S_frontomargin	Fronto-marginal gyrus (of Wernicke) and sulcus
18	G_insular_short	**Short insular gyri**
27	G_parietal_sup	**Superior parietal lobule** (lateral part of P1)
45	S_central	**Central sulcus** (Rolando's fissure)
46	S_cingul-Marginalis	**Marginal branch** (or part) **of the cingulate sulcus**
49	S_circular_insula_sup	Superior segment of the **circular sulcus of the insula**
53	S_front_middle	Middle frontal sulcus
59	S_occipital_ant	Anterior occipital sulcus and **preoccipital notch** (temporo-occipital incisure)
61	S_oc-temp_med_and_Lingual	Medial occipito-temporal sulcus (**collateral sulcus**) and lingual sulcus

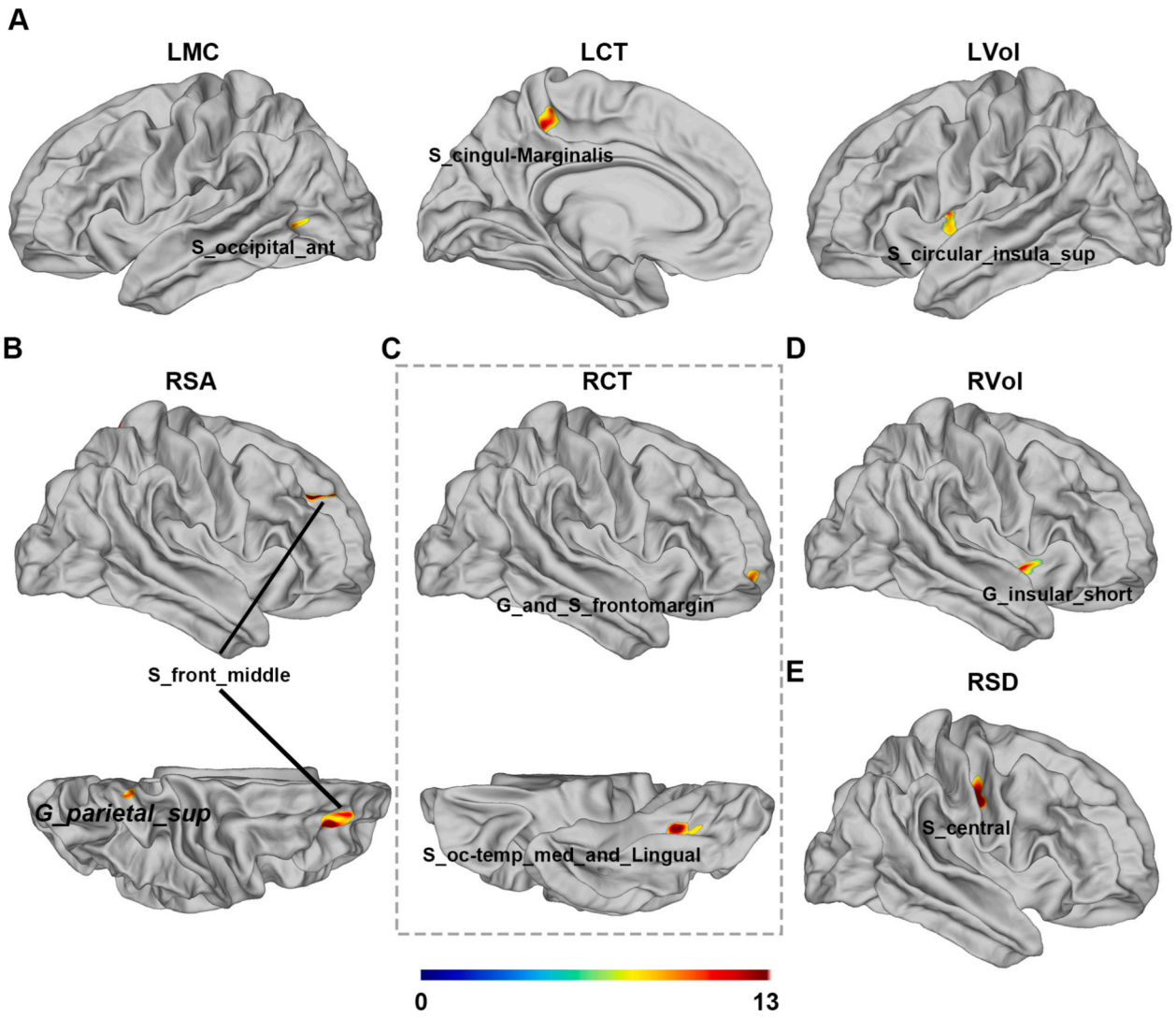

Fig. 2. Differences in cortical structure among the three groups. (A) Differences in the left hemisphere of MC, CT and Vol; (B), (C), (D), (E) showed the altered regions in the right hemisphere of SA, CT, Vol and SD, respectively. **Abbreviation:** L, left; R, right; CT, cortical thickness; MC, mean curvature; SD, sulcal depth; SA, surface area; Vol, gray matter volume.

were observed primarily in the left hemisphere, including middle-posterior part of the cingulate gyrus and sulcus (pMCC) [G_and_S_cingul-Mid-Post, 8] (ALFF) and posterior-dorsal part of the cingulate gyrus (dPCC) [G_cingul-Post-dorsal, 9] (ALFF), precuneus (medial part of P1) [G_precuneus, 30] (fALFF), and inferior frontal sulcus [S_front_inf, 52] (ReHo) and superior frontal sulcus [S_front_sup, 54] (ReHo) (Fig. 6). In the right hemisphere, significant differences in brain activity were limited to ALFF, with alterations noted in transverse frontopolar gyri and sulci [G_and_S_transv_frontopol, 5], superior temporal sulcus (parallel sulcus) [S_temporal_sup, 73], and pericallosal sulcus (S of corpus callosum) [S_pericallosal, 66] (Fig. 8A and Table 3). Post-hoc analyses revealed significant differences between the HC and ALS groups, while no significant differences were found between ALS 1 and ALS 2. The ALS group, particularly the ALS 1 group, exhibited increased local activity in several cortical regions, such as G_and_S_cingul-Mid-Post (LALFF), G_precuneus (LfALFF), S_front_inf (LReHo), S_front_sup(LReHo), and G_and_S_transv_frontopol (RALFF), while activity in other regions was reduced compared to the HC group (Fig. 7A and 8B). After adjusting for *p*-values, partial correlation analysis also revealed that activity in most altered regions correlated more strongly with emotional and cognitive functions than with motor functions (Fig. 7B and 8C). Notably, although no significant associations were found after correction for multiple comparisons, activity in G_cingul-Post-dorsal (LALFF), S_pericallosal (RALFF), and S_front_sup (LReHo) showed nominal positive correlations with NfL levels (p = 0.022, p = 0.03, p = 0.047, respectively) (Fig. 7B and 8C).

3.4. *The moderating role of the brain cortex between emotional and cognitive functions*

Given the utility of the MoCA in screening for early cognitive impairment in ALS (Aiello et al., 2022; Taule et al., 2020), no significant correlation was found between MoCA scores and HAMA (r = -0.135, p = 0.223), but a negative correlation with HAMD was observed (r = -0.315, p = 0.004) using Pearson correlation analysis. Therefore, cortical regions differentially affected by both emotional and cognitive functions were considered as potential mediators between HAMD and MoCA. Six cortical regions exhibiting significantly different ALFF showed varying degrees of mediating effects, suggesting that depression may reduce cognitive function by suppressing the activity of these regions. These findings were further validated through sensitivity analyses (Fig. 9 and Supplementary Fig. 1). Among them, three right-sided differential cortex regions demonstrated greater moderating effects, with S_pericallosal exhibiting the largest mediating effect (mediated proportion: 41.30 %, β:

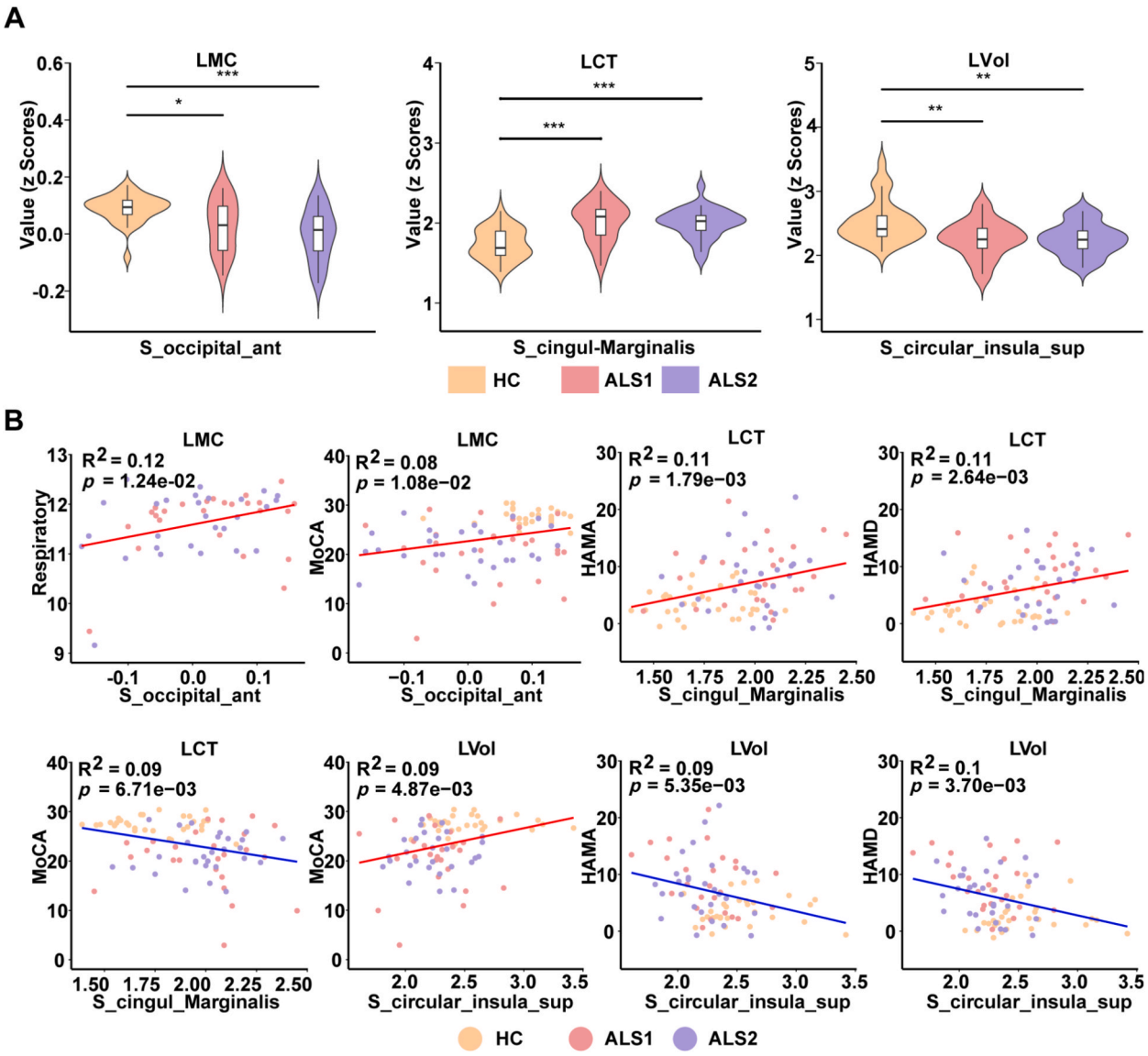

Fig. 3. Comparative analysis of cortical structural metrics and their correlation with neuropsychological assessments across groups. (A) Post hoc test violin plots of cortical structural features in the left hemisphere among ALS 1, ALS 2, and HC. (B) Correlation analysis of cortical structural feature indices in different brain regions with clinical data and neuropsychological scales. The trend lines in this panel represent the relationships between cortical features and clinical/neuropsychological measures. Red lines indicate positive correlations, while blue lines indicate negative correlations. Group color coding: HC (orange), ALS 1 (pink), ALS 2 (purple). *$p < 0.05$; **$p < 0.01$; ***$p < 0.001$. **Abbreviation:** HC, healthy control; ALS 1: ALS Patients in King's College Stage 1; ALS 2: ALS Patients in King's College Stage 2A and 2B; MoCA, Montreal Cognitive Assessment Scale; HAMA, Hamilton Anxiety Scale; HAMD, Hamilton Depression Scale; L, left; MC, mean curvature; CT, cortical thickness; Vol, gray matter volume. (For interpretation of the references to color in this figure legend, the reader is referred to the web version of this article.)

-0.147 (-0.260, -0.06)). Additionally, the cortical structure did not show any significant mediating effects. Detailed information is provided in Fig. 9 and Supplementary Table 4.

3.5. Analysis of the altered cortical thickness and ALFF as biomarkers

SVM models were constructed using both CT and ALFF features to evaluate their diagnostic and staging potential in ALS (Figs. 10 and 11). When distinguishing HC from total ALS patients, both CT and ALFF features demonstrated comparable discriminative capabilities. The combined ALFF model achieved slightly higher performance (AUC = 0.853, 95 %CI: 0.687–1.000, $p < 0.001$) compared to CT (AUC = 0.779, 95 %CI: 0.587–0.972, $p < 0.001$). Individual regional analysis revealed significant performance in ALFF of RS_temporal_sup (AUC = 0.831, $p < 0.001$) and CT of S_cingul_Marginalis (AUC = 0.724, $p < 0.001$). Stage-specific analyses revealed distinct patterns. For early-stage detection (HC vs ALS 1), ALFF features exhibited perfect discrimination (AUC = 1.000, 95 %CI: 1.000–1.000), but the high performance did not reach statistical significance ($p = 0.232$). In contrast, CT showed robust and significant performance (AUC = 0.819, 95 %CI: 0.607–1.000, $p < 0.001$). For late-stage detection (HC vs ALS 2), both modalities demonstrated strong performance, with CT of S_cingul_Marginalis (AUC = 0.914, 95 %CI: 0.775–1.000, $p = 0.008$) and ALFF of LG_cingul_Post_dorsal (AUC = 0.951, 95 %CI: 0.860–1.000, $p < 0.001$) showing particularly high discriminative power. However, distinguishing between disease stages (ALS 1 vs. ALS 2) yielded moderate performance for both modalities (ALFF: AUC = 0.719, 95 %CI: 0.455–0.983; CT: AUC = 0.618, 95 %CI: 0.308–0.928, $p = 0.017$).

4. Discussion

Using multiparametric MRI techniques, we identified significant

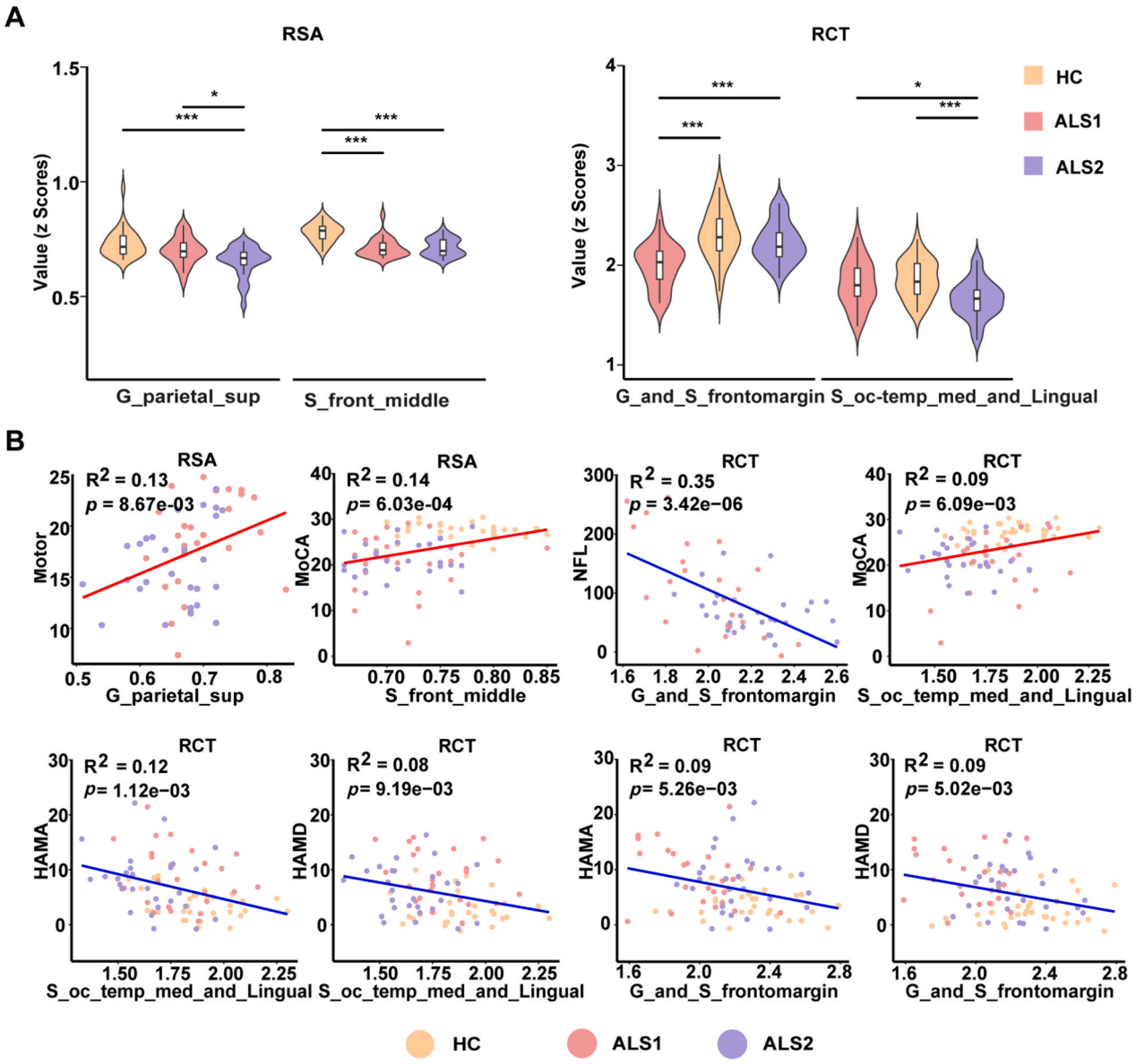

Fig. 4. Analysis of cortical metrics and their associations with neuropsychological outcomes in ALS patients. (A) Post hoc test violin plot of cortical structural features in the right hemisphere among the ALS 1, ALS 2, and HC. (B) Scatter plots illustrating the correlation between cortical metrics and neuropsychological assessments. The trend lines indicate the nature of the relationship; red lines indicate positive correlations, while blue lines indicate negative correlations. Group color coding: HC (orange), ALS 1 (pink), ALS 2 (purple). *$p < 0.05$; **$p < 0.01$; ***$p < 0.001$. **Abbreviation:** HC, healthy controls; ALS 1: ALS Patients in King's College Stage 1; ALS 2: ALS Patients in King's College Stage 2A and 2B; MoCA, Montreal Cognitive Assessment Scale; NFL, Neurofilament Light Chain; HAMA, Hamilton Anxiety Scale; HAMD, Hamilton Depression Scale; SA, surface area; CT, cortical thickness. (For interpretation of the references to color in this figure legend, the reader is referred to the web version of this article.)

cortical differences in ALS patients compared to controls, even at early stages, and found correlations with neuropsychological scores and NfL levels. Mediation analysis further revealed that altered ALFF values in multiple cortical regions mediated the negative impact of depression on cognitive function, emphasizing the complex interplay between emotion and cognition in ALS. Finally, SVM analysis demonstrated the potential of cortical metrics as diagnostic biomarkers across ALS stages. These findings not only suggest the diagnostic potential of cortical parameters but also contribute to a deeper understanding of ALS neuropathology and neuropsychology.

4.1. *Multiple cortical structures exhibit early alterations in ALS*

Our study revealed distinctive early cortical alterations in ALS, predominantly affecting non-motor regions. We observed reduced surface area in the parietal and medial frontal lobes, decreased volume in the insula, and reduced sulcal depth in the occipital gyri. The ALS 2 group exhibited the most pronounced alterations, particularly in the right superior parietal surface area, middle temporal and lingual gyrus thickness, and central sulcus depth. Our findings are consistent with those of Trojsi et al., who observed reduced functional connectivity in the default mode and frontoparietal networks (Trojsi et al., 2021), suggesting that frontotemporal alterations may precede overt cognitive decline in ALS. And these findings align with previous reports of progressive cortical atrophy in ALS (Consonni et al., 2020; Consonni et al., 2018; Schuster et al., 2014; Mezzapesa et al., 2013), and the documented gradient of cortical degeneration across the ALS-FTD spectrum, particularly in the presence of cognitive impairment (Schuster et al., 2014; Mioshi et al., 2013; Agosta et al., 2016), consistent with the King staging system (Braak et al., 2013). Furthermore, structural alterations

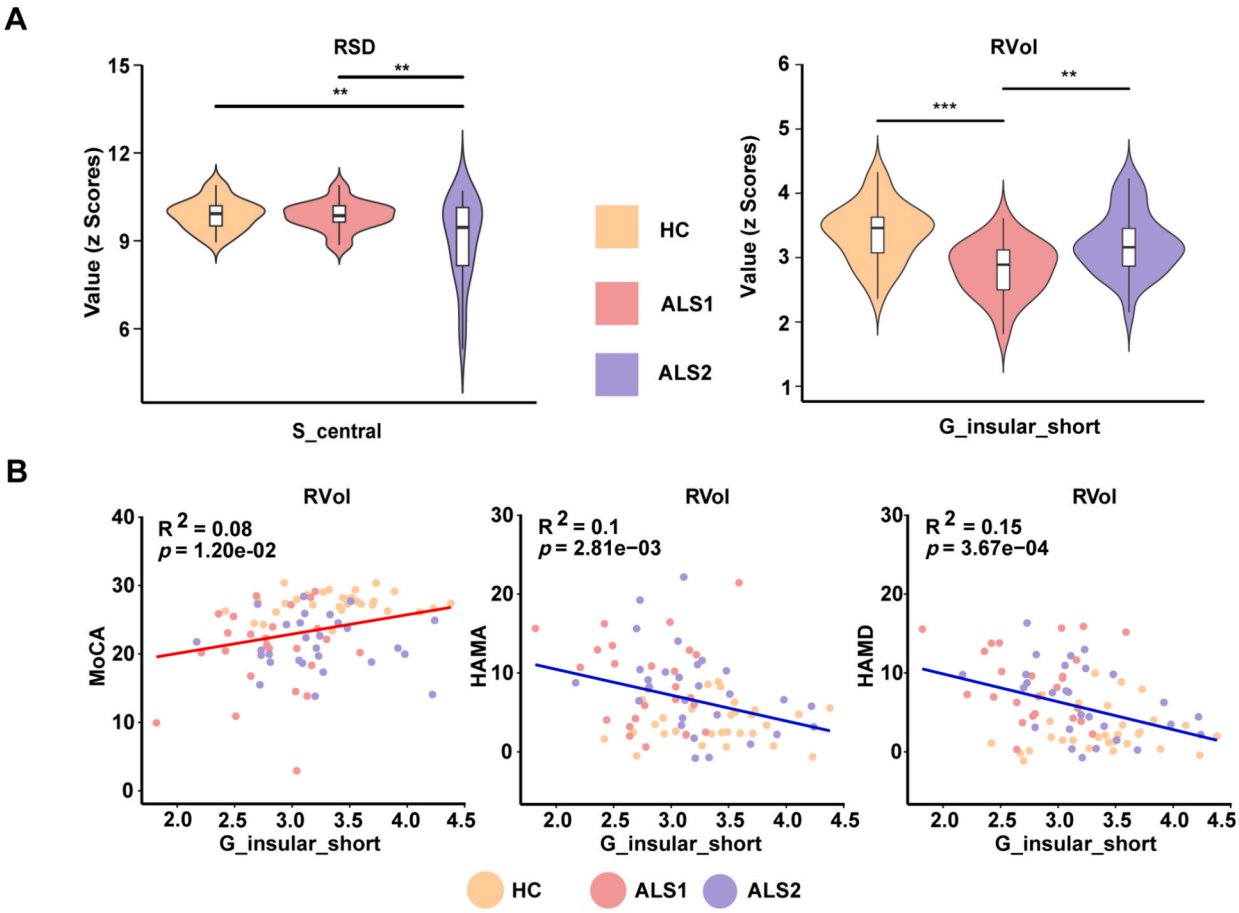

Fig. 5. Assessment of cortical characteristics in ALS and their linkages to cognitive and emotional parameters. (A) Violin plots displaying z-scores for regional RSD in S_central and RVol in G_insular_short. Significant differences between the groups are indicated by asterisks (**$p < 0.01$; ***$p < 0.001$). (B) Scatter plots illustrate the relationships between volumetric measures and clinical assessments. R^2 values and corresponding p-values are provided for each correlation. Color coding for groups: HC (orange), ALS 1 (pink), ALS 2 (purple). The trend lines indicate the nature of the relationship; red lines indicate positive correlations, while blue lines indicate negative correlations. **Abbreviation:** HC, healthy controls; ALS 1: ALS Patients in King's College Stage 1; ALS 2: ALS Patients in King's College Stage 2A and 2B; MoCA, Montreal Cognitive Assessment Scale; HAMA, Hamilton Anxiety Scale; HAMD, Hamilton Depression Scale; SD, sulcal depth; Vol, gray matter volume. (For interpretation of the references to color in this figure legend, the reader is referred to the web version of this article.)

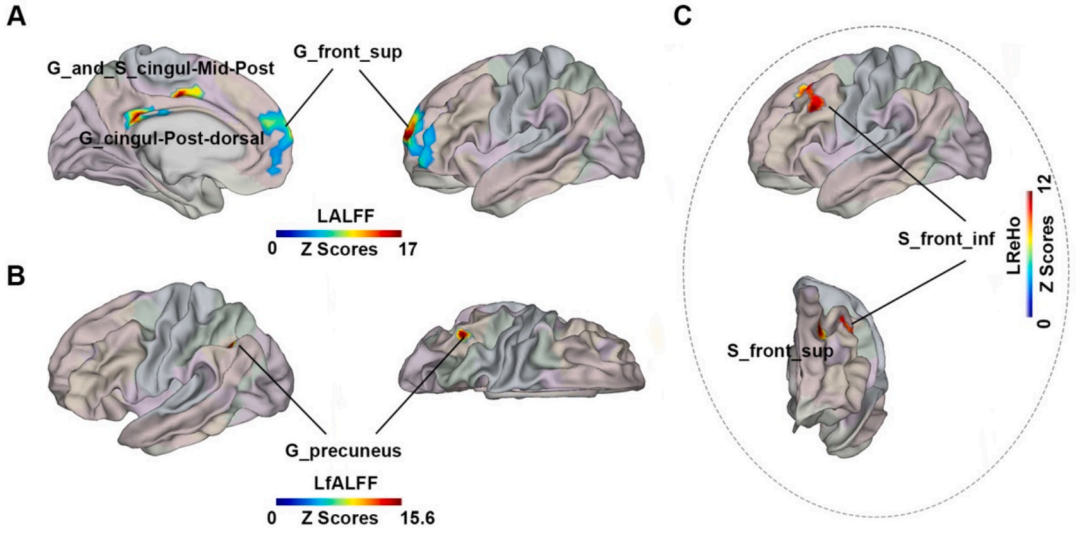

Fig. 6. Variations in cortical functional activities within the left hemisphere across three cohorts. (A), (B) and (C) showed the differential cortex regions in ALFF, fALFF and ReHo, respectively. **Abbreviation:** L, left; ALFF, Amplitude of Low-Frequency Fluctuations; fALFF, fractional Amplitude of Low-Frequency Fluctuations; ReHo, Regional Homogeneity.

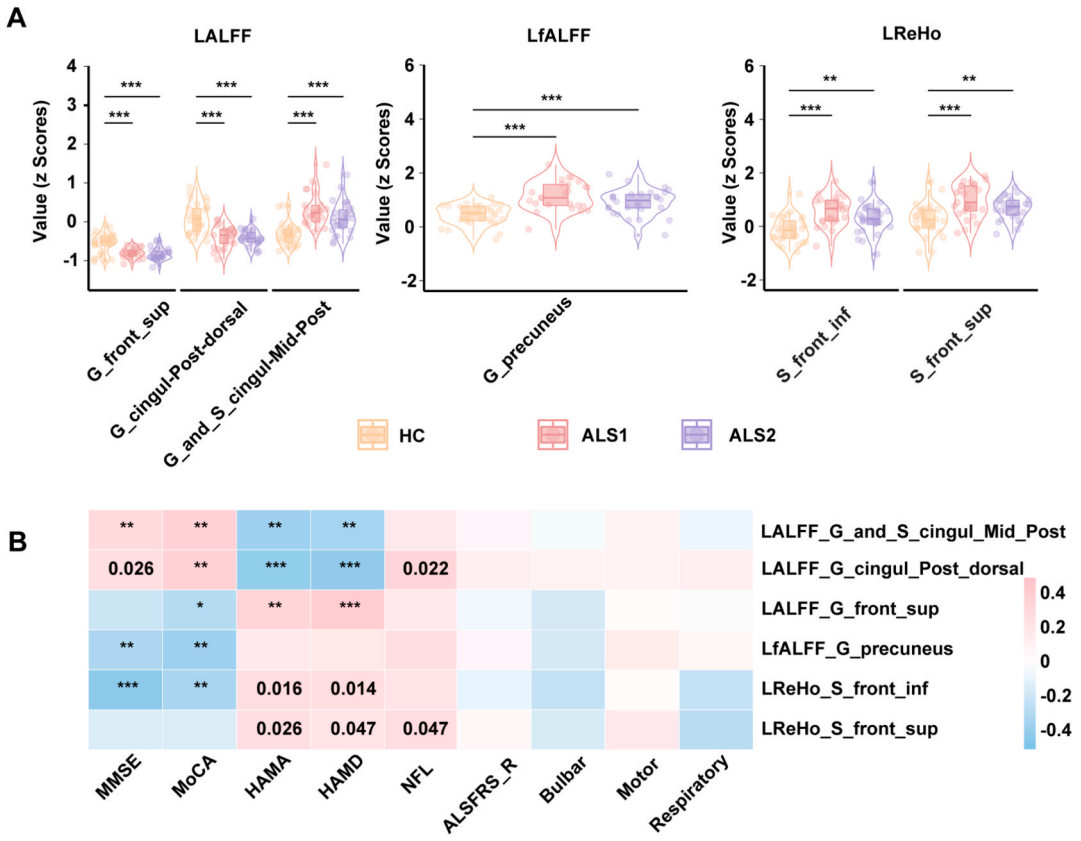

Fig. 7. Functional activity differences and partial correlation analysis in the left hemisphere across groups. (A) Violin plots depicting z-scores for ALFF, fALFF and ReHo (**$p < 0.01$; ***$p < 0.001$). (B) Matrix of partial correlation coefficients between functional activity measures and clinical assessments (*$p < 0.0125$; **$p < 0.01$; ***$p < 0.001$). Color coding for groups: HC (orange), ALS 1 (pink), ALS 2 (purple). The color scale represents correlation strength from negative (blue) to positive (red). **Abbreviation:** HC, healthy controls; ALS 1: ALS Patients in King's College Stage 1; ALS 2: ALS Patients in King's College Stage 2A and 2B; L, left; ALFF, Amplitude of Low-Frequency Fluctuations; fALFF, fractional Amplitude of Low-Frequency Fluctuations; ReHo, Regional Homogeneity; MMSE, Mini-Mental State Examination; MoCA, Montreal Cognitive Assessment Scale; HAMA, Hamilton Anxiety Scale; HAMD, Hamilton Depression Scale; NFL, Neurofilament light chain; ALSFRS-R, Amyotrophic Lateral Sclerosis Functional Rating Scale-Revised. (For interpretation of the references to color in this figure legend, the reader is referred to the web version of this article.)

in the left uncinate fasciculus (UF), which links the frontal and temporal lobes, may contribute to cognitive impairments of ALS (Ghaderi et al., 2024). The UF often exhibits ALS-related microstructural abnormalities, which may underlie the memory impairments in ALS patients, highlighting the critical role of frontotemporal connectivity in the cognitive profile of the disease (Christidi et al., 2017).

Notably, we found increased CT in the left cingulate gyrus and frontal pole in ALS 1 patients, followed by a decreasing trend in ALS 2. These regions are critical for emotional processing, memory (Rolls, 2019), and higher-order cognitive functions (Bludau et al., 2014). Previous research has documented disrupted connectivity in the cingulate cortex (Sudharshan et al., 2011; Illán-Gala et al., 2020) and enhanced functional connectivity within the anterior cingulate, posterior cingulate, and medial frontal networks during early ALS (Yabe et al., 2012). Additionally, we found a significant negative correlation between the CT of the right frontal pole and NfL levels, a biomarker associated with increased pathological activity in ALS and negative correlations with survival outcomes (Lu et al., 2015; Verde et al., 2021). These findings suggest that structural increases in the cingulate cortex and frontal pole during early ALS may reflect compensatory responses, which diminish as the disease progresses.

Several structurally distinct cortical regions, including the left cingulate gyrus, right fusiform gyrus, and bilateral insula, were associated with cognitive and emotional functions. These results indicate that structural alterations in these areas may mediate the complex relationship between emotion and cognition in ALS patients, offering new insights into the underlying mechanisms of these processes.

4.2. Alterations in cortex activities among groups

Analysis of cortical functional activity using ALFF, fALFF, and ReHo revealed complex activity patterns in ALS patients. While previous studies have reported decreased activity and functional connectivity in both motor and non-motor regions (Trojsi et al., 2017; Mohammadi et al., 2009; Goldstein et al., 2011), our findings are consistent with these observations. The neuronal alterations observed in non-motor regions may be attributed to TDP-43 deposition, which disrupts frontostriatal and frontotemporal connectivity (Jellinger, 2025). Notably, we observed enhanced cortical activity, particularly in ALS 1 patients, with alterations primarily linked to emotional and cognitive changes rather than motor function. This heightened activation in prefrontal regions aligns with previous findings that show increased cortical excitability in ALS, where prefrontal hyperactivation is associated with limbic system dysfunction (Passamonti et al., 2013). Studies have shown that ALS patients with better cognitive performance exhibit increased frontal activation and enhanced precuneus activity during cognitive tasks (Keller et al., 2018). The observed asymmetrical enhancement of frontoparietal circuits, predominantly in the left hemisphere (Cosottini et al., 2012), suggests compensatory mechanisms through cortical reorganization (Konrad et al., 2002). This cortical hyperexcitability, a hallmark of ALS, may result from reduced interneuron inhibition, although activity levels generally decline as the disease progresses

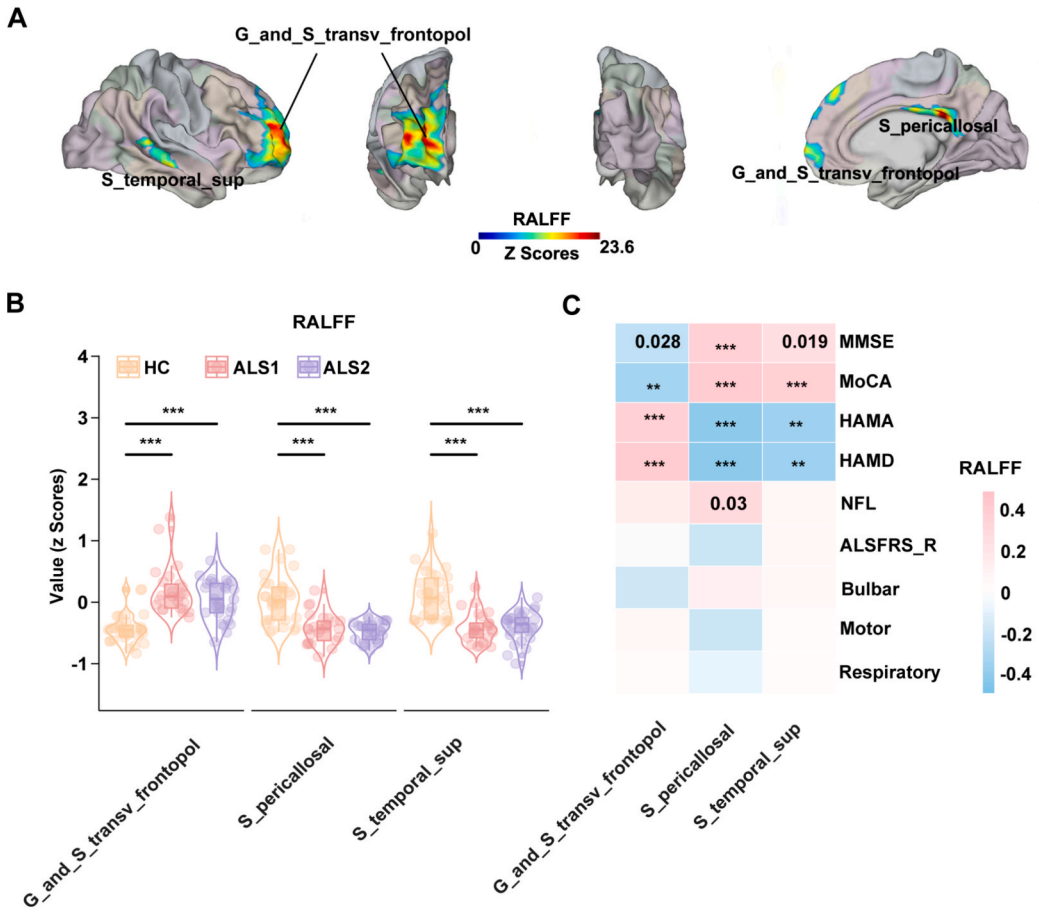

Fig. 8. Cortical analysis revealing regional amplitude of low-frequency fluctuations (RALFF) in ALS. (A) Differences of cortical functional activities in the right hemisphere among the three groups. (B) Post hoc test violin plot of cortical functional activities in the right hemisphere among the ALS 1, ALS 2, and HC (**$p < 0.01$; ***$p < 0.001$). (C) Correlation analysis of cortical functional activities features indices in different brain regions with clinical data and neuropsychological scales (*$p < 0.0125$; **$p < 0.01$; ***$p < 0.001$). Color coding for groups: HC (orange), ALS 1 (pink), ALS 2 (purple). The color scale represents correlation strength from negative (blue) to positive (red). **Abbreviation:** HC, healthy controls; ALS 1: ALS Patients in King's College Stage 1; ALS 2: ALS Patients in King's College Stage 2A and 2B; R, right; ALFF, Amplitude of Low-Frequency Fluctuations; MMSE, Mini-Mental State Examination; MoCA, Montreal Cognitive Assessment Scale; HAMA, Hamilton Anxiety Scale; HAMD, Hamilton Depression Scale; NFL, Neurofilament light chain; ALSFRS-R, Amyotrophic Lateral Sclerosis Functional Rating Scale-Revised. (For interpretation of the references to color in this figure legend, the reader is referred to the web version of this article.)

Table 3
List of Cortical-Functional Abbreviations.

index	short name	Long name (TA nomenclature is bold typed)
5	G_and_S_transv_frontopol	Transverse frontopolar gyri and sulci
8	G_and_S_cingul-Mid-Post	Middle-posterior part of the **cingulate gyrus and sulcus** (pMCC)
9	G_cingul-Post-dorsal	Posterior-dorsal part of the **cingulate gyrus** (dPCC)
16	G_front_sup	**Superior frontal gyrus** (F1)
30	G_precuneus	**Precuneus** (medial part of P1)
52	S_front_inf	**Inferior frontal sulcus**
54	S_front_sup	**Superior frontal sulcus**
66	S_pericallosal	Pericallosal sulcus (**S of corpus callosum**)
73	S_temporal_sup	**Superior temporal sulcus** (parallel sulcus)

(Mohammadi et al., 2011; Grolez et al., 2016; Schoenfeld et al., 2005). Interestingly, some regions showed nominal positive correlations with NfL levels, although these did not reach statistical significance after correction, indicating their potential involvement in ALS pathophysiology. These functional alterations underscore the critical role of cognitive and emotional factors in ALS progression, suggesting that the disease affects more than just the motor system.

4.3. Various cortical regions modulate the adverse effects of depression on cognitive functioning

Numerous studies have highlighted the involvement of various brain regions in regulating cognition and depression in ALS patients, including the cingulate, frontal, parietal, and temporal gyri, which are particularly affected in depressed individuals compared to healthy controls (Guo et al., 2011; Wu et al., 2011; Yao et al., 2009). However, the exact mechanisms underlying these alterations remain unclear. Also, compared with ALS, ALS-FTD showed hypometabolic areas and cortical thinning in regions such as the temporal gyri, cingulate, orbitofrontal, prefrontal and insular cortex (Schuster et al., 2014; Cistaro et al., 2014). Further mediation analysis found that all six cortical regions with significantly altered ALFF exhibited negative regulatory effects between ALS-associated depression and cognition, particularly in the cingulate gyrus and pericallosal areas. Depression-related volume reductions in the anterior corpus callosum correlate with atrophy in the prefrontal cortex (Ozalay et al., 2013), and prolonged disease duration is associated with more severe callosal damage (Zhao et al., 2021), which may contribute to executive dysfunction and attention deficits. These findings offer valuable insights into the pathophysiology of non-motor symptoms in ALS and suggest the potential for early targeted interventions in specific brain regions.

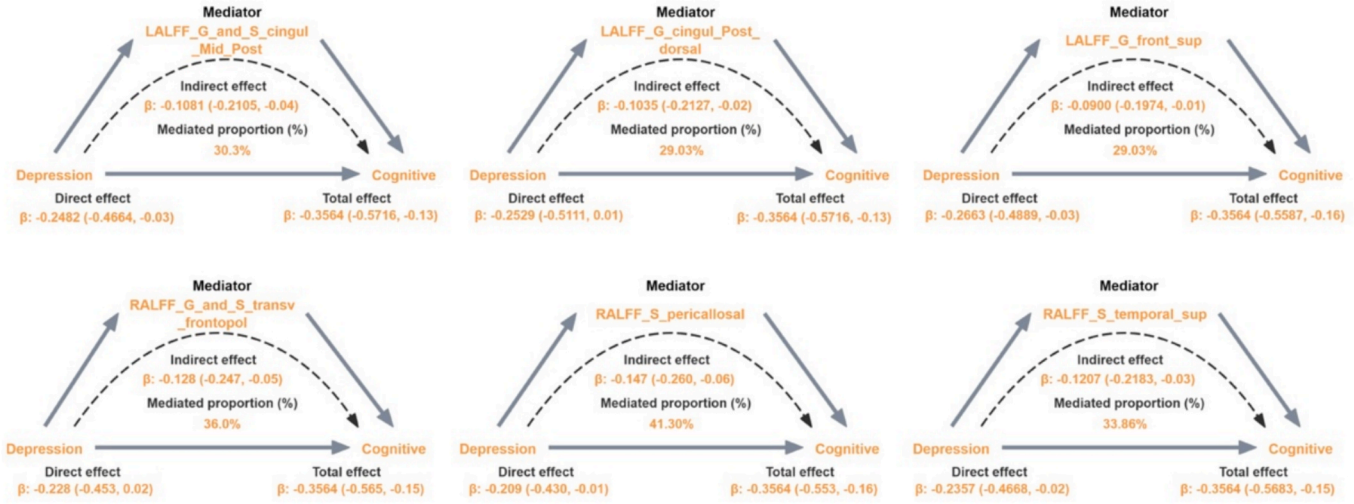

Fig. 9. Mediation analysis of the relationship between depression and cognitive function via different brain regions. Each estimate is presented with 95% confidence intervals (CI). Each panel illustrates the mediator (altered ALFF regions), the direct effect of depression on cognitive function, the total effect, and the indirect effect mediated by the regions. **Abbreviation:** L, left; R, right.

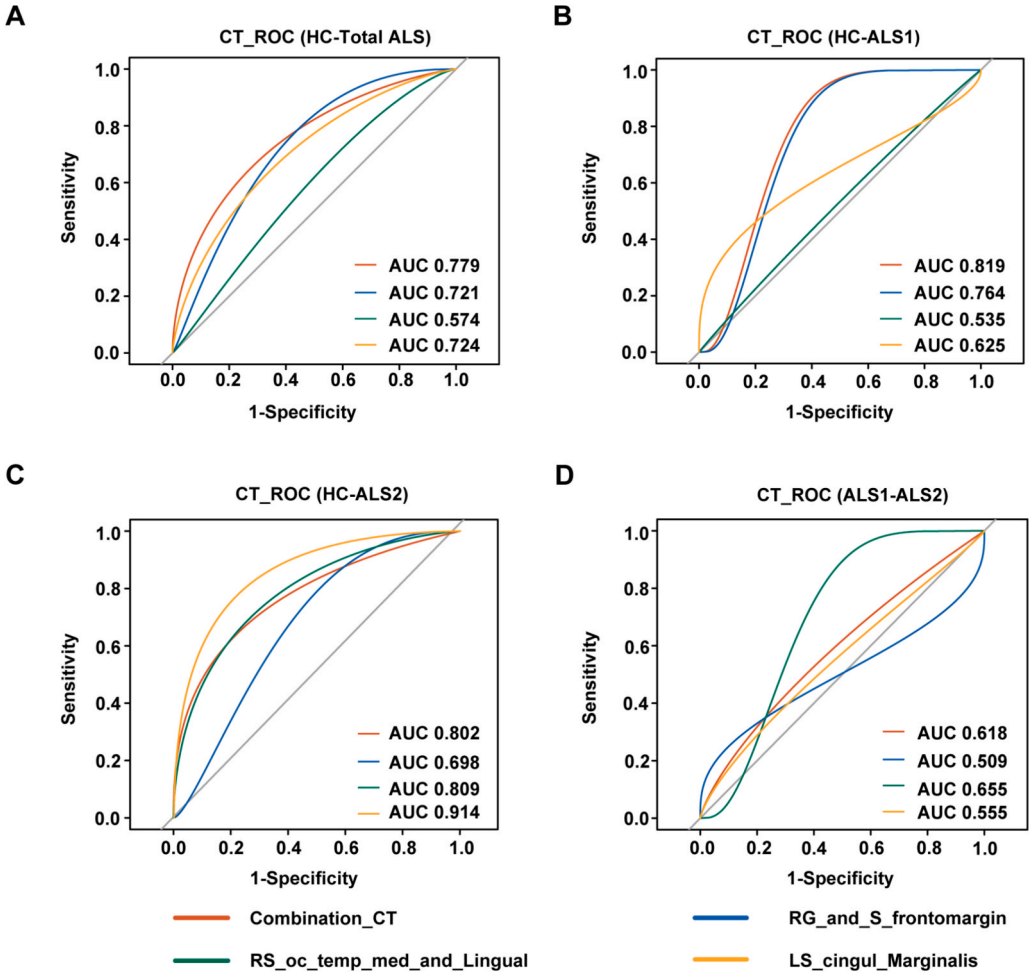

Fig. 10. ROC curve analysis utilizing CT metrics for ALS diagnosis. (A) HC and total ALS, (B) HC and ALS 1, (C) HC and ALS 2, (D) ALS 1 and ALS 2. The curves represent different CT metrics, with color assignments as follows: Combination_CT (red), RG_and_S_frontomargin (blue), RS_oc_temp_med_and_Lingual (green) and LS_cingul_Marginalis (yellow). Each curve is annotated with its respective AUC value, quantitatively measuring the metric's diagnostic performance. **Abbreviation:** CT, cortical thickness; ROC, Receiver Operating Characteristic; AUC, Area Under the Curve; HC, healthy controls; ALS, Amyotrophic Lateral Sclerosis; ALS 1: ALS Patients in King's College Stage 1; ALS 2: ALS Patients in King's College Stage 2A and 2B; L, left; R, right. (For interpretation of the references to color in this figure legend, the reader is referred to the web version of this article.)

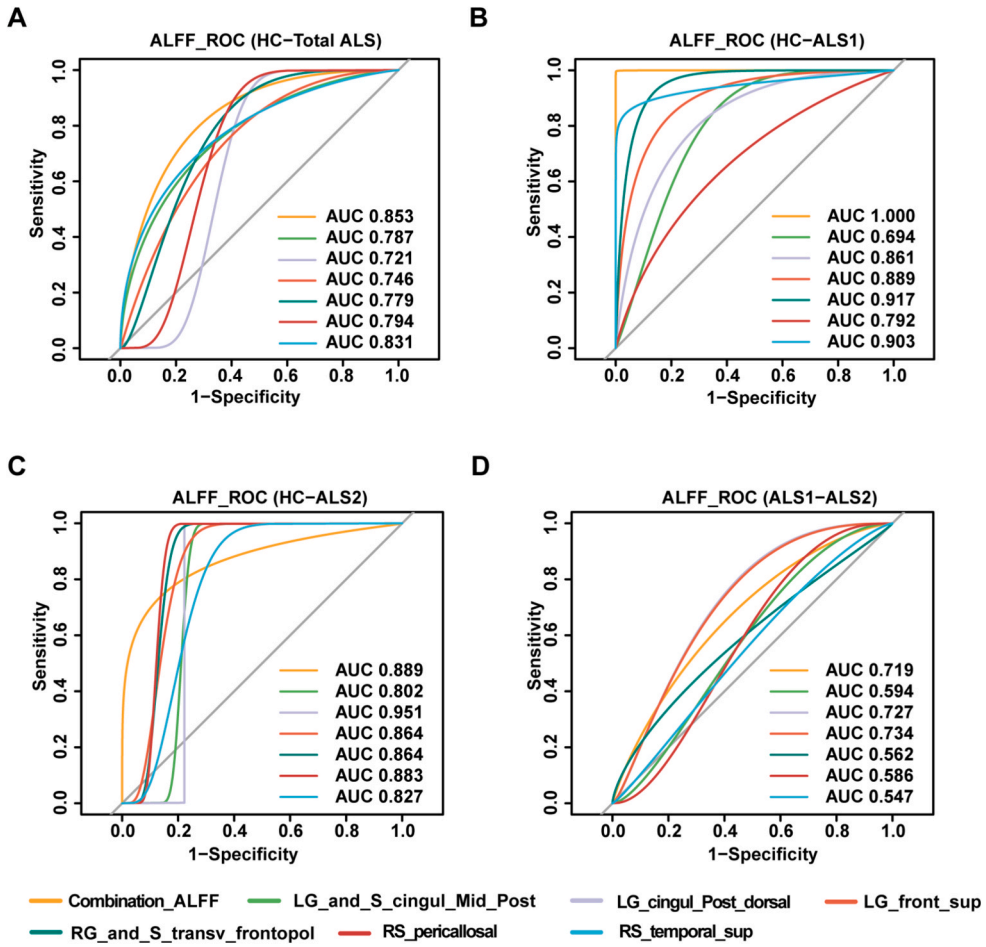

Fig. 11. ROC curves for distinguishing ALS patients from healthy individuals based on the ALFF of various cortical regions. (A) HC and total ALS, (B) HC and ALS 1, (C) HC and ALS 2, (D) ALS 1 and ALS 2. The curves correspond to specific cortical regions, color-coded as follows: Combination_ALFF (orange), LG_and_S_cingul_Mid_Post (green), LG_cingul_Post_dorsal (purple), LG_front_sup (red), RG_and_S_transv_frontopol (dark green), RS_pericallosal (red-brown), and RS_temporal_sup (blue). AUC values are provided for each region, with higher values indicating better diagnostic performance. **Abbreviation:** ALFF, Amplitude of Low-Frequency Fluctuations; ROC, Receiver Operating Characteristic; AUC, Area Under the Curve; HC, healthy controls; ALS, Amyotrophic Lateral Sclerosis; ALS 1: ALS Patients in King's College Stage 1; ALS 2: ALS Patients in King's College Stage 2A and 2B; L, left; R, right.

4.4. The potential diagnostic role of differential cortical regions with thickness and ALFF in ALS

Radiological changes have been proposed as potential diagnostic biomarkers for ALS (Foerster et al., 2012; Qin et al., 2024; Foerster et al., 2014), but few studies have incorporated machine learning to construct robust classification models, particularly for the early stages of ALS. Our machine learning analyses revealed distinct patterns in the diagnostic utility of cortical alterations across different ALS stages. ALFF features demonstrated superior discriminative capability between HC and ALS compared to CT, suggesting that functional measures are more sensitive to ALS-related changes. Notably, while ALFF achieved perfect classification in early-stage detection, CT exhibited more robust statistical significance. In late-stage detection, both modalities showed strong performance, with specific regions exhibiting remarkable discriminative power (LS_cingul_Marginalis: AUC = 0.914; LG_cingul_Post_dorsal: AUC = 0.951). However, both modalities showed moderate performance in stage differentiation, with variable significance across individual regions. ALS progression may be better understood as a continuous spectrum rather than discrete stages, with specific regions tracking disease progression while overall patterns evolve gradually. The complementary performance of functional and structural measures suggests a temporal sequence, where functional alterations occur early in the disease, followed by structural alterations.

Several limitations must be acknowledged in the study. First, the relatively small sample size may restrict the generalizability of the findings. Larger sample sizes are necessary to validate the results. Second, although the use of SVM improved classification accuracy, the lack of external validation limits the applicability of the models to independent datasets. Validation through large-scale, multicenter studies is crucial to confirm model reliability and generalizability. Additionally, ALS's heterogeneity, including variations in genetic subtypes, clinical phenotypes, and progression rates, may result in distinct cortical patterns and disease responses across patients. This could explain the lack of significant differentiation between ALS 1 and ALS 2 in our study. Future research should include more detailed subgroup analyses for a deeper understanding. Finally, the cross-sectional design captures only alterations at a single time point. Longitudinal studies are necessary to fully comprehend the evolving nature of these alterations. Furthermore, increased cortical thickness in extra-motor regions may not indicate a true increase in neuronal density and could instead result from compensatory mechanisms or reactive gliosis. Variability in cortical thickness measurements may be influenced by patient subtype, disease stage, and the imaging or analysis techniques employed. Further studies involving larger cohorts and standardized methodologies are necessary to validate and clarify these findings.

5. Conclusion

In conclusion, the study observed increased CT and abnormal activation in specific cortical regions during the early stages of ALS, which correlate with neuropsychological scores and NfL levels. Mediation analysis showed that activity alterations in the perigenual and frontotemporal cortices mediate the negative effects of depression on cognitive function. Additionally, classification models based on CT and ALFF demonstrated strong diagnostic performance for ALS. These findings reveal the neural mechanisms underlying neuropsychological disorders in ALS and highlight potential biomarkers for early diagnosis.

6. Submission declaration

We have not published these data elsewhere and it is not under consideration by any other journal. There are no conflicts of interest to declare, and all the listed authors have read and approved the final version of the manuscript.

Ethics statement

The studies involving human participants were reviewed and approved by Research Ethics Committee of the First Affiliated Hospital of Nanjing Medical University (Nanjing, China). The patients/participants provided their written informed consent to participate in this study (2019-SR-120).

CRediT authorship contribution statement

Qianqian Zhang: Writing – original draft, Software, Methodology, Formal analysis, Data curation, Conceptualization. **Yu Ding:** Writing – original draft, Methodology, Formal analysis, Data curation. **Yu Zhang:** Visualization, Software, Methodology, Investigation. **Qingyang Li:** Validation, Software, Investigation. **Shiyu Shi:** Formal analysis, Data curation. **Yaxi Liu:** Validation, Data curation. **Sijie Chen:** Visualization. **Qian Wu:** Visualization. **Xiaoquan Xu:** Visualization. **Feiyun Wu:** Visualization. **Xi Cheng:** Writing – review & editing, Project administration, Methodology, Conceptualization. **Qi Niu:** Writing – review & editing, Supervision, Project administration, Funding acquisition, Conceptualization.

Declaration of competing interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

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Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.nicl.2025.103809.

Data availability

The data that has been used is confidential.

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