Research Article

Structural and Functional Deficits in Patients with Poststroke Dementia: A Multimodal MRI Study

Huaying Cai,1 Zhiyong Zhao,2 Linhui Ni,1 Guocan Han,3 Xingyue Hu,1 Dan Wu,2 Xianjun Ding,4 and Jin Wang1

1Department of Neurology, Neuroscience Center, Sir Run Run Shaw Hospital, Zhejiang University, Hangzhou, China
2Key Laboratory for Biomedical Engineering of Ministry of Education, Department of Biomedical Engineering, College of Biomedical Engineering & Instrument Science, Zhejiang University, Hangzhou, China
3Department of Radiology, Sir Run Run Shaw Hospital, Zhejiang University, Hangzhou, China
4Department of Orthopaedic Surgery, Sir Run Run Shaw Hospital, Zhejiang University, Hangzhou, China

Correspondence should be addressed to Jin Wang; wangjinjoy@zju.edu.cn

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Although many neuroimaging studies have reported structural and functional abnormalities in the brains of patients with cognitive impairments following stroke, little is known about the pattern of such brain reorganization in poststroke dementia (PSD). The present study was aimed at investigating alterations in spontaneous brain activity and gray matter volume (GMV) in PSD patients. We collected T1-weighted and resting-state functional magnetic resonance imaging data from 20 PSD patients, 24 poststroke nondementia (PSND) patients, and 21 well-matched normal controls (NCs). We compared the differences among the groups in GMV and the fractional amplitude of low-frequency fluctuations (fALFF). Then, we evaluated the relationship between these brain measures and cognitive assessments and explored the possible distinguisher for PSD by receiver operating characteristic (ROC) curve analysis. PSD patients showed smaller GMV in the right superior temporal gyrus and lower fALFF values in the right inferior frontal gyrus than both PSND patients and NCs, but such differences were not observed between PSND patients and NCs. Moreover, GMV in the left medial prefrontal cortex showed a significant positive correlation with the Mini-Cog assessment in PSD patients, and GMV in the left CPL displayed the highest area under the ROC curve among all the features for classifying PSD versus PSND patients. Our findings suggest that PSD patients show dementia-specific structural and functional alteration patterns, which may help elucidate the pathophysiological mechanisms underlying PSD.

1. Introduction

Poststroke dementia (PSD), irrespective of the presumed cause, is a clinical entity that encompasses all types of dementia following a stroke and characterized as cognitive decline [1]. Previous studies have reported the prevalence of poststroke dementia (PSD) ranging from 13% to 27% [2–4], and this variation may be related to many factors, including race [5, 6], educational level [7], economic level [4], lifestyle [8], and aging population [3]. Moreover, PSD may have potential influences on various aspects of daily living activities, especially stroke recurrence [9] and functional outcome [10], and has become a significant public health burden [11]. Although previous neuroimaging studies based on structural or functional MRI have attempted to explore PSD-related patterns in brain reorganization [12–14, 42], few studies used multimodal MRI to explore the neural mechanisms underlying PSD.

In the neuroimaging field, functional magnetic resonance imaging (fMRI) has been widely used to investigate the pathogenesis of neurological diseases [15–17]. Compared with task-based fMRI, resting-state fMRI (rs-fMRI) shows the advantage of application in stroke studies since it does not require specific tasks [18, 19]. rs-fMRI mainly examines the low-frequency (0.01-0.08 Hz) fluctuations in
blood oxygenation level-dependent (BOLD) fMRI signals at rest [20, 21]. As a valid method to detect local spontaneous neuronal activity [22], the amplitude of low-frequency fluctuations (ALFF) has been used to study various cognitive and neuropsychiatric disorders, including mild cognitive impairment [23] and schizophrenia [24]. However, compared with ALFF, the fractional amplitude of low-frequency fluctuations (fALFF) could be robust against non-specific signal components [25], allows the analysis of frequency-specific activity [26], and improves the sensitivity and specificity in detecting regional spontaneous brain activity [27]. Using this method, previous stroke studies found that compared to normal controls (NCs), patients with acute cerebellar infarction showed increased fALFF values in the right fronto-lateral cortex, left hippocampus, and right cingulate gyrus and decreased fALFF values in the cerebellum posterior lobe (CPL) [18]; stroke patients with depression symptoms have higher fALFF values in the left dorsolateral prefrontal cortex and the right precentral gyrus compared to nondepressed patients [26]. Moreover, depressive symptom scores in stroke patients were positively correlated with fALFF values in the left insula, superior temporal lobe, thalamus, cerebellum, and right cingulate [28]. These findings suggest that fALFF could be used to explore neuronal functional alterations in patients after stroke. However, this method has never been used to detect changes in spontaneous neural activity in PSD patients.

In addition, gray matter volume (GMV), quantitatively calculated by voxel-based morphometry (VBM) [29] analysis of T1-weighted images, has become an ideal morphological measurement to explore structural alterations in poststroke patients [30, 31]. For example, Stebbins et al. found that patients with cognitive impairments after stroke showed significant GMV reductions in the thalamus, cingulate gyrus, and frontal, temporal, parietal, and occipital lobes compared with patients without cognitive impairments [32]. Ahn et al. observed significantly lower GMV in the bilateral cerebellum in chronic stroke patients with cognitive impairments than in NCs [33]. In addition, Yang and colleagues reported that compared with NCs, patients with poststroke aphasia showed increased GMV in the right superior temporal gyrus, right inferior parietal lobule, and left middle occipital gyrus and decreased GMV in the right cingulate gyrus and bilateral thalamus [34]. These results indicated that patients with different poststroke cognitive dysfunctions show different GMV alteration patterns. However, the GMV alterations in PSD patients remain unclear, and the utility of structural neuroimaging studies with MRI has not been fully explored.

The current study was aimed at exploring the potential structural and functional changes using fALFF and GMV methods in patients with PSD. Based on previous findings of alterations in fALFF and GMV in patients with different poststroke dysfunctions [18, 26, 32], we hypothesized that disease-specific patterns of fALFF and GMV changes would be discovered in patients with PSD. Furthermore, based on the report that clinical symptoms were correlated with neural alterations in stroke patients [23], we also hypothesized that the fALFF/GMV alterations in patients with PSD would be related to their cognitive functions.

2. Materials and Methods

2.1. Participants. Fifty-nine poststroke patients (PSD/PSND: N = 25/34) and twenty-five NCs were recruited at Sir Run Run Shaw Hospital from September 2017 to October 2019. The Institutional Review Board provided ethical approval of this study at the local hospital. All participants provided informed consent. The inclusion criteria for the patients were as follows: (1) age > 18 years, (2) complement of neuropsychological tests at the acute phase and the third month after stroke, (3) eligibility for a scan between 1 and 6 months after stroke onset, (4) first-episode stroke, and (5) definitive acute ischemic stroke based on DWI of the head. The exclusion criteria for all participants were as follows: (1) any neuropsychiatric comorbidity such as depression (total score ≥ 8 on the 17-item Hamilton Depression Rating Scale), anxiety (total score ≥ 7 on the Hamilton Anxiety Rating Scale), epilepsy, brain tumor, brain trauma, and drug or alcohol abuse; (2) any clinically significant or unstable medical disorder; (3) any contraindication for MRI; (4) prestroke dementia (Informant Questionnaire on Cognitive Decline in the Elderly (IQCODE) score > 3:31); and (5) aphasia before or after the stroke. A total of 19 subjects were excluded because of the excessive head motion (>2 mm/degree) (4 PSD patients, 7 PSND patients, and 4 NCs) and lesion volume (>10 ml) (1 PSD and 3 PSND patients). Finally, based on matching age and education among the three groups, 21 NCs, 20 PSD, and 24 PSND patients were included in the final analysis in the present study.

2.2. Clinical Assessments. The National Institutes of Health Stroke Scale (NIHSS) and modified Rankin Scale (mRS) scores were recorded upon patient consent. According to the poststroke cognitive impairment assessment guideline by the Chinese Stroke Centre Alliance, the IQCODE was used to evaluate the pre-stroke cognitive status of each patient [35], and both the Mini-Mental State Examination (MMSE) [36] and Mini-Cog [37] assessments were used to evaluate the cognitive performance of each patient both at the acute stage and at the third month poststroke. We controlled for vascular risk factors, such as blood pressure, blood lipids, blood sugar, and smoking, for each patient after stroke via antihypertensive drugs, glucose-lowering drugs, and lipid-lowering drugs. All patients underwent standardized treatment based on the “Guideline for Early Management of Adults with Ischemic Stroke” [38] and were followed up in the outpatient clinic with the same clinician. All normal controls underwent cognitive assessment (both the MMSE and Mini-Cog) before the MRI scan. Two neurologists (HY C and LH N) who were blinded to the MRI data recorded the clinical data and performed the cognitive examinations.

PSD was diagnosed by two neurologists with 15 years of experience and 4 years of experience according to the 2019 Chinese Vascular Cognitive Impairment Guideline, which defines PSD as a status in which cognitive impairment lasts for three months after a stroke [39]. We therefore determined the diagnosis at three months after stroke onset, which is also consistent with the international consensus [40] (within 6 months). PSD was identified if the patient satisfied one of the following two criteria: (1) MMSE scores
below a certain cutoff value depending on the education level: (i) MMSE < 24 for patients with education higher than junior middle school, (ii) MMSE ≤ 19 for patients with primary school education, or (iii) MMSE ≤ 17 for patients with illiteracy, and (2) an adjusted Mini-Cog score of <3. Finally, poststroke patients were divided into two subgroups (PSD and PSND).

2.3. MRI Data Acquisition. Multimodal MRI scans, including resting-state fMRI and T1- and diffusion-weighted images, were performed for each patient approximately three months after stroke. All data were acquired on a Siemens 3 T MAGNETOM Skyra MRI scanner (Siemens Healthcare, Erlangen, Germany) with a 20-channel head coil. The sequences and parameters were identical to those in our previous study [41].

2.4. Lesion Analysis. We manually drew lesion regions slice by slice on the nondiffusion-weighted image (b0) using MRicron software (http://www.mricron.com) (Figure 1), and lesion masks were confirmed by two neurologists (HY C and LH N). Then, we determined the location and number of lesions and calculated the lesion volume for each patient.

2.5. FMRI Data Processing. We preprocessed the resting-state fMRI data using the Advanced DPARSF (http://www.restfmri.net) and SPM12 (http://www.fil.ion.ucl.ac.uk/spm) toolkits. The first 5 functional volumes were discarded, and the remaining 115 volumes underwent slice timing and head motion corrections. Then, white matter, cerebrospinal fluid, and the Friston 24-parameter model of head motion were regressed out as nuisance variables. Next, the data were spatially normalized to an EPI template in the MNI space. Finally, we conducted the fALFF analysis. Specifically, a ratio of the low-frequency amplitude within 0.01-0.1 Hz from fast Fourier transformation to the power spectrum of the entire frequency range was computed at each voxel to obtain fALFF values [25]. The fALFF maps were normalized by subtracting the mean value for the entire brain and then dividing by the whole-brain standard deviation. The maps were further smoothed by a Gaussian kernel at a full width half maximum (FWHM) of 6 mm [42, 43].

2.6. VBM Analysis. We performed the VBM analysis with SPM12. We first registered the T1 images to the Montreal Neurological Institute (MNI) template and then segmented the whole-brain structural data into white matter, gray

Figure 1: Lesion display for each patient in the PSD and PSND groups. The red region represents an individual lesion.
matter, and cerebrospinal fluid. We conducted bias correction to remove intensity nonuniformities. Segmented images of the gray matter were preserved to assess the number of volume changes based on spatial registration, and the modulated images of the gray matter could reflect the tissue volumes for using VBM analysis. Finally, we smoothed the

Table 1: Demographic and clinical information of all participants.

|                     | NCs (n = 21) | PSND (n = 24) | PSD (n = 20) | F/t/χ² | p value |
|---------------------|--------------|---------------|--------------|--------|---------|
| Age, mean (SD)      | 60.71 (10.36) | 61.67 (7.21)  | 66.95 (9.04) | 2.94   | 0.06    |
| Male, n (%)         | 9 (43)       | 20 (83)       | 11 (55)      | 8.27   | 0.02∗   |
| Handiness           | R            | R             | R            | N/A    | N/A     |
| ICV (L), mean (SD)  | 1.46 (0.14)  | 1.41 (0.31)   | 1.30 (0.26)  | 8.35   | 0.02∗   |
| FD, mean (SD)       | 0.09 (0.07)  | 0.11 (0.07)   | 0.08 (0.05)  | 5.16   | 0.08    |
| Education level, n (%) |           |               |              |        |         |
| None                | 0            | 4 (17)        | 7 (35)       |        |         |
| Primary             | 14 (67)      | 6 (25)        | 5 (25)       |        |         |
| Junior high school  | 5 (24)       | 8 (33)        | 5 (25)       |        |         |
| Senior high school  | 2 (9)        | 5 (21)        | 3 (15)       |        |         |
| Superior            | 0            | 1 (4)         | 0            |        |         |
| Duration of illness (day), mean (SD) | 99.04 (62.14) | 104.55 (69.69) | -0.28 | 0.78    |
| NIHSS, mean (SD)    | N/A          | 1.79 (2.36)   | 1.55 (2.21)  | 0.35   | 0.73    |
| NIHSS, mean (SD)    | N/A          | 0.17 (0.38)   | 0.25 (0.44)  | -0.67  | 0.51    |
| mRS, n (%)          |              |               |              |        |         |
| 0-1-2-4             | N/A          | 15 (63)-7 (29)-0-2 (8) | 14 (70)-5 (25)-1 (5)-0 | 3.03   | 0.39    |
| mRS, n (%)          |              |               |              |        |         |
| 0-1                 | N/A          | 19 (79)-5 (21) | 15 (75)-5 (25) |        |         |
| MMSE, mean (SD)     | 25.88 (3.04) | 26.88 (2.91)  | 20.30 (4.50) | 20.77 <0.001*** |
| MMSE, mean (SD)     | 25.88 (3.04) | 27.17 (2.32)  | 20.45 (4.38) | 24.19 <0.001*** |
| Mini-Cog, n (%)     |              |               |              |        |         |
| 0-1-2-3-4-5-6-7     | 0-0-0-0-1 (5)-5 (24) -3 (14)-12 (57) | 0-0-3 (13)-12 (50)-0-9 (37)-0-0 | 2 (10)-0-7 (35)-9 (45)-2 (10)-0-0 | -0.28 | 0.78    |
| Mini-Cog, n (%)     |              |               |              |        |         |
| 0-1-2-3-4-5-6-7     | 0-0-0-0-1 (5)-5 (24) -3 (14)-12 (57) | 0-0-2 (8)-8 (33)-1 (5)-13 (54)-0-0 | 3 (15)-1 (5)-4 (20)-7 (35)-1 (5)-4 (20)-0-0 | 65.34 <0.001*** |

1Acute phase; 2third month; 3one-way ANOVA analysis/two-sample t-test; 4chi-square test. Age, ICV, duration of illness, and MMSE are shown as mean (standard deviation); other data (n %) are number of participants (percentage). *, **, and *** represent p < 0.05, p < 0.01, and p < 0.001, respectively. NCs: normal controls; PSND: poststroke nondemented; PSD: poststroke demented; ICV: intracranial volume; FD: framewise displacement; NIHSS: National Institutes of Health Stroke Scale; mRS: modified Rankin Scale; MMSE: Mini-Mental State Examination.

Table 2: Lesion information of all patients.

| Location of stroke | PSND (n = 24) | PSD (n = 20) | t/χ² | p value |
|-------------------|---------------|--------------|------|---------|
| Left              | 11            | 11           |      | 0.45    | 0.80    |
| Right             | 11            | 8            |      |         |         |
| Bilateral         | 2             | 1            |      |         |         |
| Lesion volume (ml), mean (SD) | 1.28 (1.32) | 0.96 (1.12) | 0.87 | 0.39 |
| Lesion number     | 1-2-3         | 17:7:0       | 16:3:1 | 2.29 | 0.32 |

1Two-sample t-test; 2chi-square test. PSND: poststroke nondemented; PSD: poststroke demented; SD: standard deviation.
normalized gray matter images using an 8 mm FWHM Gaussian filter [42, 43].

2.7. Statistical Analysis. We first performed one-way ANCOVA to compare fALFF and GMV maps among the three groups within a gray matter mask with age, sex, education, head motion, intracranial volume (ICV) and volume, location, and number of lesions as the covariates. A two-tailed Gaussian random field correction with a voxel-level $p < 0.01$ and a cluster-level $p < 0.05$ was used to control false

| Patient ID | Hemisphere | Location | Number | Volume (ml) |
|------------|------------|----------|--------|-------------|
| PSND_01    | Bilateral  | White matter | 2      | 0.65        |
| PSND_02    | Right      | White matter, cerebellum | 1      | 0.35        |
| PSND_03    | Left       | White matter, caudate | 1      | 2.73        |
| PSND_04    | Right      | White matter | 1      | 1.19        |
| PSND_05    | Right      | White matter | 1      | 0.36        |
| PSND_06    | Right      | White matter | 1      | 2.23        |
| PSND_07    | Left       | Cerebellum | 2      | 0.47        |
| PSND_08    | Left       | Occipital lobe | 1      | 3.22        |
| PSND_09    | Left       | White matter, cingulate gyrus | 2      | 0.52        |
| PSND_10    | Right      | White matter | 1      | 1.06        |
| PSND_11    | Bilateral  | White matter | 2      | 1.65        |
| PSND_12    | Right      | Insula | 1      | 0.21        |
| PSND_13    | Left       | Occipital, temporal lobes | 2      | 2.06        |
| PSND_14    | Left       | White matter | 2      | 0.83        |
| PSND_15    | Left       | Cerebellum | 1      | 0.12        |
| PSND_16    | Right      | Thalamus | 1      | 0.65        |
| PSND_17    | Left       | Thalamus | 1      | 0.26        |
| PSND_18    | Right      | White matter | 1      | 0.96        |
| PSND_19    | Right      | White matter | 1      | 1.90        |
| PSND_20    | Left       | Cerebellum | 1      | 0.44        |
| PSND_21    | Right      | White matter | 1      | 1.86        |
| PSND_22    | Right      | White matter, frontal lobe | 2      | 0.57        |
| PSND_23    | Left       | Occipital lobe | 1      | 6.02        |
| PSND_24    | Left       | White matter | 1      | 0.47        |
| PSD_01     | Left       | White matter, frontal lobe | 3      | 0.42        |
| PSD_02     | Left       | White matter | 1      | 0.24        |
| PSD_03     | Right      | White matter, putamen, thalamus, insula | 1      | 4.79        |
| PSD_04     | Left       | White matter | 1      | 0.28        |
| PSD_05     | Left       | White matter, caudate | 1      | 1.84        |
| PSD_06     | Left       | White matter | 1      | 0.59        |
| PSD_07     | Right      | White matter | 1      | 1.28        |
| PSD_08     | Left       | White matter, putamen | 2      | 2.27        |
| PSD_09     | Left       | Thalamus | 1      | 0.84        |
| PSD_10     | Left       | White matter | 1      | 0.35        |
| PSD_11     | Left       | White matter, frontal lobe | 2      | 0.81        |
| PSD_12     | Bilateral  | White matter, putamen | 2      | 1.43        |
| PSD_13     | Right      | White matter, parietal/frontal lobe | 1      | 2.03        |
| PSD_14     | Right      | White matter | 1      | 0.23        |
| PSD_15     | Left       | Thalamus | 1      | 0.15        |
| PSD_16     | Right      | Temporal lobe | 1      | 0.32        |
| PSD_17     | Right      | Thalamus | 1      | 0.03        |
| PSD_18     | Right      | White matter, putamen | 1      | 0.40        |
| PSD_19     | Left       | White matter | 1      | 0.34        |
| PSD_20     | Right      | White matter | 1      | 0.48        |
discoveries due to multiple comparisons. Then, for the regions showing a significant group-level main effect, post hoc t-tests were performed to detect the pairwise differences in fALFF and GMV (Bonferroni corrected, \( p < 0.05 \)). Next, to examine the relationships between the fALFF/GMV values in the regions with between-group differences and cognitive functions (MMSE or Mini-Cog scores) and between fALFF and GMV values, partial correlation analyses were separately performed in each patient group while controlling for age, sex, education, head motion, ICV and volume, location, and number of lesions. Finally, we used the fALFF/GMV in the regions showing significant differences between groups as the feature to perform receiver operating characteristic (ROC) curve analysis to discriminate PSD from PSND patients.

3. Results

The three groups did not have significant differences in age, handedness, head motion, or intracranial volume (Table 1). Additionally, the duration of illness and stroke severity were matched between the two patient groups. Notably, sex and education showed significant differences between NCs and the patient groups but not between PSD and PSND (sex: \( p = 0.053 \); education: \( p = 0.60 \)). Cognition scores (MMSE and Mini-Cog) in the PSD patients were significantly lower than those in the PSND group (Table 1). In addition, the two patient subgroups did not have significant differences in the volume, location, or number of stroke lesions (Table 2). None of the patients showed hemorrhagic transformation after stroke. The number of patients with cortical/subcortical lesions was 4/20 in the PSND group and 4/16 in the PSD group (Table 3).

ANCOVA found that GMV showed significant differences between the three groups in the left CPL, left medial prefrontal cortex (mPFC), superior frontal gyrus (SFG), and right superior temporal gyrus (STG); significant differences in fALFF values were observed in the right inferior frontal gyrus (IFG) (Figure 2 and Table 4). Post hoc analysis showed that both PSND and PSD patients had smaller GMV than NCs in the left medial prefrontal cortex (mPFC) and SFG; the left CPL displayed larger GMV in the PSND group compared with the NC and PSD groups. Importantly, we found dementia-specific changes in which the PSD group showed decreased GMV in the right STG and decreased fALFF in the right IFG compared with PSND and NC groups, but such differences were not found between PSND and NC groups (Figure 3).

Moreover, we found significant positive correlations between GMV in the left mPFC and Mini-Cog scores at the third month in the PSD group (\( p = 0.04 \), \( r = 0.56 \)) and between GMV in the right STG and MMSE scores at the third month in the PSND group (\( p = 0.03 \), \( r = 0.52 \)) (Figure 4), although they did not pass the Bonferroni correction of \( p < 0.05 \). In addition, ROC analysis showed that GMV in the left CPL and right STG and fALFF values in the right IFG significantly discriminated the PSD patients from the PSND patients (Figure 5 and Table 5). Specifically, the AUC in left CPL, left mPFC, left SFG, right STG, and right IFG were 0.804, 0.531, 0.502, 0.783, and 0.717, respectively. Also, the performance was improved (AUC = 0.898, \( p < 0.001 \)) after combining the three brain regions with high AUC values.

4. Discussion

The present study evaluated alterations in GMV and fALFF in patients with PSD, and the results supported our hypotheses that (1) PSD patients showed dementia-specific decreases in GMV in the right STG and fALFF in the right IFG; (2) GMV in the left mPFC in the PSD group was significantly positively correlated with Mini-Cog scores at the third month, and such a relationship was also found between GMV in the right STG in the PSND group and MMSE scores at the third month; and (3) fALFF values in the right IFG and GMV in the left CPL and right STG may be used to discriminate PSD patients from PSND patients. These findings provide a new insight into the neurophysiological mechanisms underlying PSD, which may motivate the development of a theoretical basis for clinical diagnosis.

4.1. PSD-Related Structural Alterations. As two core components of the prefrontal cortex, the medial gyrus and superior frontal gyrus have been linked to a variety of cognitive functional domains, especially in memory [44] and cognitive control [45]. Compared with NCs, Bhalsing et al. found GMV loss in the right mPFC in essential tremor patients with cognitive impairments [46]; Yang et al. reported significantly reduced GMV in the left SFG in silent cerebral infarction patients with cognitive impairment [47]; Li et al. observed a GMV reduction in the SFG in subcortical vascular dementia patients [48]. Moreover, Stebbins and colleagues reported decreased GMV in the bilateral mPFC and SFG in stroke patients with impaired cognitive performance compared with those without cognitive impairment [32]. These studies collectively demonstrated decreased GMV in the SFG and mPFC in patients with cognitive dysfunction, and the present study provided supporting evidence that PSD patients displayed GMV reductions in these two regions compared with NCs. Additionally, previous neuroimaging studies revealed GMV atrophy in the mPFC and SFG areas in transient ischemic attack patients [49], poststroke pain patients [50], and poststroke...
represent
tent cognitive de
sub
with subcortical vascular dementia [57] and in left cerebellar
reductions in GMV in the right cerebellar region in patients
tive functions [56]. Previous studies have found signi

due to the presence of cerebellar activations in higher cogni-
tics in remitted major depression patients with persis-
tuent disease. Consistent with previous studies, the present
findings suggest that the STG might be a potential neural biomarker in cognitive impair-
diseases. Consistent with previous studies, the present
study found that the right STG displayed a smaller GMV in
PSD patients than in PSND patients and NCs, but such a dif-
rence was not observed between PSND patients and NCs,
which implied that the structural reduction in the right STG
was more likely to be speci
tic to dementia rather than stroke. Moreover, studies have demonstrated that functional alter-
ations in the inferior frontal gyrus (IFG), which is also consid-
ered to be related to cognition [65], have been reported in
several previous neuroimaging studies. For example, Zhong
et al. reported decreased ALFF in the left opercular part of
the IFG in patients with cognitive control impairment com-
pared with NCs [66]. Han et al. and Li et al. both observed that
compared with NCs, patients with left hemisphere subcortical stroke showed
increased GMV in the ipsilesional cerebellum VI [60]. These
findings suggest that the decreased GMV in the cerebellum-
related region in PSD compared with PSND in the present
study may be associated with both cognitive dysfunction and stroke. Moreover, the increased GMV in the cerebellum
in PSND patients compared with NCs may represent motor compensation after stroke [61].

4.2. Dementia-Specific Structural and Functional Alterations.
The superior temporal gyrus is considered a key structure
involved in cognitive processing [62, 63]. Previous neuroim-
aging studies have explored structural alterations in the STG
in patients with dementia or cognitive impairments. For
instance, one study based on VBM analysis showed that Par-
kinson’s disease patients with dementia had a significant
decrease in GMV in the bilateral STG compared to those
without dementia [64]. Using a similar method, another
study revealed that compared with NCs, patients with sub-
cortical vascular mild cognitive impairment exhibited atrophy
in the bilateral STG [48]. These findings suggest that the STG
might be a potential neural biomarker in cognitive impair-
ment diseases. Consistent with previous studies, the present
study found that the right STG displayed a smaller GMV in
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the IFG in patients with cognitive control impairment com-
pared with NCs [66]. Han et al. and Li et al. both observed that
compared with NCs, patients with mild cognitive impairment
had decreased ALFF values in the left IFG [67, 68]. Agreeing
with these studies, the present study demonstrated decreased
fALFF values in the right IFG in the PSD patients compared
with the PSND patients and NCs, whereas the PSND patients
did not show significant GMV changes in this region com-
pared with the NCs. This suggests that the functional alter-
ations in the right IFG could be a related biomarker of
dysphagia patients [51]. Notably, the stroke patients in these
studies did not have cognitive dysfunction, implying that
GMV decreases in these two regions may be related to impair-
ments in attentional and executive control in stroke patients
[52, 53]. Consistently, the present study also found that PSND
patients had a smaller GMV than NCs in the left mPFC and
SFG. Hence, we speculate that reduced GMV in the left mPFC
and SFG are correlated with both stroke and dementia, which
may help to further understand the neural mechanisms under-
lying PSD.

Furthermore, the cerebellum not only is involved in
motor function [54, 55] but also acts as a general modulator
due to the presence of cerebellar activations in higher cogni-
tive functions [56]. Previous studies have found significant
reductions in GMV in the right cerebellar region in patients
with subcortical vascular dementia [57] and in left cerebellar
subfields in remitted major depression patients with persis-
tent cognitive deficits [58]. Similar results were also observed

Table 4: Brain regions showing significant differences in GMV and fALFF values among the PSND, PSD, and NC groups.

| Region                        | Hemisphere | X   | Y   | Z   | Cluster size | F value |
|-------------------------------|------------|-----|-----|-----|--------------|---------|
| GMV                           |            |     |     |     |              |         |
| Cerebellum posterior lobe     | Left       | -12 | -64.5 | -36 | 417          | 20.85   |
| Medial prefrontal cortex      | Left       | -3  | 70.5 | -9  | 711          | 24.57   |
| Superior frontal gyrus       | Left       | -22.5 | 28.5 | 60  | 511          | 16.01   |
| Superior temporal gyrus      | Right      | 60  | -24  | 21  | 633          | 14.91   |
| Inferior frontal gyrus       | Right      | 45  | 3    | 48  | 138          | 11.16   |
| fALFF                         |            |     |     |     |              |         |
| Inferior frontal gyrus       | Right      | 45  | 3    | 48  | 138          | 11.16   |

GMV: gray matter volume; fALFF: fractional amplitude of low-frequency fluctuation; NC: normal control; PSND: poststroke nondemented; PSD: poststroke demented.

Figure 3: The differences in GMV and fALFF values among the PSND, PSD, and NC groups. GMV: gray matter volume; fALFF: fractional amplitude of low-frequency fluctuation; CPL: left cerebellum posterior lobe; MPFC: left medial prefrontal cortex; SFG: left superior frontal gyrus; STG: right superior temporal gyrus; IGF: right inferior frontal gyrus. *: represents p < 0.05, **: p < 0.01, and ***: p < 0.001, respectively.
dementia in PSD patients. Inspired by all the findings, we speculate that exploring the specific structural and functional alterations in the right STG and IFG might facilitate a deeper understanding of the pathological mechanisms underlying PSD.

4.3. Clinical Implications of the Structural Alterations. Several studies have focused on the relationships between structural alterations in the mPFC/STG and cognitive function. For example, Bhalsing et al. demonstrated a positive correlation between GMV in the right mPFC and visual memory in patients with cognitive impairments [39]. Vidoni and colleagues reported that poor performance on cognitive measures was associated with lower GMV in the mPFC in subjects with early-stage AD [69]. Tong et al. found a significant positive correlation between cognitive maturity and GMV in the STG in young normal participants with relatively low cognitive maturity [70]. In addition, Ren et al. showed significant positive correlations between gray matter

| Variables | AUC   | SE    | p value | CI               |
|-----------|-------|-------|---------|------------------|
| CPL_L     | 0.804 | 0.066 | 0.001   | 0.675-0.933      |
| mPFC_L    | 0.531 | 0.093 | 0.724   | 0.350-0.713      |
| SFG_L     | 0.502 | 0.092 | 0.981   | 0.322-0.682      |
| STG_R     | 0.783 | 0.071 | 0.001   | 0.644-0.923      |
| IFG_R     | 0.717 | 0.077 | 0.014   | 0.565-0.868      |

AUC: area under the curve; SE: standard error; CI: confidence interval; CPL_L: left cerebellum posterior lobe; mPFC_L: left medial prefrontal cortex; SFG_L: left superior frontal gyrus; STG_R: right superior temporal gyrus; IFG_R: right inferior frontal gyrus.

Figure 4: Correlations between clinical cognitive assessments and GMV in the mPFC_L (a) and STG_R (b) in different groups. GMV: gray matter volume; miniCog2: Mini-Cog assessment at the third month; MMSE2: Mini-Mental State Examination assessment at the third month; mPFC_L: left medial prefrontal cortex; STG_R: right superior temporal gyrus.

Figure 5: The receiver operating characteristic (ROC) curves for using GMV/fALFF values for the classification of PSND versus PSD patients. Specifically, the AUC in the left cerebellum posterior lobe, left medial prefrontal cortex, left superior frontal gyrus, right superior temporal gyrus, and right inferior frontal gyrus are 0.804, 0.531, 0.502, 0.783, and 0.717, respectively. AUC: area under the curve; fALFF: fractional amplitude of low-frequency fluctuation; CPL_L: left cerebellum posterior lobe; mPFC_L: left medial prefrontal cortex; SFG_L: left superior frontal gyrus; STG_R: right superior temporal gyrus; IFG_R: right inferior frontal gyrus.
density in the left STG and accuracy of object working memory in healthy college students [71]. Similarly, the present study found significant positive correlations between GMV in the left mPFC and Mini-Cog scores at the third month in the PSND group and between GMV in the right STG and MMSE scores at the third month in the PSND group. Hence, we speculate that GMV reductions in the left mPFC and right STG may serve as a biomarker to predict cognitive function in poststroke patients. Meanwhile, using ROC analysis, the present study indicated that GMV in the left CPL has the best performance to discriminate PSD patients from PSND patients among all features. Consistently, previous studies found that structural alterations in cerebellar regions could distinguish dementia with Lewy bodies and Alzheimer’s disease (AD) [72] and could discriminate AD patients from non-AD patients [73]. Therefore, decreased GMV in the CPL may be a prospective indicator to identify dementia among patients after stroke.

4.4. Limitations. Several limitations in the present study should be noted. First, the sample size was relatively small, and a larger sample size would be necessary to confirm our findings. Second, the stroke patients recruited in the present study included cortical and subcortical lesions in the bilateral hemispheres. Although we controlled for the lesions in the statistical analysis, they may still have had a certain impact on the results. In the future, we need to explore the alterations in GMV and fALFF values in PSD patients with unilateral lesions. Third, the current study was cross-sectional; therefore, we were unable to capture dynamic abnormalities in brain structure and function in PSD patients. A longitudinal study in the future may be effective in resolving this problem.

5. Conclusion

In summary, the present study was the first to use multimodal MRI data to detect alterations in GMV and fALFF in patients with PSD and found that PSD patients showed dementia-related GMV reductions in the left CPL and right STG and a decrease in fALFF in the right IFG. Moreover, GMV in the left mPFC showed a significant positive correlation with Mini-Cog scores in PSD patients, and GMV in the left CPL could effectively distinguish PSD from PSND patients. Taken together, these findings could provide new evidence to understand the neurophysiological mechanisms underlying PSD, which may promote the development of a theoretical basis for clinical diagnosis.

Data Availability

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

Conflicts of Interest

The authors declare that there are no conflicts of interest regarding the publication of this article.

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