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Original Research

Brain Functional Alterations Associated With Postural Stability Across the Frailty Continuum: A Resting-State fMRI Study

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Abstract

Background: Frailty is a common geriatric syndrome characterized by a progressive decline in physical function and an increased susceptibility to adverse outcomes, including falls. Although diminished postural stability is a hallmark of frailty, the neural correlates associated with balance impairments throughout the progression of the syndrome remain unclear. This study aims to elucidate the brain functional activity of older adults with varying degrees of frailty during a resting state, as well as the relationship between this activity and postural stability. **Methods:** Sixty-eight older adults were divided into non-frail (n = 23), pre-frail (n = 30), and frail (n = 15) groups based on the Fried frailty phenotype. Postural stability was assessed using the Huber®360 neuromuscular control training and assessment system. Resting-state functional magnetic resonance imaging (rs-fMRI) data were acquired on a 3.0 T scanner, and the amplitude of low-frequency fluctuations (ALFF) and regional homogeneity (ReHo) were utilized as indicators of brain functional activity. Spearman correlation analysis was employed to examine the correlations between the brain functional activity and the postural stability. **Results:** Compared to the non-frail group, the frail and pre-frail groups were significantly older and exhibited poorer performance in grip strength, Short Physical Performance Battery (SPPB) scores, and Timed Up and Go Test (TUGT) results, as well as a greater burden of comorbidities—such as depressive symptoms and sleep disturbances (all $p < 0.05$). Significant inter-group differences were observed across all postural stability parameters. Relative to the non-frail group, the pre-frail group exhibited significantly decreased ALFF in the left inferior frontal gyrus (pars opercularis) extending to the insula, while the frail group demonstrated reduced ALFF in bilateral posterior cerebellum; additionally, the frail group showed decreased ReHo in the left posterior cerebellum/pons and increased ReHo in the right middle temporal/occipital gyrus. ALFF was significantly correlated with right single-leg sway area, the limits of stability, SPPB score, and TUGT completion time, whereas ReHo was significantly correlated only with SPPB score and TUGT completion time (all $p < 0.05$). **Conclusions:** Resting-state brain function exhibits significant differences among older adults in varying states of frailty, primarily involving spontaneous activity and local synchronization within the cerebellum-pons circuitry and cognition-related brain regions. These functional brain abnormalities are closely associated with diminished postural stability, suggesting that alterations in central nervous system function may represent a significant neural correlate of impaired balance in frail older adults. This study provides neuroimaging evidence to support the early screening of frailty and balance-related interventions in older adults, while also laying a foundation for future longitudinal and multimodal investigations.

Keywords: frailty; aged; magnetic resonance imaging; postural balance

1. Introduction

As the global population ages at an accelerating pace, frailty has emerged as one of the most pressing public health challenges of our time, with its prevalence projected to rise substantially in the coming decades [1]. Frailty has become a major threat to the health and quality of life of older adults. Frail individuals face a heightened risk of adverse health outcomes, including falls, disability, hospitalization, and mortality [2,3]. In China, the prevalence of frailty among community-dwelling older adults is approximately 12.7%, while the prevalence of pre-frailty reaches as high as 47.3%; both rates increase significantly with advancing age [4]. On a positive note, however, frailty is a dynamic and potentially reversible syndrome [5,6]. Early prediction and proactive intervention can help delay or reverse the progression of frailty and reduce the incidence of falls and functional disability—steps that are crucial for alleviating societal and healthcare burdens [7].

Falls are the most common adverse events among older adults, resulting from a complex interplay between declining neuromuscular function and postural instability

[8]. Maintaining postural stability is a complex neuromodulatory process that relies on the central nervous system to integrate diverse sensory inputs and dynamically modulate motor outputs. Previous studies have primarily investigated postural control in frail older adults from a peripheral biomechanical perspective, highlighting significant deficits in gait kinematics and postural regulation. These peripheral biomarkers include reduced ankle plantarflexion, overall ankle range of motion, and knee landing angles, as well as a potential compensatory increase in initial hip angles [9]. However, these biomarkers fail to elucidate the central neural correlates of the decline in postural stability associated with frailty.

Accumulating neuroimaging evidence suggests that alterations in central nervous system functional activity play a pivotal role in postural control deficits among older adults. Functional connectivity studies have revealed that, as the degree of frailty increases, stronger connections emerge between certain brain regions that are typically uncorrelated; this may represent a compensatory neural mechanism in the frail brain [10]. Notably, degenerative changes in cerebellar functional activity disrupt both motor control and cognitive processes, thereby contributing to the decline in postural stability observed in frail populations [11].

The amplitude of low-frequency fluctuations (ALFF) reflects the intensity of local spontaneous neural activity, while regional homogeneity (ReHo) indicates the temporal synchronization of adjacent voxels, thereby providing an observable perspective on local brain functional activity [12,13]. These two metrics demonstrate robust stability and explanatory value within the field of frailty research. Furthermore, functional connectivity involving the cerebellum and brainstem has been demonstrated to play a pivotal role in maintaining postural stability [14]. Consequently, ALFF and ReHo offer a multidimensional analytical lens for investigating the central neural correlates associated with frailty.

This study aims to analyze the intrinsic relationship between changes in functional activity across three specific brain regions and postural stability. Based on the Fried frailty phenotype, the study population was categorized into non-frail, pre-frail, and frail groups. The Huber®360 neuromuscular assessment system was utilized to objectively quantify postural stability in this population, followed by an analysis of the variations in ALFF and ReHo across the three groups. Ultimately, this research seeks to explore the central neural correlates associated with changes in postural stability throughout the frailty continuum, thereby providing theoretical support for the early identification and precise intervention of frailty.

2. Materials and Methods

2.1 Participants

A total of 68 community-dwelling and hospital-attending older adults from Fujian Provincial Hospital affiliated with Fuzhou University and surrounding communities were enrolled. Because frailty status was assigned after enrollment according to the Fried frailty phenotype rather than by fixed per-group quotas, and because the number of eligible and consenting older adults during the recruitment period exceeded this planned target, enrollment was not capped at 60. A total of 68 participants ultimately completed all assessments and were included in the analysis, distributed as non-frail ($n = 23$), pre-frail ($n = 30$), and frail ($n = 15$). This cross-sectional study was reported according to the STROBE guideline (see **Supplementary Material**).

2.2 Frailty Assessment

Frailty status was assessed using the Fried frailty phenotype [15], which evaluates five domains: unintentional weight loss, slow gait speed, low grip strength, low physical activity, and self-reported exhaustion. Participants meeting three or more criteria were classified as frail, those meeting one or two criteria as pre-frail, and those meeting none as non-frail.

2.3 Inclusion and Exclusion Criteria

Inclusion criteria were: (1) age 65–80 years; (2) ability to walk independently without assistive devices; (3) ability to communicate and cooperate with questionnaire surveys, assessments, and MRI procedures; (4) no history of neurological or psychiatric disorders, or substance dependencies that may affect brain structure or function; and (5) voluntary participation with signed informed consent.

Exclusion criteria were: (1) severe hearing, vision, or cognitive impairment precluding assessment; (2) acute injury, severe cardiopulmonary disease, or terminal illness; (3) history of alcohol or substance abuse; and (4) presence of metallic implants or other MRI contraindications.

2.4 Clinical Assessments

Demographic information included age, sex, height, weight, body mass index (BMI), educational level, number of comorbidities, and number of medications. The following standardized clinical assessments were performed by trained research team members:

Grip strength was measured using a Jamar Smart Hand Dynamometer (Model 081669928, Patterson Medical, Warrenville, IL, USA) with the participant seated, elbow at 90°, shoulder in a neutral adducted position, and wrist at 0–30° of extension. Three trials were performed on the dominant hand and the mean value recorded.

The Timed Up and Go Test (TUGT) quantifies the time required to rise from a chair, walk 3 meters, turn around, walk back, and sit down. Performance criteria: <10 s, freely mobile; 10–19 s, independent mobility; 20–29 s, assistance required; ≥30 s, severe mobility impairment [16].

The Short Physical Performance Battery (SPPB) evaluates lower extremity function across balance, gait speed,

and chair-rise domains, yielding a total score of 0–12 (0–6: poor; 7–9: moderate; 10–12: good physical function) [17].

Nutritional status, depression, and sleep quality were assessed using the Mini Nutritional Assessment Short Form (MNA-SF) [18], the 15-item Geriatric Depression Scale (GDS-15) [19], and the Athens Insomnia Scale (AIS) [20], respectively.

2.5 Resting-State fMRI Data Acquisition

MRI data were acquired using a Siemens Prisma 3.0 T scanner (Siemens, Erlangen, Germany) with a 16-channel head-neck coil at the Department of Radiology, Fujian Provincial Hospital. Participants were instructed to lie still with eyes open, remain awake without systematic thinking, and were equipped with earplugs for noise reduction. Head motion was minimized using a flexible head pad.

Structural T1-weighted images: repetition time (TR) = 2300 ms, echo time (TE) = 2.27 ms, flip angle = 8°, slice thickness = 1.0 mm, field of view (FOV) = 250 × 250 mm, matrix = 256 × 256, voxel size = 0.98 × 0.98 × 1 mm^3, 160 slices.

Resting-state Blood Oxygen Level-Dependent (BOLD) images: TR = 2000 ms, TE = 30 ms, flip angle = 90°, slice thickness = 3.6 mm, FOV = 230 × 230 mm, matrix = 64 × 64, voxel size = 3.6 × 3.6 × 3.9 mm^3, 37 slices, 300 time points.

2.6 fMRI Data Preprocessing

Data preprocessing was performed in MATLAB 2024b (MathWorks Inc., Natick, MA, USA) using SPM12 (Wellcome Department of Cognitive Neurology, London, UK) and the Data Processing & Analysis for Brain Imaging (DPABI) toolbox (version 4.2, Institute of Psychology, Chinese Academy of Sciences, Beijing, China) [21]. Steps included: (1) Digital Imaging and Communications in Medicine (DICOM)-to-Neuroimaging Informatics Technology Initiative (NIfTI) conversion with removal of the first 10 time points (290 retained); (2) slice timing correction (odd-even interleaved, reference slice 37); (3) head motion correction using the Friston 24-parameter model, with participants excluded for translation >3 mm or rotation >3°; (4) reorientation to the anterior commissure; (5) skull stripping of structural images; (6) coregistration of functional to structural images; (7) segmentation of structural images into gray matter, white matter, and cerebrospinal fluid; (8) nuisance covariate regression (head motion parameters, white matter, and Cerebrospinal Fluid (CSF) signals); (9) detrending; (10) spatial normalization to standard Montreal Neurological Institute (MNI) space; (11) spatial smoothing with a 6 mm full-width at half-maximum Gaussian kernel; and bandpass filtering (0.01–0.08 Hz).

2.7 Computation of Resting-State Functional Indices

Following preprocessing, two resting-state indices were calculated using DPABI:

ALFF: Time-series data were transformed to the frequency domain using fast Fourier transform. The square root of the mean power spectrum within 0.01–0.08 Hz was computed for each voxel. ALFF maps were subsequently Fisher Z-transformed for group-level statistical analysis.

ReHo: Kendall's coefficient of concordance was computed between each voxel's time series and those of its 26 neighboring voxels, yielding a ReHo map. The map was smoothed in standard space and Fisher Z-transformed (zReHo map) for subsequent statistical analyses.

2.8 Postural Stability Assessment

Postural stability was assessed using the Huber®360 neuromuscular control training and assessment system (DJO, Carlsbad, CA, USA) in a quiet, well-lit environment. Participants completed the following standardized tasks in order: (1) bipedal stance with eyes open for 50 s; (2) bipedal stance with eyes closed for 50 s; (3) unilateral (left and right) single-leg stance for 30 s each; and (4) dynamic limits of stability (LOS) assessment with bipedal stance on the platform. One practice trial was permitted before formal testing. Outcome measures included bilateral eyes-open and eyes-closed trajectory length (mm), area (mm^2), and velocity (mm/s); single-leg trajectory length and area; and limits of stability (mm^2).

2.9 Statistical Analysis

Demographic and postural stability data were analyzed using IBM SPSS Statistics 28.0 (IBM Corp., Armonk, NY, USA). Normally distributed continuous variables are expressed as mean ± SD and analyzed by one-way ANOVA; non-normally distributed variables are expressed as median (interquartile range) and analyzed by Kruskal-Wallis test. Categorical variables are presented as frequencies (percentages) and compared by chi-square test. Multiple comparisons among the three groups for balance parameters were conducted using Bonferroni post-hoc analysis. The alpha level was set at $p < 0.05$.

Group-level Resting-state functional magnetic resonance imaging (rs-fMRI) analyses were performed using the Statistical Analysis module in DPABI. For each index (ALFF and ReHo), a one-way analysis of covariance (ANCOVA) was conducted across the three frailty groups within a gray-matter mask derived from the DPABI template, with sex, age, educational level, and the mean framewise displacement included as nuisance covariates. Multiple-comparisons correction was performed using Gaussian Random Field (GRF) theory, as implemented in DPABI, which controls the family-wise error rate at the cluster level by jointly applying a voxel-level height threshold and a cluster-level extent threshold. The voxel-level height threshold was set to $p < 0.001$ for ALFF and $p < 0.001$ for ReHo, and the cluster-level GRF-Family-Wise Error (FWE)-corrected threshold was set to $p < 0.05$ for both indices. A minimum cluster extent of 20 contiguous vox-

els for ALFF and 10 voxels for ReHo was further applied as a reporting criterion, motivated by the smaller voxel-wise signal magnitude of ReHo and by the relatively small anatomical scale of the cerebellar and pontine regions of interest in this study. Pairwise post-hoc contrasts between groups were carried out within the same GRF-corrected framework. Significant clusters were anatomically labeled in MNI space using the Automated Anatomical Labeling (AAL) atlas.

The normality of the variables was assessed using the Shapiro-Wilk test. Due to the non-normal distribution of the data, Spearman's rank correlation analyses were conducted to evaluate the associations between postural stability parameters and the mean rs-fMRI indices from regions showing significant group differences. Correlation magnitude was interpreted as follows: $|\rho| \geq 0.8$, high; $0.5 \leq |\rho| < 0.8$, moderate; $0.3 \leq |\rho| < 0.5$, low; $|\rho| < 0.3$, negligible. $p < 0.05$ was considered statistically significant.

The correlation analyses between resting-state indices (ALFF, ReHo) and postural stability parameters were considered exploratory and hypothesis-generating in nature. Given the relatively modest sample size and the absence of pre-specified hypotheses regarding which specific postural parameters would correlate with which neural indices, no formal correction for multiple comparisons was applied. Uncorrected two-tailed p values are reported throughout, and the corresponding Spearman ρ coefficients are provided so that readers can evaluate the magnitude of each association independently of its nominal significance. The correlation findings should therefore be interpreted as preliminary signals that warrant confirmation in larger, pre-registered cohorts.

3. Results

3.1 Demographic and Clinical Characteristics

Among the 68 enrolled participants, 23 (33.8%) were non-frail, 30 (44.1%) were pre-frail, and 15 (22.1%) were frail, with a mean age of 71.40 ± 5.18 years. Compared with the non-frail group, both the frail and pre-frail groups showed significantly higher age, TUGT times, and comorbidity counts, depressive status, and sleep disturbances, as well as significantly lower grip strength and SPPB scores (all $p < 0.05$). No significant differences were observed among the three groups in sex, BMI, educational level (all $p \geq 0.05$; Table 1).

3.2 Postural Stability

Significant inter-group differences were observed for all postural stability parameters, including bipedal eyes-open and eyes-closed trajectory length, area, and velocity; single-leg trajectory length and area; and limits of stability (all $p < 0.05$; Table 2). Post-hoc analyses demonstrated that the frail group showed the most pronounced postural instability across all conditions, followed by the pre-frail group, with the non-frail group displaying the best performance. Specifically, limits of stability were significantly reduced in both the frail and pre-frail groups compared with the non-frail group, while single-leg stance parameters primarily distinguished the frail group from the other two.

3.3 Resting-State Brain Functional Activity

3.3.1 ALFF Analysis

One-way ANCOVA of ALFF maps revealed significant inter-group differences primarily in the right posterior cerebellar Crus I/Lobule VIII region. Tukey post-hoc comparisons showed that, relative to the non-frail group, the pre-frail group exhibited significantly decreased ALFF in the left inferior frontal gyrus (pars opercularis) extending to the insula. The frail group showed significantly decreased ALFF in bilateral posterior cerebellar regions, including the right posterior cerebellum (Crus I/Lobule VIII), left posterior cerebellum (Crus I/Lobule VIII), and the left cerebellar anterior/posterior lobule junction, compared with the non-frail group. Furthermore, the frail group showed further bilateral posterior cerebellar ALFF reductions compared with the pre-frail group. No significant differences were observed in other brain regions (Table 3, Fig. 1).

3.3.2 ReHo Analysis

One-way ANCOVA of ReHo maps revealed significant inter-group differences, primarily in the left pons. Tukey post-hoc comparisons showed no significant differences between the pre-frail and non-frail groups. Compared with the non-frail group, the frail group demonstrated significantly decreased ReHo in the left posterior cerebellum, left pons/anterior cerebellar lobule junction, right posterior cerebellum/vermis, and left lingual/fusiform gyrus. Compared with the pre-frail group, the frail group showed significantly decreased ReHo in the left posterior cerebellum/pons and left pons/anterior cerebellum, and significantly increased ReHo in the right middle temporal gyrus/middle occipital gyrus (Table 4, Fig. 2).

3.4 Correlation Analysis Between Resting-State Indices and Postural Stability

Table 5 and Fig. 3 summarize the Spearman correlation results between rs-fMRI indices and postural stability parameters.

ALFF showed a significant low-magnitude positive correlation with sway area during right single-leg standing ($\rho = 0.339$, $p = 0.006$), and significant negative correlations with the limits of stability ($\rho = -0.279$, $p = 0.025$), SPPB total score ($\rho = -0.257$, $p = 0.040$), and TUGT completion time ($\rho = -0.411$, $p = 0.001$). Among these, the association with TUGT completion time was the strongest. No significant correlations were detected for sway area during bipedal eyes-open standing, bipedal eyes-closed standing, or left single-leg standing (all $p > 0.05$).

ReHo showed significant negative correlations with SPPB total score ($\rho = -0.363$, $p = 0.003$) and TUGT com-

Table 1. Comparison of demographic and clinical characteristics among the three groups.

Variable	Frail (n = 15)	Pre-frail (n = 30)	Non-frail (n = 23)	Statistic (*p*-value)
Sex, n (%)				0.941 (0.332)[a]
Male	6 (40.0)	13 (43.3)	12 (52.2)	
Female	9 (60.0)	17 (56.7)	11 (47.8)	
Age (years)	73.00 (67.00, 79.00)	73.50 (70.00, 76.00)	68.50 (65.00, 70.50)	10.902 (0.004)[c]*
BMI (kg/m^2)	24.05 ± 3.40	24.52 ± 3.58	24.21 ± 3.15	0.113 (0.893)[b]
Grip strength (kg)	17.51 ± 4.48	21.81 ± 4.25	25.29 ± 6.35	10.451 (<0.001)[b]*
TUGT (s)	13.82 ± 6.09	9.31 ± 2.45	8.33 ± 2.02	12.304 (<0.001)[b]*
Comorbidity (n)	3.00 (1.00, 5.00)	1.00 (1.00, 2.00)	1.00 (1.00, 2.00)	6.113 (0.045)[c]*
SPPB total score	6.00 (5.00, 7.00)	9.00 (7.00, 10.00)	9.00 (9.00, 10.00)	20.462 (<0.001)[c]*
Education level, n (%)				2.404 (0.308)[c]
Elementary school	4 (26.7)	5 (16.7)	4 (17.4)	
Junior high school	6 (40.0)	8 (26.7)	8 (34.8)	
Senior high school	4 (26.7)	11 (36.7)	4 (17.4)	
University/College	1 (6.7)	6 (20.0)	7 (30.4)	
Depression status (GDS-15), n (%)				19.945 (<0.001)[c]*
Depressive disorder	2 (13.3)	1 (3.3)	0 (0.0)	
Depression tendency	6 (40.0)	2 (6.7)	0 (0.0)	
Normal	7 (46.7)	27 (90.0)	23 (100.0)	
Sleep disturbance (AIS), n (%)				8.537 (0.012)[c]*
Insomnia	9 (60.0)	7 (23.3)	0 (0.0)	
Significant insomnia	1 (6.7)	12 (40.0)	13 (56.5)	
Normal	5 (33.3)	11 (36.7)	10 (43.5)	

Note: a, chi-square test; b, one-way ANOVA; c, Kruskal–Wallis test. *, $p < 0.05$. TUGT, Timed Up and Go Test; SPPB, Short Physical Performance Battery; BMI, body mass index; GDS-15, 15-item Geriatric Depression Scale; AIS, Athens Insomnia Scale.

Table 2. Comparison of postural stability parameters among the three groups.

Variable	Frail (n = 15)	Pre-frail (n = 30)	Non-frail (n = 23)	F (*p*-value)
BO trajectory length (mm)	864.91 ± 92.26	673.74 ± 83.40	684.79 ± 130.21	19.095 (<0.001)*
BO trajectory area (mm^2)	404.88 ± 119.74	304.08 ± 91.22	273.86 ± 80.94	9.070 (<0.001)*
BO trajectory velocity (mm/s)	17.30 ± 3.18	14.04 ± 2.17	13.60 ± 2.51	10.987 (<0.001)*
BC trajectory length (mm)	1204.36 ± 175.51	1034.39 ± 147.87	918.46 ± 142.15	15.976 (<0.001)*
BC trajectory area (mm^2)	671.51 ± 114.74	570.72 ± 209.37	483.70 ± 143.38	5.502 (0.006)*
BC trajectory velocity (mm/s)	22.88 ± 3.57	19.68 ± 2.84	19.50 ± 3.62	5.831 (0.005)*
Left single-leg length (mm)	2121.30 ± 422.94	1698.05 ± 231.81	1753.87 ± 215.49	12.158 (<0.001)*
Left single-leg area (mm^2)	1056.71 ± 152.42	880.56 ± 128.85	822.18 ± 163.63	12.083 (<0.001)*
Right single-leg length (mm)	1864.48 ± 424.53	1756.14 ± 248.87	1549.19 ± 208.23	6.266 (0.003)*
Right single-leg area (mm^2)	1131.64 ± 235.60	854.99 ± 140.99	852.51 ± 193.84	13.443 (<0.001)*
Limits of stability (mm^2)	36,746.85 ± 7738.56	38,655.90 ± 8710.39	50,033.86 ± 10,072.24	13.772 (<0.001)*

Note: *, $p < 0.05$. BO, bipedal eyes-open; BC, bipedal eyes-closed.

pletion time ($\rho = -0.352$, $p = 0.004$). No significant associations were observed between ReHo and sway area during bipedal eyes-open, bipedal eyes-closed, left single-leg, or right single-leg standing, nor with the limits of stability (all $p > 0.05$).

4. Discussion

This study investigated changes in brain functional activity in frail older adults across varying degrees of frailty, and explored the relationship between these changes and postural control capabilities. The results indicate that postural stability progressively deteriorates as the degree of frailty increases. This decline is manifested by abnormalities in the trajectory length, sway area, and velocity of the center of pressure during both bipedal and unipedal standing, as well as a significant reduction in the limits of stability. Consistent with these peripheral biomechanical findings, corresponding alterations were observed in resting-state brain function. These functional changes spanned multiple key regions, primarily involving the cerebello-pontine circuitry and parieto-frontal areas associated with sensory integration and motor control. The ALFF and ReHo indices exhibited distinct spatial distribution patterns and demonstrated significant correlations with various mea-

Table 3. Inter-group differences in brain regions of ALFF values from resting-state fMRI.

Contrast	Cluster (voxels)	Brain Region	Peak t	X	Y	Z
Overall difference	42	R posterior cerebellum Crus I/Lobule VIII	9.82	27	–51	–42
G1 > G2	56	L inferior frontal gyrus (pars opercularis)/insula	3.78	–51	12	6
G1 > G3	230	R posterior cerebellum Crus I/Lobule VIII	–4.10	27	–51	–42
G1 > G3	141	L posterior cerebellum Crus I/Lobule VIII	–4.16	–51	–51	–45
G1 > G3	50	L cerebellar anterior/posterior junction	–3.96	–12	–66	–33
G2 > G3	111	R posterior cerebellum Crus I/Lobule VIII	–3.98	21	–72	–51
G2 > G3	32	L posterior cerebellum	–3.55	–18	–66	–57

Note: GRF-corrected, voxel-level $p < 0.001$, cluster-level $p < 0.05$; minimum cluster extent ≥20 voxels. G1: non-frail; G2: pre-frail; G3: frail. MNI coordinates reported. L, left; R, right; cluster voxels ≥20; ALFF, Amplitude of Low-Frequency Fluctuations; GRF, Gaussian Random Field; MNI, Montreal Neurological Institute.

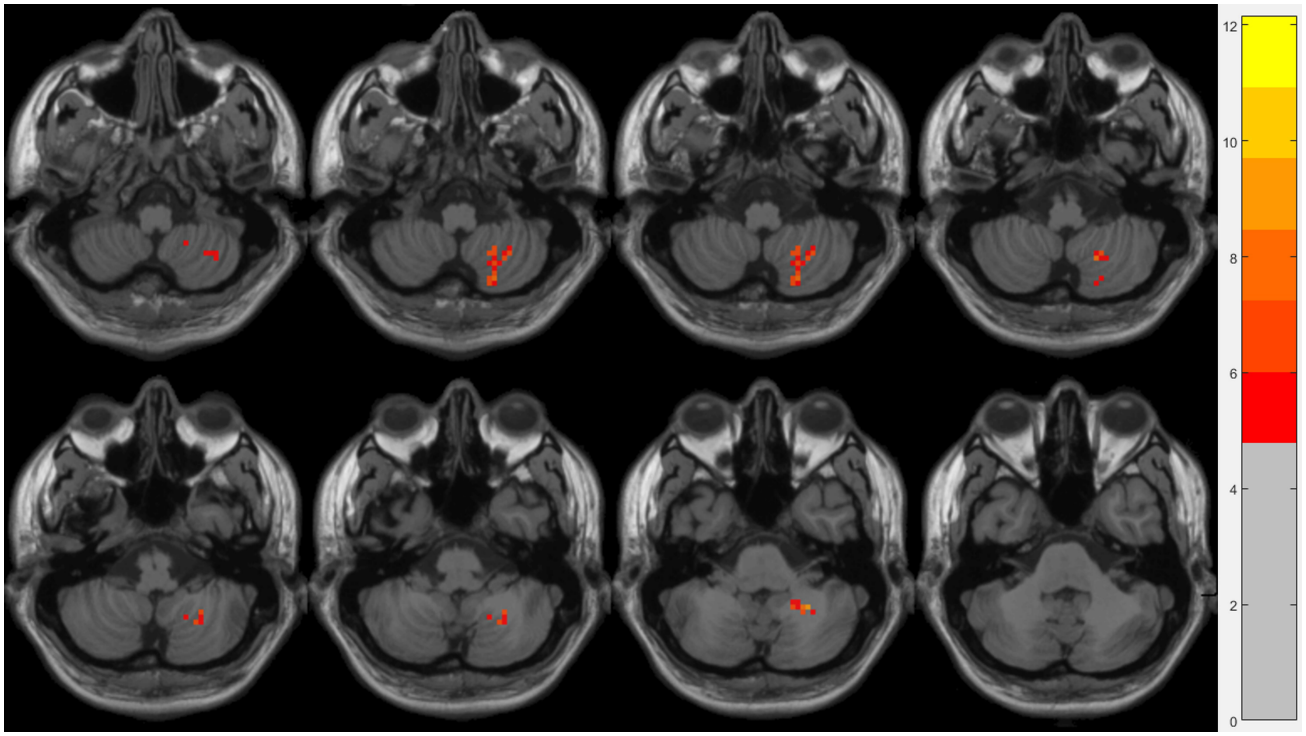

Fig. 1. Whole-brain ALFF differences among the three groups. Statistical maps show brain regions exhibiting a significant group main effect (one-way ANCOVA, voxel-level $p < 0.001$, cluster-level GRF-corrected $p < 0.05$).

Table 4. Inter-group differences in brain regions of ReHo values from resting-state fMRI.

Contrast	Cluster (voxels)	Brain region	Peak t	X	Y	Z
Overall difference	23	L pons	12.36	–3	–33	–33
G1 vs. G2	—	No significant clusters above threshold	—	—	—	—
G1 > G3	20	L posterior cerebellum	–4.64	–21	–42	–45
G1 > G3	13	R posterior cerebellum	–3.98	18	–57	–39
G1 > G3	28	L pons/anterior cerebellar lobule junction	–4.01	–3	–33	–36
G1 > G3	18	R posterior cerebellum/vermis	–3.65	9	–66	–27
G1 > G3	16	L lingual/fusiform gyrus	–4.33	–21	–81	–3
G2 > G3	16	R middle temporal/middle occipital gyrus	3.86	51	–69	27
G2 < G3	14	L posterior cerebellum/pons	–4.20	–6	–72	–54
G2 < G3	17	L pons/anterior cerebellum	–3.97	–6	–42	–21

Note: GRF-corrected, voxel-level $p < 0.001$, cluster-level $p < 0.05$; minimum cluster extent ≥10 voxels.

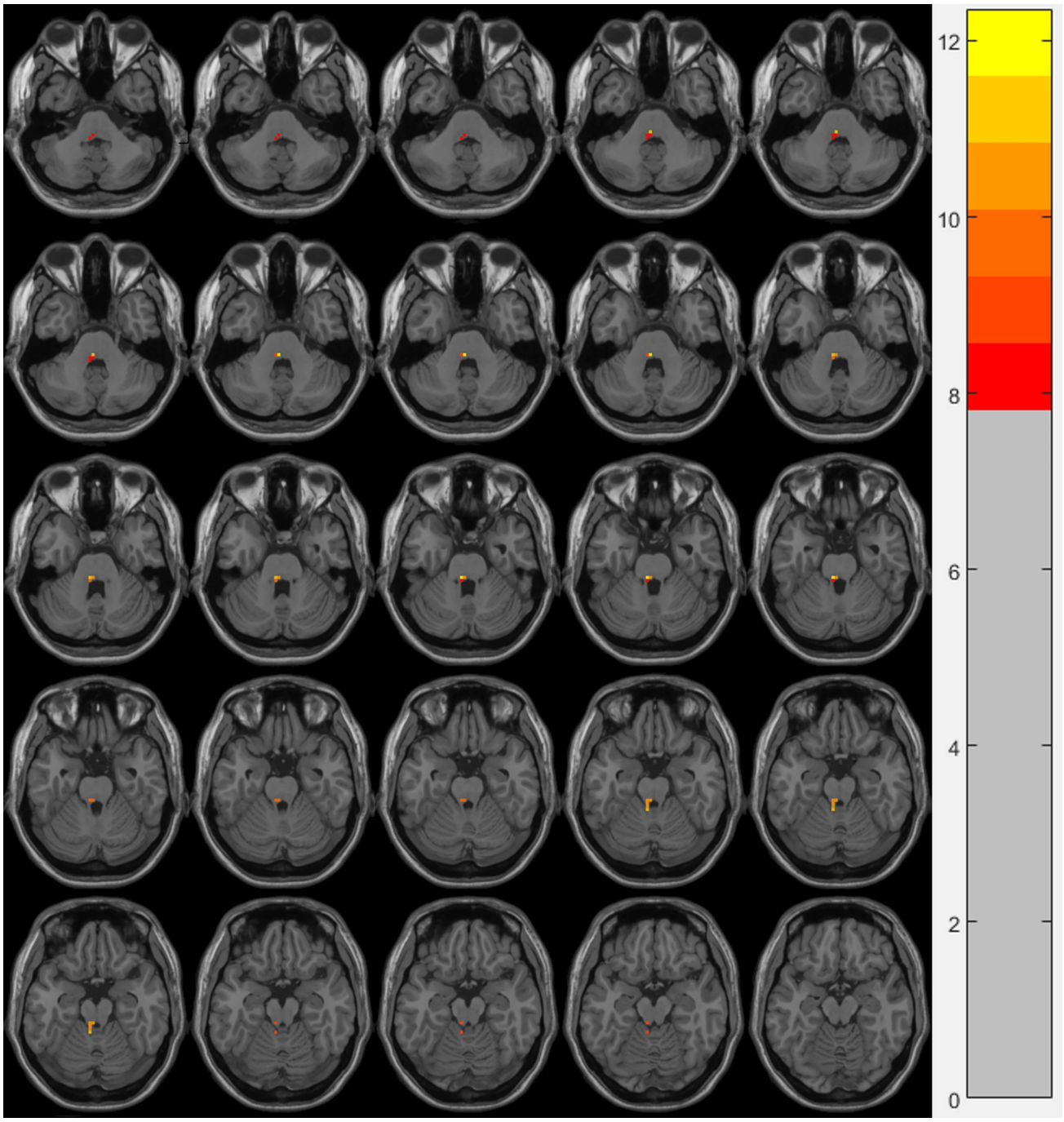

Fig. 2. Whole-brain ReHo differences among the three groups. Statistical maps show brain regions exhibiting a significant group main effect (one-way ANCOVA, voxel-level $p < 0.001$, cluster-level GRF-corrected $p < 0.05$). ReHo, Regional Homogeneity.

Table 5. Correlation analysis between resting-state brain functional indices and postural stability parameters.

Index	BO Area ρ(*p*)	BC Area ρ(*p*)	L Leg Area ρ(*p*)	R Leg Area ρ(*p*)	LOS ρ(*p*)	SPPB ρ(*p*)	TUGT ρ(*p*)
ALFF	0.207	0.236	0.158	0.339**	−0.279*	−0.257*	−0.411**
	(0.101)	(0.061)	(0.213)	(0.006)	(0.025)	(0.040)	(0.001)
ReHo	0.212	0.203	0.207	0.211	−0.191	−0.363**	−0.352**
	(0.093)	(0.108)	(0.100)	(0.094)	(0.131)	(0.003)	(0.004)

Note: **, $p < 0.01$ (two-tailed); *, $p < 0.05$ (two-tailed). LOS, limits of stability.

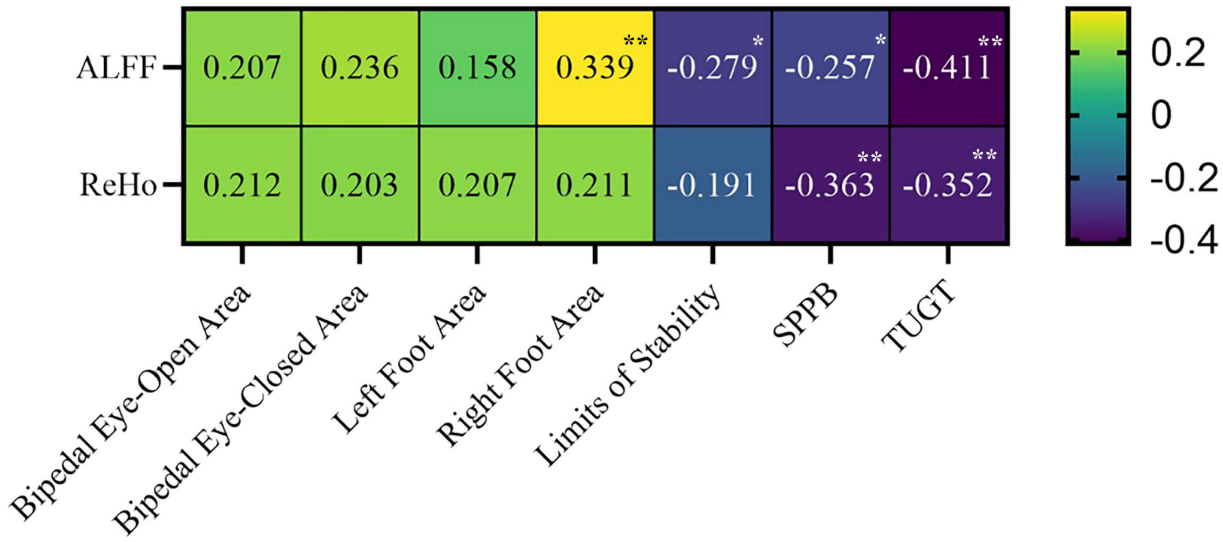

Fig. 3. Heatmap of Spearman correlation coefficients between resting-state brain functional indices and postural stability parameters. Numbers within cells represent Spearman correlation coefficients (ρ). **, $p < 0.01$; *, $p < 0.05$.

sures of postural stability and functional scales. These correlations suggest that abnormal functional activity within the central nervous system may reflect key neural correlates associated with the decline in postural stability observed in frail older adults.

4.1 Demographic and Clinical Characteristics

Frailty is a multisystem geriatric syndrome characterized by reduced physiological reserve and diminished resilience to stressors. The onset and progression of frailty are closely associated with advancing age [5,15]. Study results indicate that individuals in the frail and pre-frail groups were significantly older than those in the non-frail group, a finding consistent with existing literature. A higher prevalence of comorbidities was observed within the frail and pre-frail groups. Chronic diseases increase the physiological burden on frail individuals through shared pathophysiological pathways, including chronic inflammation, dysregulated energy metabolism, and the depletion of multisystem functional reserves [22]. The significant differences observed in handgrip strength, SPPB scores, and TUGT performance highlight the progressive decline in physical function associated with frailty. Reduced handgrip strength reflects a decline in overall neuromuscular capacity and serves as a recognized biomarker for screening for both frailty and sarcopenia, as established by the European Working Group on Sarcopenia in Older People 2 consensus [23]. For every 0.1 m/s increase in gait speed, the risk of mortality decreases by approximately 12% (hazard ratio (HR) = 0.88; 95% CI: 0.87–0.90), indicating that frail individuals with slower gait speeds face a higher risk of mortality. Impairments in lower-extremity strength, gait function, and dynamic balance are significantly associated with an increased risk of mortality, a finding consistent with the nature of the frail state and its impact on an individual's overall health [24]. Depressive symptoms and poor sleep quality not only increase the risk of frailty but may also be reciprocally exacerbated by the presence of frailty [25,26]. It is therefore essential to incorporate these psychosocial factors into the assessment framework for frailty.

4.2 Postural Stability Across Frailty Groups

The decline in stability associated with frailty was not consistent across all biomechanical parameters. It exhibited periodic characteristics with a gradual trend of deterioration. Compared to the non-frail group, the limits of stability were significantly reduced in both the pre-frail and frail groups. There were no statistically significant differences between the pre-frail and frail groups.

Specifically, the limits of stability were significantly reduced in both the pre-frail and frail groups relative to the non-frail group, with no further significant decline observed between the pre-frail and frail cohorts. A study showed that improvements in LOS parameters are significantly negatively correlated with the probability of falling. For every 1% increase in LOS capacity percentage, the probability of falling decreases by about 5% (OR = 0.95, 95% CI: 0.91–0.99). For every 1% increase in maximum excursion, the probability of falling decreases by about 6% (OR = 0.94, 95% CI: 0.90–0.99). These results indicate that better limits of stability are closely related to a lower risk of falls [27]. Under eyes-open conditions, there were no significant differences in trajectory length, area, and velocity between the non-frail and pre-frail groups. The frail group showed significant deficits in all parameters. The results of this study indicate that LOS is more useful for detecting the decline in dynamic balance during early frailty.

In this study, trajectory length gradually increased with the progression of frailty, while the frail group mainly exhibited increases in trajectory area and velocity. Previous studies showed a significantly lower risk of frailty for every one-unit increase in the Center of Pressure (CoP) path with eyes closed (OR = 0.323, $p < 0.001$). Frail individuals also showed increased sway variability during balance control. This shows a relationship between frailty and postural instability [28,29]. Consequently, the eyes-closed static stance emerges as a highly sensitive and practical screening tool for identifying early deficits in sensory integration.

During the single-leg stance task, the frail group exhibited significantly greater trajectory length and area compared to the non-frail and pre-frail groups. This observation aligns with previous reports, indicating that a decline in postural control becomes particularly pronounced during the frail stage [30]. Stability during single-leg standing reflects the combined influence of lower-limb strength and balance regulation capabilities. A systematic review confirmed that frailty in older adults is associated with diminished single-leg standing ability, and that their risk of falling is significantly higher than that of non-frail older adults (relative risk (RR) = 1.48; 95% CI: 1.27–1.73) [31]. The single-leg standing test has proven to be a particularly valuable clinical tool for identifying older adults with deficits in postural regulation.

4.3 Resting-State Brain Functional Activity Across Frailty Groups

4.3.1 ALFF Findings

The cerebellar peduncles and lobular regions exhibited the most significant reductions in ALFF within the frailty group; reduced age-related spontaneous activity in these structures has consistently been associated with the deterioration of cognitive and motor functions [32]. The gradual decline of cerebellar ALFF across the entire frailty continuum suggests that cerebellar spontaneous activity serves as a potentially sensitive neuroimaging biomarker for frailty staging.

In the pre-frailty group, a reduction in ALFF within the left inferior frontal gyrus and the insula was observed to precede changes in other brain regions. The insula acts as a multimodal integration hub, playing a critical role in cognitive and emotional processing [33]. Its functional decline during the pre-frailty stage suggests that cognitive and emotional impairments may manifest as subclinical symptoms prior to the onset of overt motor deterioration. This implies that fronto-insular ALFF could serve as an early warning biomarker.

It should be noted, however, that the cerebellar ALFF differences did not survive sensitivity analyses that additionally adjusted for comorbidity burden, depressive symptoms, or sleep disturbances (**Supplementary Table 1**), indicating that these clinical factors may partially account for the observed ALFF alterations. The fronto-insular ALFF reduction in the pre-frail group should therefore be regarded as a hypothesis-generating signal rather than a confirmed biomarker.

4.3.2 ReHo Findings

In the frailty group, significant reductions in ReHo were concentrated in the posterior cerebellum and pontine regions. This aligns with previous evidence indicating that diminished neural synchronization within subtentorial structures is associated with declines in balance and motor capabilities [11,34]. The pre-frailty group exhibited no significant differences in ReHo, suggesting that local synchronization within the cerebello-pontine network becomes disrupted only after frailty has become fully established. In contrast, changes in the intensity of spontaneous activity emerged during the pre-frailty stage. This functional dissociation between ALFF and ReHo may reflect differential patterns of neurodegeneration; a decline in activity amplitude may represent diffuse signs of functional impairment, whereas a disruption in local synchronization points to circuit-level dysfunction.

The concomitant increase in ReHo observed within the right middle temporal and middle occipital gyri in the frailty group may reflect a compensatory upregulation of regions involved in visuospatial processing [34]. This elevation may serve as a compensatory response to alterations in cerebellar activation patterns and cerebello-cortical functional connectivity [11]. The changes in ReHo observed during the frailty stage highlight a dual neural pattern that may involve secondary cortical reorganization within the sensory-perceptual network.

4.4 Associations Between Resting-State Brain Function and Postural Stability

Within the frailty continuum, a decline in postural stability is associated with not only peripheral dysfunction but also co-occurs with functional changes in the central nervous system. ALFF demonstrated a low-magnitude positive correlation with the CoP sway area during right single-leg standing, while exhibiting negative correlations with the limits of stability, SPPB total score, and TUGT completion time. These associations suggest a complex, multidirectional relationship between spontaneous neural activity and postural performance, potentially reflecting heterogeneity across different brain regions. The positive correlation observed between ALFF and sway area suggests that heightened spontaneous neural activity in specific regions may represent a compensatory recruitment pattern associated with compromised balance. This interpretation aligns with the hypothesis of neural inefficiency, wherein an increased allocation of neural resources becomes necessary to achieve a comparable motor output [33,34]. The observed correlations with SPPB scores and TUGT times indicate that ALFF captures distinct functional dimensions across various clinical paradigms. Given that these correlational patterns were derived from a heterogeneous over-

all sample, they may reflect the overlapping effects of both frailty-associated decline and compensatory hyperactivity. These findings corroborate previous neuroimaging studies conducted in similar populations, which demonstrated that abnormalities in resting-state functional activity are closely linked to motor execution efficiency, gait performance, and overall functional capacity [35].

ReHo exhibited significant negative correlations with SPPB scores and TUGT completion times, but showed no significant associations with sway area during any standing task (bipedal eyes-open, bipedal eyes-closed, left or right single-leg) or with the limits of stability. This selective pattern indicates that ReHo is more sensitive to the integrated functional capacity measured by composite scales such as the SPPB and the goal-directed locomotion of the TUGT than to instantaneous postural sway. This pattern aligns with existing evidence suggesting that ReHo primarily reflects local sensorimotor integration and the fundamental motor control mechanisms associated with visually guided postural tasks. Its explanatory power may be more limited regarding highly challenging balance tasks that necessitate extensive cross-network coordination [36,37]. Prior studies have indicated that indices of local synchronization correlate more strongly with measures of general functional activity than with measures of peak balance capacity; this suggests that ReHo is more sensitive to capturing the efficiency of neural coordination during routine functional activities rather than during peak postural stability performance [38,39]. ReHo showed no significant correlation with the limits of stability. This indicates that ReHo is highly sensitive to capturing the brain functional activity underlying routine postural maintenance, rather than maximal dynamic capacity. Understanding this clear distinction serves to inform the development of targeted rehabilitation strategies.

In summary, the observed correlation patterns of ALFF and ReHo provide a complementary neuroimaging perspective for understanding the subtle differences in the central neural correlates associated with postural instability across different frailty states.

4.5 Limitations and Future Directions

Several limitations of the present study should be acknowledged. Because the design was cross-sectional, we are unable to infer the direction of the observed associations between brain function and postural stability. Longitudinal work will be needed to clarify whether functional alterations precede, accompany, or follow the decline in balance across the frailty continuum. Furthermore, the neuroimaging characterization was restricted to ALFF and ReHo, two complementary but ultimately partial windows onto resting-state activity. Integrating measures of functional connectivity, network topology, and structural integrity in future studies would offer a richer view of how the aging brain reorganizes as frailty progresses.

The sample size deserves particular attention. Comprising 68 participants overall and only 15 in the frail subgroup, a post-hoc sensitivity power analysis (**Supplementary Table 2**) indicated that, at $\alpha = 0.05$, the three-group design afforded ≥80% statistical power to detect only large effects (Cohen's $f \geq 0.385$, equivalent partial $\eta^2 \approx 0.13$), while the correlation analyses afforded ≥80% power to detect only $|\rho| \geq 0.334$. The study was therefore well-powered to identify large effects but underpowered for medium and smaller differences. We therefore caution against reading non-significant contrasts, particularly those between pre-frail and non-frail participants across several ReHo metrics, as evidence that no underlying effect exists, since such findings could equally reflect Type II error.

Conversely, the risk of Type I error was a primary concern in our voxel-wise analyses. We addressed this by applying GRF theory alongside family-wise error correction at a stringent voxel-level threshold. Additionally, we draw reassurance from the fact that the surviving clusters fell within cerebello-pontine and fronto-insular regions, whose involvement in postural and cognitive aging is already well established. The same concern, however, applies more acutely to the brain–behavior correlation analyses. Because these analyses were exploratory and hypothesis-generating in nature (see section 2.9), no formal correction for multiple comparisons was applied, and the reported associations therefore carry an elevated risk of false-positive findings. The four nominally significant correlations identified here—ALFF with TUGT completion time, right single-leg sway area, and the limits of stability, together with ReHo with SPPB and TUGT—should accordingly be regarded as candidate effects requiring confirmation in larger, independent cohorts using pre-specified hypotheses, rather than as established brain–behavior relationships. Even so, the magnitudes we report should be regarded as preliminary. Small samples are prone to overestimating true effect sizes, and the generalizability of our conclusions to broader populations of older adults remains to be confirmed.

A few further analytical caveats also warrant mention. The covariate-adjusted group comparisons of postural stability were performed with parametric ANCOVA even though several of these measures were non-normally distributed—the reason Spearman correlations were used for the brain–behavior analyses; although ANCOVA is reasonably robust to such departures at the present group sizes, the residual skew remains a minor potential source of statistical bias. In addition, detailed medication information—particularly centrally acting agents such as sedative-hypnotics, psychotropics, and antihypertensives—was not systematically collected, so residual confounding from polypharmacy, which can independently affect both postural control and resting-state cortical activity, cannot be excluded. Lastly, the clinical postural-stability comparisons were adjusted only for age and comorbidity count and, unlike the neuroimaging analyses, did not account for depres-

sive symptoms or sleep quality; because both differed significantly across groups, these comparisons are less comprehensively controlled for confounding and the between-group differences may be modestly overestimated.

Looking ahead, replication in substantially larger and ideally multi-site cohorts will be essential. This will not only stabilize effect size estimates but also enable stratified analyses based on sex, comorbidity profiles, or individual frailty criteria that the present sample could not support.

5. Conclusions

This study demonstrates significant differences in resting-state brain function among older adults with different frailty states. ALFF and ReHo indices reflected functional activity changes from different dimensions. These changes mainly involved the cerebello-pontine circuit, insula, and other cognition-related brain regions. Furthermore, altered brain function correlated significantly with postural stability metrics. These metrics included bipedal and unipedal standing area, limits of stability, total SPPB scores, and TUGT times. This suggests abnormal central brain activity is closely associated with the decline in balance among frail older adults. In summary, this study revealed the characteristics of brain functional activity in frail older adults. It also highlighted the relationship between brain activity and postural stability. These findings provide a theoretical basis for early screening and targeted balance interventions.

Availability of Data and Materials

The datasets generated and analyzed during the current study are available from the corresponding author upon reasonable request.

Author Contributions

SH—Software, Validation, Writing-Original Draft. YX—Investigation, Data Curation. XL—Data Curation, Project Administration. SL—Formal Analysis. YL—Data Curation. CJ—Methodology, Writing-Review & Editing. XK—Formal Analysis, Resources, Funding Acquisition. ZL—Conceptualization, Resources, Writing-Review & Editing, Supervision, Funding Acquisition. All authors contributed to editorial changes in the manuscript. All authors read and approved the final manuscript. All authors have participated sufficiently in the work and have agreed to be accountable for all aspects of the work.

Ethics Approval and Consent to Participate

This study was approved by the Medical Ethics Committee of Fuzhou University Affiliated Provincial Hospital (Approval No.: K2025-02-179; Approval Date: February 21, 2025) and conducted in accordance with the Declaration of Helsinki. All participants provided written informed consent prior to enrollment.

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Conflicts of Interest

The authors declare no conflicts of interest.

Supplementary Material

Supplementary material associated with this article can be found, in the online version, at https://doi.org/10.31083/JIN51891.

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