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Original Research Article

Distinctive and Pervasive Alterations of Functional Brain Networks in Cerebral Small Vessel Disease with and without Cognitive Impairment

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Keywords
Cerebral small vessel disease · Cognitive impairment · Frontoparietal control network · Functional connectivity · White matter hyperintensities

Abstract
Objective: To explore the within- and between-network patterns of the default mode network (DMN), the frontoparietal control network (FPCN), and the dorsal attention network (DAN) in cerebral small vessel disease (CSVD) with and without cognitive impairment (CI). ***Methods:*** Twenty CSVD with CI subjects, 21 CSVD without CI subjects, and 25 healthy elderly controls were recruited. The within- and between-network patterns of the networks were identified based on resting-state functional magnetic resonance imaging data. ***Results:*** Compared with the control group, both the CSVD with CI group and the CSVD without CI group displayed decreased within-network function of the DMN and lower negative connectivity between the DMN and other networks (i.e., DMN and DAN, DMN and FPCN), whereas the CSVD with CI group additionally showed within- and between-network alterations of the FPCN (i.e., increased within-network function of the FPCN and lower negative connectivity between the FPCN and the DMN). Furthermore, these alterations of the FPCN were correlated with the cognitive function of CSVD subjects. Interestingly, the between-network connectivity of the FPCN and the DMN was negatively correlated with deep white matter hyperintensities (DWMH) volume in CSVD subjects. ***Conclusion:*** These findings suggest that cognitive alterations of CSVD subjects may be mainly regulated by the FPCN that correlates with DWMH burden, and shed light on the investigation of surrogate markers of CSVD.

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Introduction

Cerebral small vessel disease (CSVD) causes approximately 10–30% of ischemic strokes worldwide [1] and is a leading cause of vascular cognitive impairment (CI), a condition encompassing vascular dementia and mild CI caused by cerebrovascular disease [2]. CI caused by CSVD mainly involves executive function, information processing speed, and attention [3]. Early identification of the CI due to CSVD is of vital importance since managing vascular risk factors, including hypertension, smoking, diabetes, and hyperlipidemia, in a timely manner may prevent the development and progression of CI [4].

CSVD is often characterized radiologically by subcortical/lacunar infarcts and diffuse white matter hyperintensities (WMH) in periventricular and deep white matter regions [5]. Novel magnetic resonance imaging (MRI) techniques have received increasing attention in the investigation of mechanisms underlying CSVD and surrogate markers related to the progression of CSVD. Using the resting-state functional MRI (fMRI) technology, a series of resting-state networks have been defined on the basis of the temporal correlations among intrinsic fluctuations of blood oxygen level-dependent signals across functionally related areas, also known as functional connectivity (FC) [6]. fMRI studies of CSVD with CI have revealed specific distributions of FC alterations. For example, compared with healthy subjects, CSVD with CI subjects displayed lower FC of the default mode network (DMN) with the anterior cingulate cortex, temporal regions, and frontal regions [7, 8]. The FC of the medial prefrontal cortex with the supplementary motor area and anterior cingulate cortex was also decreased in CSVD with CI subjects [9]. A study of subcortical vascular CI investigated the low-frequency oscillation amplitudes in the DMN and found that the anterior portion of the DMN (e.g., the medial prefrontal cortex) displayed lower low-frequency oscillation amplitudes, while the posterior cingulate cortex (PCC) displayed higher low-frequency oscillation amplitudes [10]. Taken together, the connectivity between posterior and anterior regions within the DMN is disrupted in CSVD with CI subjects.

The maintenance of brain function relies on multiple networks that connect and interact with each other to serve different functions [11]. For example, DMN shows greater activity in the task-free state and is mainly related to internally directed cognitions [12], whereas the dorsal attention network (DAN) displays activation during performing tasks and supports external attention [13]. The two networks are anticorrelated with each other in the brain activity. On the other hand, the frontoparietal control network (FPCN) is considered to flexibly support both the DMN and the DAN according to task demands, suggesting a "regulating" role [14, 15]. Thus, the disruption of a single network may confer to the impairment of internetwork connectivity. Interestingly, all the three functional networks are related to executive function and attention impairments commonly involved in CSVD [16–18]. While the disrupted DMN pattern has been detected in CSVD, the DAN and the FPCN have been rarely studied in CSVD. The investigation of intra- and internetwork FC of these networks in the context of CI may contribute to understanding the neurological mechanisms underlying CI in CSVD.

In the present study, CSVD with CI subjects, CSVD without CI subjects, and healthy control subjects underwent multimodal MRI scans and neuropsychological tests. The intra- and internetwork FC of the DMN, DAN, and FPCN were identified in each subject. The association between FC alterations and the volume of WMH was also explored. WMH is an established radiological marker of CSVD and one of the primary pathologies in subcortical vascular CI [5]. We hypothesized that both intra- and internetwork FC patterns of functional networks were impaired in CSVD subjects, and that CSVD with CI subjects would additionally display FC alterations corresponding to CI. Thus, the present study aimed to (1) analyze the intra- and internetwork FC patterns of the resting-state networks in CSVD with and without CI subjects, (2) explore the behavioral significance of FC alterations in CSVD subjects, and (3) determine the association of FC alterations with WMH volume in CSVD subjects.

Subjects and Methods

Participants

Forty-one CSVD subjects and 25 healthy subjects were recruited at the Drum Tower Hospital, Nanjing University Medical School. All participants underwent multimodal MRI scans and a standardized diagnostic evaluation, including medical history, demographic information, and an examination of mental and neurological status. According to the status of global cognitive function, CSVD subjects were further divided into a CSVD with CI group (n = 20) and a CSVD without CI group (n = 21).

Neuropsychological Assessments

Global cognitive function was measured by Mini-Mental State Examination (MMSE) and Montreal Cognitive Assessment (MoCA). CSVD subjects with MoCA scores lower than education-adjusted norms (the cutoff was <26 for >12 years of education, ≤24 for 7–12 years of education, and ≤19 for 1–6 years of education) were defined as the CSVD with CI group, and the other CSVD subjects were defined as the CSVD without CI group. All subjects underwent a neuropsychological battery test (see online supplementary material; for all online suppl. material, see www.karger.com/doi/10.1159/000496455).

Inclusion and Exclusion Criteria

According to prior studies [19, 20], the inclusion criteria for CSVD subjects were as follows: (1) age >50 years, (2) possible subjective complaints such as dizziness, postural instability, depression, or memory impairment, and (3) presence of lacunes or/and WMH on MRI images. The definitions and imaging standards for lacunes and WMH were according to the Standards for Reporting Vascular Changes on Neuroimaging (STRIVE) criteria proposed by Wardlaw et al. [21] and others [22]. Lacunes were defined as ovoid or round, subcortical, hypointense cavities with a diameter between 3 and 15 mm on T1 and FLAIR images. WMH were described as hyperintensities on FLAIR images, without cavitation.

The exclusion criteria were as follows: (1) intracranial hemorrhage, (2) history of ischemic stroke with infarct >15 mm in diameter or cardiogenic cerebral infarction, (3) coronary atherosclerosis, heart disease, or carotid artery stenosis (>75%), (4) other neurological disorders, such as parkinsonism/Parkinson disease, Alzheimer disease, multiple sclerosis, and epilepsy, (5) systemic disease, such as shock, cancer, thyroid dysfunction, and anemia, (6) prominent decline of vision or audition, and (7) MRI contraindications.

MRI Procedures

All subjects were scanned using a 3-Tesla magnetic resonance scanner (Achieva 3.0 T Ingenia; Philips Medical Systems, Eindhoven, The Netherlands) with a 32-channel head coil at the Drum Tower Hospital, Nanjing University Medical School (see online suppl. material).

Resting-State Functional Image Preprocessing

The fMRI data were analyzed using a toolbox for Data Processing & Analysis for Brain Imaging (DPABI) v2.3 (http://rfmri.org/DPABI) (see online suppl. material).

Resting-State Networks Definition

Seed-based FC analysis was used to construct resting-state networks. Six-millimeter radius spheres centered at the PCC (Montreal Neurological Institute [MNI] space: –2, –45, 34) [23], the bilateral dorsolateral prefrontal cortex (DLPFC) (MNI space: –42, 34, 20/44, 36, 20) [24], and the bilateral intraparietal sulcus (IPS) (MNI space: –25, –53, 52/25, –57, 52) [24, 25] served as seed regions for the DMN, the bilateral FPCN, and the bilateral DAN, respectively. These seed regions have been widely used to identify the corresponding networks in prior studies (see online suppl. material).

WMH Segmentation and Quantification

See online supplementary material.

Grey Matter Volume Assessment

Since grey matter atrophy has been related to cognitive function and intrinsic FC [26], the present study also assessed grey matter volume in each subject. Grey matter volume assessment was performed using the VBM8 toolbox for SPM12 (see online suppl. material).

Statistical Analysis

Demographic and Neuropsychological Data. One-way analysis of variance and χ^2 test were applied in the comparison of age and sex, respectively, with significance at $p < 0.05$. Due to the nonnormal distributions of other demographic and neuropsychological data, the Kruskal-Wallis test was applied in the other comparisons, with significance at $p < 0.05$. All statistical procedures employed the SPSS 19.0 software (SPSS, Inc., Chicago, IL, USA).

FC Analysis. The FC between a seed and each voxel within the corresponding network mask was defined as the intranetwork FC. The FC between a seed and each voxel within another network mask, e.g., FC between PCC (the seed for the DMN) and each voxel within the FPCN or the DAN, was defined as the internetwork FC. This method contributes to identifying the functional differences of core regions in each network [27]. The between-group FC differences were analyzed by using a voxel-wise one-way analysis of covariance, controlling for age, sex, and years of education (using DPABI v2.3). The thresholds were set at a corrected $p < 0.05$, determined by Monte Carlo simulation for multiple comparisons (voxel-wise $p < 0.05$, FWHM = 6 mm, cluster size >2,538 mm^3). Then, the mean FC strength in each significant cluster was extracted in each subject. A post hoc *t* test was performed to detect the detailed group FC difference in each region using the SPSS 19.0 software. Finally, correlation analyses were performed between the mean FC strength in each significant cluster and the cognitive test scores in CSVD subjects, controlling for age, sex, and years of education. If both CSVD groups displayed significant differences in FC compared with the control group and no significant difference in FC was shown between the two CSVD groups, correlation analyses were performed in all CSVD subjects. If only the CSVD with CI or CSVD without CI group displayed significant differences in FC compared with the control group, correlation analyses were performed only in the CSVD with CI or CSVD without CI group. The association of FC strength with the WMH volume, including the total WMH, periventricular white matter hyperintensities (PWMH), and deep WMH (DWMH) volume, was also explored in subjects with CSVD. Analyses of covariance were conducted to estimate the effect size (partial η^2). To improve the normal distribution of the data, a $\log_{10}$ transformation was performed on the WMH volume data and Trail Making Test A (TMT-A) data. All statistical procedures for correlation analysis employed the SPSS 19.0 software with significance at $p < 0.05$.

Results

Demographic, Neuropsychological, and WMH Data

As shown in Table 1, no significant differences in age, years of education, or sex were shown between groups. The CSVD with CI group displayed lower MoCA scores than both the control group and the CSVD without CI group. Compared with the control group, both CSVD groups displayed poorer performances in the TMT-B test reflecting executive function. Furthermore, both CSVD groups displayed greater total WMH and PWMH volume than the control group, and no significant difference in grey matter volume was shown between groups.

Identification of Functional Networks

The spatial maps of the DMN, FPCN, and DAN were shown in Figure 1. Consistent with a previous study [28], the DMN consisted of the bilateral PCC, the medial prefrontal cortex, the inferior parietal lobule, the lateral temporal cortex, and the hippocampus. The FPCN consisted of the bilateral DLPFC, the dorsomedial prefrontal cortex, and the lateral parietal cortex, and the DAN encompassed the bilateral IPS, the frontal eye fields, and the middle temporal area, which were also consistent with previous studies [29, 30].

FC Data: Intranetwork FC

DMN. As shown in Figures 2a and b, compared with the control group, both the CSVD without CI group and the CSVD with CI group showed lower DMN FC with the right thalamus, hippocampus, and precuneus ($p = 0.014$ and $p < 0.001$, respectively).

FPCN. As shown in Figures 2c and d, compared with the control group, the CSVD with CI group showed higher FPCN FC with the right inferior parietal lobule ($p = 0.010$), whereas the CSVD without CI group showed no significant difference in FPCN FC ($p = 0.240$).

DAN. No significant difference in DAN FC was found between groups.

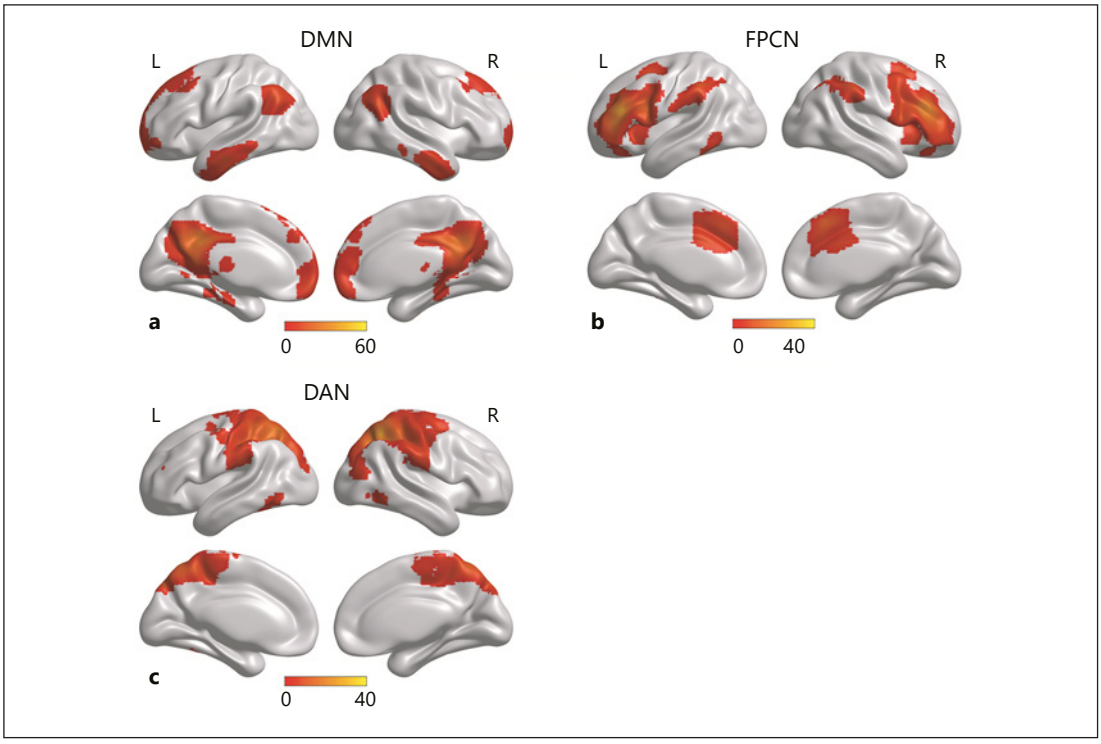

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Fig. 1. The spatial maps of the DMN (**a**), FPCN (**b**), and DAN (**c**). The thresholds were set at a corrected $p < 0.001$, determined by Monte Carlo simulation for multiple comparisons (voxel-wise $p < 0.001$, FWHM = 6 mm, cluster size >513 mm^3). The color bars are presented with t values. DAN, dorsal attention network; DMN, default mode network; FPCN, frontoparietal control network; L, left; R, right.

Table 1. Demographic, neuropsychological, and WMH data

Items	Control (n = 25)	CSVD without CI (n = 21)	CSVD with CI (n = 20)	F or χ^2	p value
Age, years	62.48±7.37	64.57±10.85	66.5±7.88	1.178	0.315
Education, years	10.48±4.25	10.48±3.61	13.05±3.76	–	0.064
Sex, male:female	13:12	10:11	10:10	0.088	0.957
MMSE	28.56±1.39	28.48±1.33	28.10±1.33	–	0.409
MoCA	26.12±2.89	25.57±1.86	22.15±2.89[a,b]	–	<0.001
TMT-A, s	52.09±18.01	51.55±19.13	66.00±20.94	–	0.117
TMT-B, s	76.60±24.75	119.95±69.22[a]	132.53±72.14[a]	–	0.002
Stroop-A, s	15.74±4.78	18.34±7.04	20.72±6.94	–	0.054
Stroop-B, s	19.70±7.70	21.21±7.02	23.83±7.83	–	0.097
Stroop-C, s	29.10±7.13	33.84±11.86	34.61±10.44	–	0.248
Total WMH volume, mL	0.58±0.51	3.18±2.99[a]	3.37±4.08[a]	–	0.001
PWMH volume, mL	0.40±0.39	2.22±2.16[a]	2.68±3.39[a]	–	0.001
DWMH volume, mL	0.18±0.27	0.96±1.86	0.69±0.85	–	0.138
Grey matter volume, mL	527.75±41.49	534.37±37.05	540.23±51.03	–	0.63

Values are presented as mean ± stand deviation. One-way analysis of variance and χ^2 test were applied in the comparison of age and sex, respectively. The Kruskal-Wallis test was applied in the other comparisons. CI, cognitive impairment; CSVD, cerebral small vessel disease; DWMH, deep white matter hyperintensities; MMSE, Mini-Mental State Examination; MoCA, Montreal Cognitive Assessment; PWMH, periventricular white matter hyperintensities; TMT-A, Trail Making Test A; TMT-B, Trail Making Test B; WMH, white matter hyperintensities. [a] $p < 0.05$, differs from the control group. [b] $p < 0.05$, differs from the CSVD without CI group.

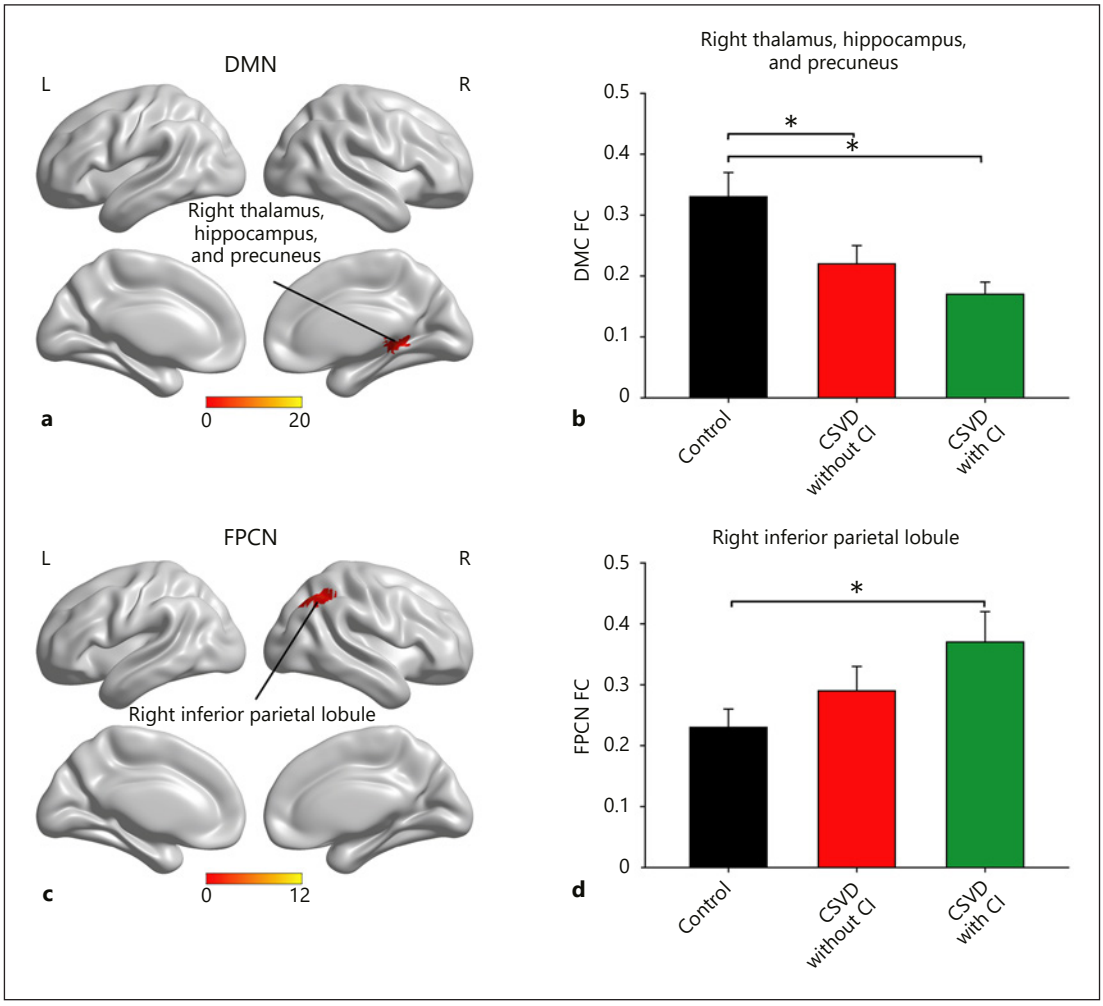

Fig. 2. The intranetwork FC differences between groups. **a** The group difference of DMN FC was shown in the right thalamus, hippocampus, and precuneus. **b** Compared with the control group, both CSVD groups showed lower DMN FC. **c** The group difference of FPCN FC was shown in the right inferior parietal lobule. **d** Compared with the control group, the CSVD with CI group showed higher FPCN FC. The thresholds were set at a corrected $p < 0.05$, determined by Monte Carlo simulation for multiple comparisons (voxel-wise $p < 0.05$, FWHM = 6 mm, cluster size >2,538 mm^3). The color bars are presented with F values. * $p < 0.05$. CI, cognitive impairment; CSVD, cerebral small vessel disease; DMN, default mode network; FC, functional connectivity; FPCN, frontoparietal control network; L, left; R, right.

FC Data: Internetwork FC

FC between the PCC and the FPCN. As shown in Figures 3a and b, in the left precentral gyrus and bilateral middle cingulate gyri, both the CSVD without CI group and the CSVD with CI group displayed lower negative FC between the PCC and the FPCN than the control group ($p = 0.001$ and $p = 0.004$, respectively).

FC between the PCC and the DAN. As shown in Figures 3c and d, in the bilateral paracentral lobule and precuneus, both the CSVD without CI group and the CSVD with CI group displayed lower FC between the PCC and the DAN than the control group ($p = 0.019$ and $p = 0.001$, respectively).

FC between the DLPFC and the DMN. As shown in Figures 3e and f, in the bilateral PCC and the right precuneus, the CSVD with CI group showed lower negative FC between the DLPFC

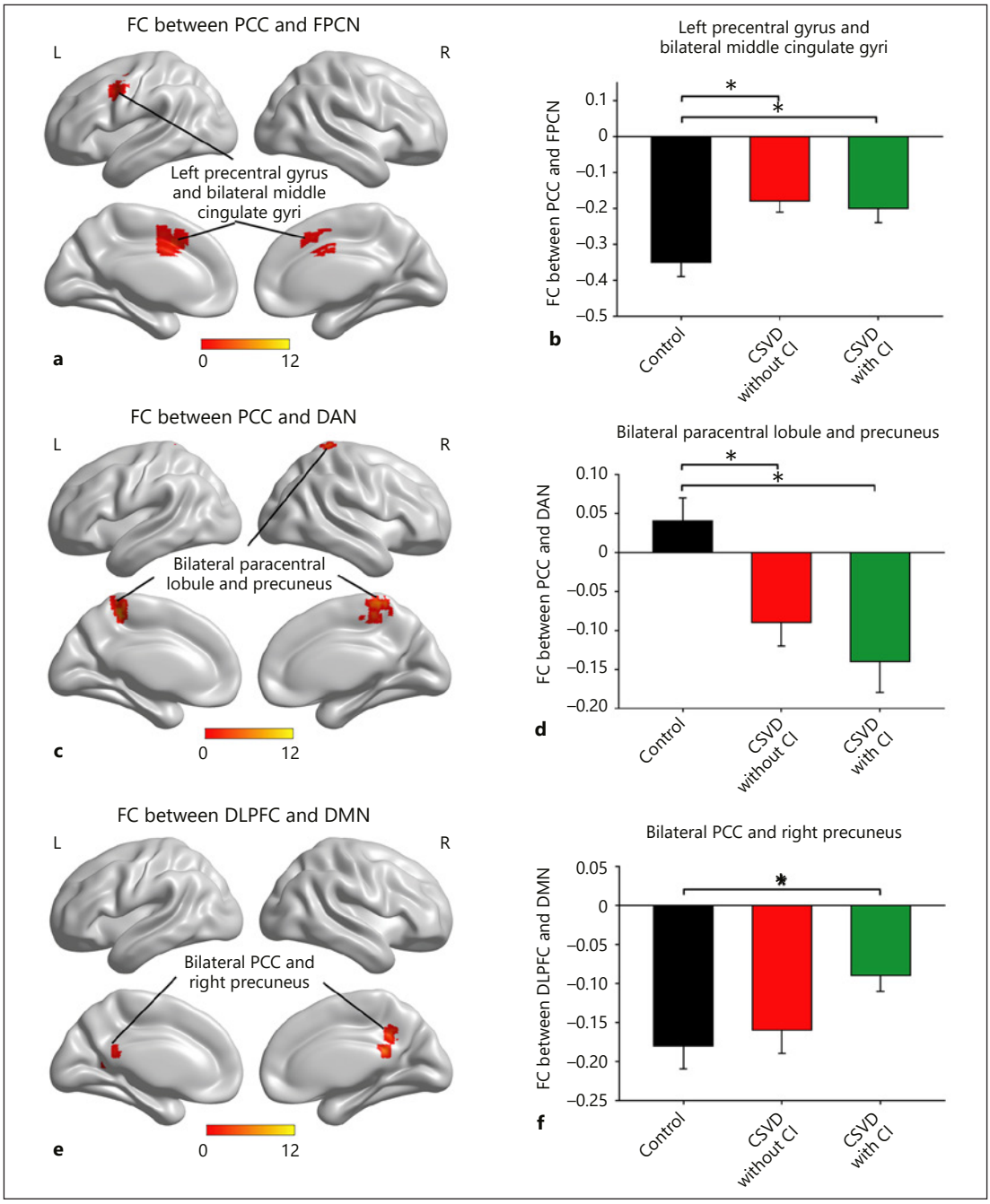

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Fig. 3. The internetwork FC differences between groups. **a** The group difference of internetwork FC between the PCC and the FPCN was shown in the left precentral gyrus and bilateral middle cingulate gyri. **b** Both CSVD groups displayed lower negative FC between the PCC and the FPCN than the control group. **c** The group difference of internetwork FC between the PCC and the DAN was shown in the bilateral paracentral lobule and precuneus. **d** Both CSVD groups displayed lower FC between the PCC and the DAN than the control group. **e** The group difference of internetwork FC between the DLPFC and the DMN was shown in the bilateral PCC and the right precuneus. **f** The CSVD with CI group showed lower negative FC between the DLPFC and the DMN than the control group. The thresholds were set at a corrected $p < 0.05$, determined by Monte Carlo simulation for multiple comparisons (voxel-wise $p < 0.05$, FWHM = 6 mm, cluster size >2,538 mm^3). The color bars are presented with F values. * $p < 0.05$. CI, cognitive impairment; CSVD, cerebral small vessel disease; DAN, dorsal attention network; DLPFC, dorsolateral prefrontal cortex; DMN, default mode network; FC, functional connectivity; FPCN, frontoparietal control network; L, left; PCC, posterior cingulate cortex; R, right.

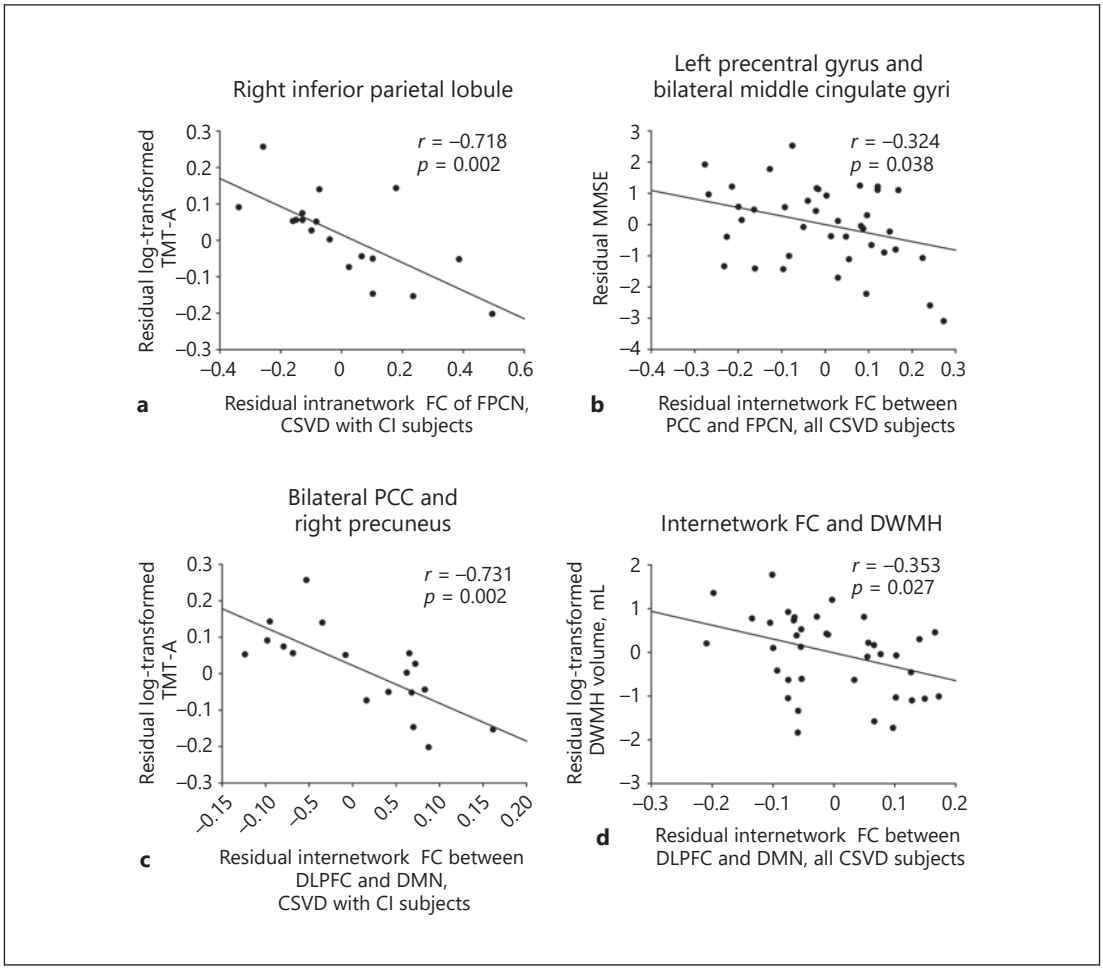

Fig. 4. Correlation analysis between FC and cognitive function and WMH volume. **a** The intranetwork FC of the FPCN with the right inferior parietal lobule was negatively correlated with TMT-A scores in the CSVD with CI group. **b** The internetwork FC between the PCC and the FPCN in the left precentral gyrus and bilateral middle cingulate gyri was negatively correlated with MMSE scores in CSVD subjects. **c** The internetwork FC between the DLPFC and the DMN in the bilateral PCC and right precuneus were negatively correlated with TMT-A scores in the CSVD with CI group. **d** The internetwork FC between the DLPFC and the DMN in the bilateral PCC and right precuneus was negatively correlated with DWMH volume in CSVD subjects. A $\log_{10}$ transformation was performed on the DWMH volume data and the TMT-A data to improve the normal distribution of the data. Correlation analyses were performed between the residuals of variables after regression on the nuisance variables (sex, age, and education years). CI, cognitive impairment; CSVD, cerebral small vessel disease; DLPFC, dorsolateral prefrontal cortex; DMN, default mode network; DWMH, deep white matter hyperintensities; FC, functional connectivity; FPCN, frontoparietal control network; L, left; MMSE, Mini-Mental State Examination; PCC, posterior cingulate cortex; R, right; TMT-A, Trail Making Test A; WMH, white matter hyperintensities.

and the DMN than the control group ($p = 0.018$), whereas the CSVD without CI group did not ($p = 0.565$).

On the other hand, no significant differences of other internetwork FC, including FC between the DLPFC and the DAN, FC between the IPS and the DMN, and FC between the IPS and the FPCN, were shown between groups. The detailed coordinate information of the above clusters is available in online supplementary Table 1.

Behavioral Significance of FC Alterations

As shown in Figures 4a and c, in the CSVD with CI group, both the intranetwork FC of the FPCN with the right inferior parietal lobule and the internetwork FC between the DLPFC and the DMN in the bilateral PCC and the right precuneus were negatively correlated with TMT-A time (r = –0.718, p = 0.002 and r = –0.731, p = 0.002, respectively). On the other hand, the internetwork FC between the PCC and the FPCN in the left precentral gyrus and the bilateral middle cingulate gyri was negatively correlated with MMSE scores in CSVD subjects (r = –0.324, p = 0.038) (Fig. 4b).

Correlation Analysis between FC Alterations and WMH Volume

As shown in Figure 4d, in CSVD subjects, the internetwork FC between the DLPFC and the DMN in the bilateral PCC and the right precuneus was negatively correlated with DWMH volume (r = –0.353, p = 0.027) rather than total WMH volume or PWMH volume.

Discussion

The present study is the first to explore the functional architectures both within and between resting-state functional networks in CSVD subjects. Both CSVD with CI subjects and CSVD without CI subjects displayed altered intra- and internetwork FC patterns, whereas CSVD with CI subjects additionally showed FPCN-related intra- and internetwork FC alterations that correlated with cognitive performance and WMH burden. The results suggest a distinctive pattern of aberrant brain functional organization underlying the CI in CSVD.

A strength of the present study is that besides CSVD with CI subjects, both CSVD without CI subjects and healthy subjects were recruited, whereas the aforementioned fMRI studies of CSVD did not recruit healthy subjects [7] or CSVD without CI subjects [8–10]. By comparing the FC data between the three groups, the present study could contribute to a more comprehensive understanding of functional network patterns in each stage of CSVD. Compared with the control group, both the CSVD with CI group and the CSVD without CI group displayed decreased DMN FC with the right thalamus, hippocampus, and precuneus. The CSVD with CI group had slightly lower FC with these regions than the CSVD without CI group, suggesting that lower DMN FC with these regions might be related to CI in CSVD subjects. Besides the seed region (PCC), most of these regions belong to the limbic system, which plays a major role in personality, cognition, emotion, and navigation. Disrupted connections of the limbic system have been related to many neuropsychiatric disorders, including amnesia, mild CI, dementia, depression, autism, and schizophrenia [31]. The present findings suggest that the disrupted FC between regions within the limbic system is also related to CSVD and the CI in CSVD.

Notably, compared with the control group, the CSVD with CI group displayed increased FPCN FC with the right inferior parietal lobule, and the CSVD without CI group showed slightly but not significantly increased FPCN FC. A previous study also found that CSVD affected the connectivity in the FPCN, and the connectivity changes were correlated with cognitive performance. However, the connectivity in the FPCN was decreased in CSVD subjects, as shown by the study. The divergence may come from the distinct methodologies. Numerous fMRI studies have shown increased fMRI activity or FC in frontoparietal regions across various CI or cognitive tasks [32–35]. The FPCN contributes to the regulation of higher-order interaction between mental representations in humans, supporting multiple higher cognitive functions [36]. The FPCN serves as a flexible hub that could be protective against neuropsychiatric disorders; the capacity of the FPCN could be enhanced against harmful dysfunction [37]. In the present study, both the increased FPCN FC and the lower negative FC between the DLPFC and the DMN were negatively correlated with TMT-A time in the CSVD with CI group,

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suggesting a compensatory effect on the impairment of information processing speed. In other words, the FPCN-related FC alterations might reflect compensatory reallocation or recruitment of cognitive resources against the CI in CSVD. Furthermore, compared with the CSVD without CI group, the CSVD with CI group displayed slightly higher FPCN FC and lower negative FC between the DLPFC and the DMN, indicating that the FPCN-related FC alterations might be more significant with the onset of CI in CSVD subjects.

The investigation of intranetwork FC alterations may further the understanding of functional specialization, whereas the exploration of internetwork FC patterns could reveal the global integration of brain functions. Compared with the control group, both the CSVD with CI group and the CSVD without CI group displayed lower negative FC between the PCC and the FPCN and between the PCC and the DAN, and the CSVD with CI group also showed lower negative FC between the DLPFC and the DMN. The disrupted connectivity between the DMN, FPCN, and DAN suggested an imbalance or dysfunction between functional networks. Specifically, the DMN is commonly activated during the resting state, and task-positive networks (including the DAN and the FPCN) are commonly activated when performing tasks [30, 38]. The anticorrelations between the DMN and task-positive networks have been related to variability in behavioral performance [38]. In the present study, correlation analysis between internetwork FC and cognitive function showed that the internetwork FC between the PCC and the FPCN in the left precentral gyrus and bilateral middle cingulate gyri was negatively correlated with MMSE scores in the CSVD with CI group. This meant that lower negative internetwork FC between the PCC and the FPCN was associated with poor global function in the CSVD with CI group. Furthermore, the disrupted internetwork FC patterns mainly involved the FPCN and the DMN, and the intranetwork FC alterations were also shown in the FPCN and the DMN. Thus, the dysfunction and imbalance between the FPCN and the DMN were the main character of functional reorganization in CSVD with CI and affected the cognitive function in CSVD subjects.

WMH are strongly related to vascular risk factors and cerebrovascular disease and serve as one of the "classical" MRI markers of CSVD [39]. The present study found that the internetwork FC between the DLPFC and the DMN in the bilateral PCC and right precuneus was negatively correlated with DWMH volume in CSVD subjects; a greater DWMH volume was associated with lower FC between the DLPFC and the DMN. From the aspect of histopathologic correlates, DWMH is associated with ischemic tissue damages including patchy rarefaction of myelin and microcystic infarcts, whereas smooth PWMH mostly reflects nonischemic damages [40]. Thus, the disrupted functional communication between networks might be related to ischemic damages in CSVD. In fact, intact white matter integrity plays a major role in the synchronous activity and neural activation of functional networks [41, 42]. The association between internetwork FC and DWMH volume suggested that connectivity between functional networks could reflect the structural damages in CSVD and might have the potential to serve as a new marker of the disorder.

Some limitations should be addressed. First, the sample size was relatively small. Several subjects did not complete the whole neuropsychological battery test, conferring to a smaller sample size in the correlation analyses between FC and cognition. The results of FC analyses and correlation analyses were not corrected by the Bonferroni correction principle due to the small sample size and a large number of FC comparisons and correlation analyses. These findings should be validated in a larger population. Second, this is a correlational study that could not explore the cause and effect relationship among functional alterations, WMH burden, and CI. Also, the results might be affected by multiple confounding factors, e.g., mental status, medical history, and medication condition. Furthermore, the impact of other imaging markers of CSVD, including lacunes, cerebral microbleeds, and enlarged perivascular spaces, on functional networks and cognition was not analyzed. Future studies on the relationship

among these structural markers, functional networks, and cognition may further the understandings of mechanisms underlying the onset of CI in CSVD.

In conclusion, cognitive alterations of CSVD subjects may be mainly regulated by the FPCN, which highly correlates with DWMH burden. These findings provide novel insights into the functional alterations in CSVD and shed light on the investigation of surrogate markers of the disorder.

Statement of Ethics

This study was carried out in accordance with the recommendations of the Drum Tower Hospital Research Ethics Committee. The protocol was approved by the Drum Tower Hospital Research Ethics Committee. All subjects gave written informed consent in accordance with the Declaration of Helsinki.

Disclosure Statement

The authors have no conflict of interest to report.

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