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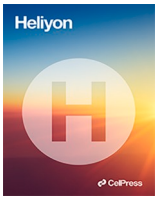

Research article

Dysfunction of the triple-network model is associated with cognitive impairment in patients with cerebral small vessel disease

Heng-Le Wei [a,1], Cunsheng Wei [b,1], Yu-Sheng Yu [a], Xiaorong Yu [b], Yuan Chen [b], Junrong Li [b], Hong Zhang [a,*], Xuemei Chen [b,**]

[a] *Department of Radiology, The Affiliated Jiangning Hospital of Nanjing Medical University, Nanjing 211100, Jiangsu, PR China*
[b] *Department of Neurology, The Affiliated Jiangning Hospital of Nanjing Medical University, Nanjing 211100, Jiangsu, PR China*

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ABSTRACT

Purpose: This study aimed to demonstrate the correlations between the altered functional connectivity patterns in the triple-network model and cognitive impairment in patients with cerebral small vascular disease (CSVD).

Methods: Resting-state functional magnetic resonance imaging data were obtained from 22 patients with CSVD and 20 healthy controls. The resting-state data were analyzed using independent component analysis and functional network connectivity (FNC) analysis to explore the functional alterations in the intrinsic triple-network model including the salience network (SN), default mode network (DMN), and central executive network (CEN), and their correlations with the cognitive deficits and clinical observations in the patients with CSVD.

Results: Compared to the healthy controls, the patients with CSVD exhibited increased connectivity patterns in the CEN-DMN and decreased connectivity patterns in the DMN-SN, CEN-SN, intra-SN, and intra-DMN. Significant negative correlations were detected between the intra-DMN connectivity pattern and the Montreal Cognitive Assessment (MoCA) total scores ($r = -0.460$, $p = 0.048$) and MoCA abstraction scores ($r = -0.565$, $p = 0.012$), and a positive correlation was determined between the intra-SN connectivity pattern and the MoCA abstraction scores ($r = 0.491$, $p = 0.033$).

Conclusions: Our study findings suggest that the functional alterations in the triple-network model are associated with the cognitive deficits in patients with CSVD and shed light on the importance of the triple-network model in the pathogenesis of CSVD.

Abbreviations: ACC, anterior cingulate cortex; CEN, central executive network; CMB, cerebral microbleed; CSVD, cerebral small vessel disease; dlPFC, dorsolateral prefrontal cortex; DMN, default mode network; FNC, functional network connectivity; ICA, independent component analysis; IC, independent components; IPL, inferior parietal lobule; MoCA, Montreal Cognitive Assessment; mPFC, medial prefrontal cortex; MRI, magnetic resonance imaging; PCC, posterior cingulate cortex; PVS, perivascular space; SN, salience network; SPL, superior parietal lobule; WMH, white matter hyperintensity.

* Corresponding author.
** Corresponding author.
E-mail addresses: jnyyfsk@126.com (H. Zhang), 13347808579@189.cn (X. Chen).
[1] Heng-Le Wei and Cunsheng Wei contributed equally to this work.

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1. Introduction

Cerebral small vessel disease (CSVD) is a common age-related disease leading to various clinical, imaging, and pathologic deficits caused by perforating cerebral small vessels, such as arterioles, venules, and capillaries [1]. As the aging population increases, the incidence of CSVD is also rising. Statistically, CSVD accounts for approximately 25 % of ischemic stroke and most intracerebral hemorrhage in older people worldwide [2,3]. It is characterized by multiple structural alterations visibly on brain magnetic resonance imaging (MRI) in older people, including but not limited to lacunar infarct (LI), white matter hyperintensity (WMH), cerebral microbleed (CMB), and enlarged perivascular space (PVS), which are considered the core neuroimaging findings of CSVD [1,4,5]. Of these, the prevalence rate of WMH is as high as 70 % in the Chinese population [6]. Moreover, cognitive decline is a major consequence of CSVD, resulting in impairments in executive function, processing speed, attention, and memory [7]. All these heterogenous syndromes not only disrupt normal cerebral blood flow and alter cerebral function, but also result in vascular cognitive deficits and dementia [8,9]. Patients may be detected with CSVD based on imaging signs during a general neurological examination, but they may be completely asymptomatic from a cognitive perspective. Therefore, the underlying neuromodulatory mechanisms involved in CSVD with cognitive impairment still require further elucidation.

In the last decade, neuroimaging technology has been used extensively to diagnose and identify CSVD in vivo, particularly MRI [10]. However, conventional MRI detects only significant structural lesions, which are downstream consequences [10,11]. The human brain is a complex patchwork of interconnected regions, each with its own specialized function. However, these regions do not work in isolation, but rather communicate and cooperate with each other through different functional networks. Functional MRI (fMRI) technology has received great attention and has become an important tool for reflecting functional change of cerebral intrinsic networks associated with the cognitive impairment in neurological diseases [12,13]. Recent fMRI studies have investigated the functional alterations in CSVD with a focus on some core brain regions, including the three major regulatory networks: the default mode network (DMN), salience network (SN), and central executive network (CEN) [14–16]. These networks are sets of brain regions that show synchronized activity at rest or during task performance, and reflect distinct cognitive processes or mental states [17,18].

The DMN mainly consists of the posterior cingulate cortex (PCC) and medial prefrontal cortex (mPFC) that are active when the brain is at rest and is shown to involve self-referential processing and memory retrieval [19,20]. The CEN, anchored in the dorsolateral frontoparietal cortex, is involved in higher-order cognitive processes, including working memory and executive control [21–23]. Moreover, the SN mainly locates in the anterior cingulate cortex (ACC) and anterior insula which are associated with detecting and responding to salient stimuli and responsible for switching between the DMN and the CEN [24]. These functional networks contribute to the triple-network model that offers a powerful perspective for investigating cognitive and affective dysfunction in psychiatric and neurological disorders [25]. The triple-network model proposes that the DMN and CEN are mutually inhibitory under the regulation of the SN, meaning that if a task activates one of these networks, the SN will suppress the activity of the other network. This ensures that the brain can switch and balance effectively between different cognitive states [26,27]. Although functional alterations of these networks in CSVD have been investigated independently, only a few studies have examined the functional alterations in the triple-network model in CSVD, which may underlie a potential correlation with CSVD-associated cognitive impairment [28,29]. Therefore, further research is warranted to address these research gaps.

In this study, the Montreal Cognitive Assessment (MoCA) scale is chosen as the cognitive assessment tool due to several reasons. The MoCA scale is widely used as a reliable and valid tool with multiple cognitive domains, allowing for a more comprehensive assessment of cognitive function in patients with CSVD. Moreover, its brevity and ease of administration make it suitable for use in clinical practice [30]. By utilizing this scale, we aimed to obtain a reliable and accurate measurement of cognitive impairment in patients with CSVD. Therefore, we proposed the following hypotheses: (1) patients with CSVD have abnormal resting-state functional alterations in the triple-network model and (2) the functional alterations in these networks have significant associations with CSVD-related cognitive deficits.

2. Methods

2.1. Participants

This study included consecutive patients with CSVD who were hospitalized in the Department of Neurology from November 2020 to June 2022. The inclusion criteria were as follows: (1) age equal to or greater than 45 years old; (2) MRI showing significant imaging characteristics of CSVD, including WMH, LIs, CMB, PVS, or cerebral atrophy; (3) with or without dizziness, memory loss, or gait instability. Patients who met the following exclusion criteria were excluded: (1) cerebral cortical or watershed infarction, or non-lacunar infarction with diameter >20 mm in the cortex; (2) white matter lesions caused by non-vascular factors; (3) acute cerebral hemorrhage; (4) Alzheimer's disease (AD), Parkinson's disease, epilepsy, multiple sclerosis, central nervous system infection, craniocerebral trauma, intracranial tumor, or other diseases causing cognitive impairment; (5) obvious mental illness or alcoholism; or (6) any other severe systemic disease. Participants were classified according to their educational level using the following five categories: (1) illiterate, (2) primary school, (3) junior high school, (4) senior high school, and (5) university. Each participant provided signed informed consent before enrollment. This study was approved by the Ethics Committee of Jiangning Hospital, Nanjing, Jiangsu Province, China (2016YFC1300500).

2.2. MoCA scale assessment

The MoCA scale is a valid tool for evaluating cognitive function, with a maximum score of 30 points [30]. All participants were administered a Chinese version of the MoCA (MoCA Beijing) [31]. The MoCA scale assesses multiple cognitive dimensions including visuospatial/executive function, naming, attention, language, abstraction, delayed recall and orientation. The test duration is approximately 10 min, and a score below 26 indicates the presence of cognitive impairment and dementia.

2.3. Acquisition of fMRI images

Resting-state fMRI data were obtained using a 3.0 T scanner (SIEMENS MAGNETOM Vida) with a 64-channel receiver array head coil. Participants were asked to lie quietly with their eyes closed and not move their heads. High resolution T1-weighted three-dimensional structural images were acquired utilizing a sagittal magnetization-prepared rapid gradient echo sequence consisting of the following parameters: repetition time (TR) = 5000 ms, echo time (TE) = 2.98 ms, flip angle (FA) = 9°, matrix size = 256 × 256, field of view (FOV) = 230 × 230 mm, slice thickness = 1.0 mm, and slice number = 176. The structural sequence took 8 min and 22 s. Functional images were obtained axially using an echo-planar imaging sequence with the following parameters: TR = 2000 ms, TE = 30 ms, slice number = 36, slice thickness = 4 mm, gap = 0 mm, FOV = 230 mm × 230 mm, matrix size = 64 × 64, FA = 90°, and volumes = 230. The scanning plane was parallel to the anterior commissure-posterior commissure line, and the functional data were collected using a parallel imaging acquisition approach with an acceleration factor of two. The functional sequence took 7 min and 52 s.

2.4. Preprocessing of fMRI data

Image preprocessing was performed using the Resting-state fMRI Data Analysis Toolkit plus v1.24 (http://restfmri.net/forum/). The first 10 time points were discarded to avoid signal instability during the initiation of the examination. The remaining 220 vol were then processed as follows: slice-timing adjustment, realignment, and spatial normalization into Montreal Neurological Institute space (resampling voxel size = 3 × 3 × 3 mm^3), followed by smoothing with a 6-mm Gaussian kernel. The data of only those participants who exhibited a head motion of less than 2.0 mm displacement or a 2.0° rotation in any direction were included. The mean frame-wise displacement (FD) was calculated to represent instantaneous head motion [32].

2.5. Group independent component analysis (ICA) of fMRI data

The fMRI data were parcellated using the Group ICA of fMRI Toolbox (GIFT 4.0b) (http://icatb.sourceforge.net/) to extract independent intrinsic component networks [33,34]. The preprocessed data were decomposed via the minimum description length criteria with the first 120 spatial independent components (ICs) selected for dimension reduction, which preserved more than 99 % of the variance [35]. Using the Infomax algorithm, the data were then concatenated and reduced by principal component analysis to improve the reliability of the decomposition and retain 100 group-level ICs. Subsequently, the GICA-3 back-reconstruction step was performed to separate single-subject components from the aggregate components. Finally, the spatial component maps were visualized.

Additionally, the static functional network connectivity (FNC) analysis was conducted to determine the relationship between the

Table 1
Demographic and clinical data of patients with CSVD and healthy controls.

	Patients with CSVD (n = 22)	Healthy controls (n = 20)	t/χ^2	*p* value
Age (years)	63.182 (7.992)[a]	59.700 (4.378)[a]	1.772	0.086
Sex (male/female)	13/9	10/10	0.349	0.554
Education level			3.566	0.488
illiterate	3	1		
primary school	7	6		
junior high school	8	8		
senior high school	1	4		
university	3	1		
MoCA total scores	23.364 (4.776)[a]	/	/	/
visuospatial/executive	4.000 (2.000, 5.000)[b]	/	/	/
naming	3.000 (2.000, 3.000)[b]	/	/	/
attention	1.500 (0.000, 4.000)[b]	/	/	/
language	6.000 (5.000, 6.000)[b]	/	/	/
abstraction	3.000 (2.000, 3.000)[b]	/	/	/
delayed recall	2.000 (1.000, 2.000)[b]	/	/	/
orientation	6.000 (6.000, 6.000)[b]	/	/	/

CSVD: cerebral small vascular disease; MoCA: Montreal Cognitive Assessment.
[a] normally distributed data, mean (standard deviation).
[b] non-normally distributed data, median (interquartile range).

different intrinsic ICs of the triple-network model. A band-pass filter (0.01–0.15 Hz) was applied to reduce the potential influence of low-and high-frequency noise on the time course. Pearson correlation coefficient was performed between each paired ICs to determine the pairwise FNC patterns.

2.6. Statistical analysis

All statistical analyses were performed using the SPSS 24.0 statistical software package (IBM Statistics for Windows, version 24.0). Demographic data differences between the two groups were determined using a two-tailed *t*-test for continuous variables with a normal distribution or with the Mann–Whitney *U* test for continuous variables with a non-normal distribution. Categorical covariables were analyzed using the chi-square or Fisher's exact tests. For the statistical analysis of the fMRI data, the FNC differences between the two groups were considered significant after controlling for age, sex, and education level as covariates (false discovery rate correlation with a threshold of 0.05). The correlations between the abnormal FNC patterns and cognitive impairment were evaluated by partial correlation analyses with age, sex, and education level as covariates. A p value of <0.05 was considered statistically significant.

3. Results

3.1. Demographics and clinical characteristics

Five patients with CSVD were excluded because of their excessive head motion. Therefore, the final cohort consisted of 22 patients with CSVD and 20 control participants. There were no significant between-group differences with regard to age, sex, and education level ($p > 0.05$) (Table 1). Moreover, no difference in mean FD was observed between the CSVD (0.25 ± 0.13) and control (0.20 ± 0.14) groups ($t = -1.264$, $p = 0.215$).

3.2. Component selection of the triple-network model

In this study, 100 ICs were obtained, among which eight components were selected as the main components of the triple-network model for further analysis according to prior studies [36–38] (Fig. 1). The CEN (IC2 and IC31) mainly consists of the dorsolateral prefrontal cortex (dlPFC), along with part of the inferior parietal lobule (IPL) and superior parietal lobule (SPL). The DMN (IC21, IC27, IC81, and IC98) predominantly comprises the mPFC, PCC, precuneus, and angular gyrus. The SN (IC30 and IC54) largely includes the ACC, insular cortex, and part of the PFC.

3.3. Group-level FNC analysis

A FNC matrix with the dimensions of 8×8 (selected ICs) $\times$ 42 (participants) was generated. patients with CSVD exhibited an increased connectivity pattern in the CEN (IC31)-DMN (IC81) and decreased connectivity patterns in the DMN (IC21)-DMN (IC81), DMN (IC27)-DMN (IC98), DMN (IC81)-SN (IC30), DMN (IC81)-SN (IC54), DMN (IC98)-SN (IC54), CEN (IC2)-SN (IC30) and SN (IC30)-SN (IC54) (Fig. 2).

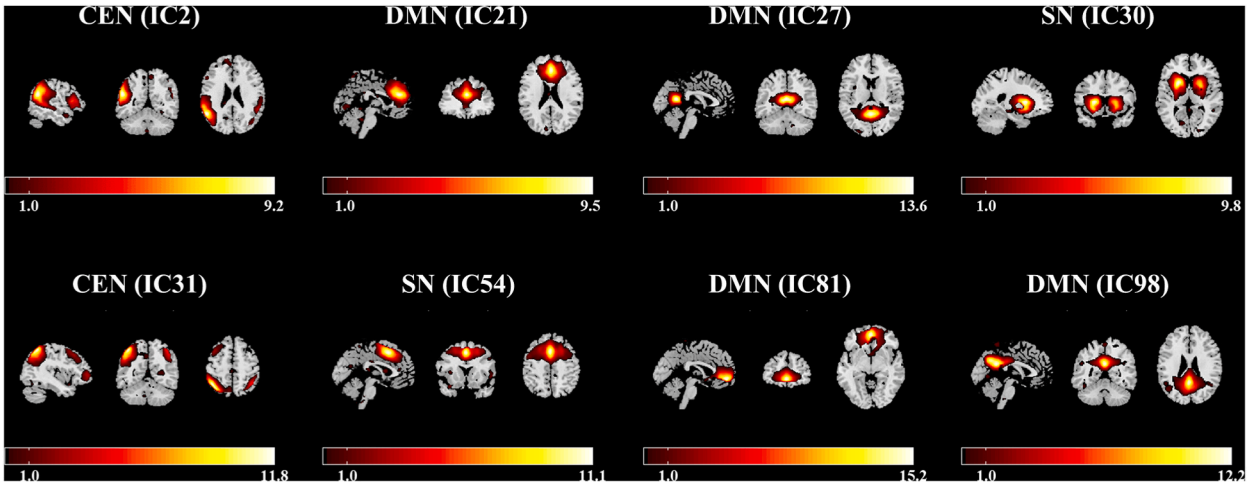

Fig. 1. The spatial maps of the eight main components in the triple-network model. DMN: default mode network; CEN: central executive network; IC: independent component; SN: salient network.

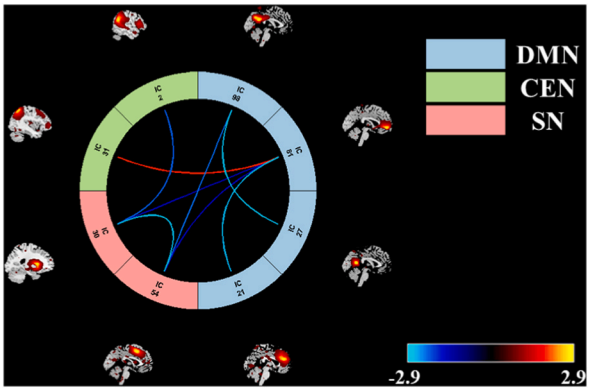

Fig. 2. Group-level differences in static functional network connectivity patterns among the triple-network model between the patients with cerebral small vascular disease and healthy controls. The abbreviations are shown in Fig. 1 legend.

3.4. Correlation analysis

Significant negative correlations were found between the DMN (IC27)-DMN (IC98) connectivity pattern and the MoCA total scores ($r = -0.460$, $p = 0.048$) and MoCA abstraction scores ($r = -0.565$, $p = 0.012$), and a positive correlation was detected between the SN (IC30)-SN (IC54) connectivity pattern and the MoCA abstraction scores ($r = 0.491$, $p = 0.033$) (Fig. 3(A–C)).

4. Discussion

In this study, we used resting-state fMRI to investigate the organization of the triple-network model in patients with CSVD, focusing on the inter- and intra-network functional connectivity patterns in the SN, DMN, and CEN. Consistent with our hypothesis, we obtained the following results: 1) the abnormal SN-centered cross-component FNC patterns in the triple-network model were significantly impaired in patients with CSVD, and 2) the decreased SN- and CEN-centered intra-network functional connectivity patterns significantly correlated with cognitive function. The abnormal FNC patterns mainly overlapped with the key nodes of the three networks, including the subregions of the dorsal ACC (dACC) and insula in the SN, the mPFC and PCC in the DMN, and the dlPFC and IPL in the CEN. Furthermore, other inter-network FNC patterns showed no significant correlations with the MoCA scores.

Here, our primary findings were predominantly SN-oriented decreased connectivity patterns in patients with CSVD, along with several specific overlapping regions in the DMN and CEN. These affected brain regions are involved in functions such as motor execution, emotional processing, and cognitive control [39]. The SN receives convergent input from multiple sensory modalities and is sensitive to internal signals associated with the autonomic nervous system to process physiological information. This process enables the allocation of appropriate resources to monitor and respond to important stimuli for cognitive behaviors [40,41]. When a salient stimulus or cognitive task is at hand, the SN functions as a switch between the DMN and CEN by suppressing the former and activating the latter, thereby facilitating prompt reaction through its connection with the dlPFC [27]. A large community study using ecological momentary assessment of daily self-control and resting-state functional MRI examination to investigate the intrinsic organization of the triple-network model showed that higher SN-centered network connections were related to increased self-control [42]. Therefore, the SN-centered regulation of cross-network interactions in the triple-network model may be an important aspect of cognitive control. Furthermore, these findings suggest that the SN-centered abnormalities may cause the imbalance in the triple-network model due to abnormal suppression or activation in the DMN and CEN. These dysfunctional patterns lead to inefficient cognitive control and reduced cognitive reaction.

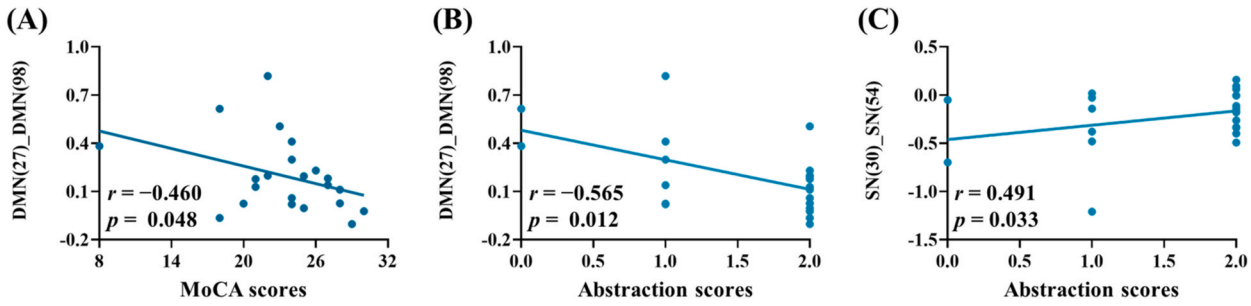

Fig. 3. Correlations between the abnormal functional network connectivity patterns and cognition-related characteristics in patients with cerebral small vascular disease. MoCA: Montreal Cognitive Assessment. The other abbreviations are shown in Fig. 1 legend.

Our findings in the triple-network model are similar to the results that suggest a direct causal influence between asymmetric patterns in the core regions of the SN, DMN, and CEN and cognitive controllability [43]. The SN showed greater complex connectional relationships and a dominant role in driving interactions among the SN, DMN, and CEN. A previous study indicated that patients with mild cognitive impairment exhibited altered whole-brain functional connectivity (FC) of the cingulate cortex, including decreased FC patterns in the ACC [44], similar to our results. Additionally, an experimental animal study showed that the activation of the ACC might alleviate cognitive deficits [45]. Furthermore, the disengagement of the DMN from the SN and CEN under high cognitive load was caused by reduced outflow signals from the PCC [43]. However, we found a disconnection between the SN and posterior DMN in the resting state. These findings support the role of resting-state abnormalities in the cingulate cortex, offering a fresh perspective and better understanding of the brain mechanisms of cognitive impairment in CSVD. Furthermore, Li et al. proposed that in patients with AD, enhanced SN function might necessitate additional resources to maintain brain function and compensate for the decreased DMN function, contributing to an abnormal mapping of internal events and external stimuli, and ultimately resulting in clinical cognitive decline [28]. In contrast, our study showed decreased SN-centered network connections but increased inter-network connectivity patterns between the DMN and CEN. This discrepancy might be due to the differences in the cognitive levels between patients with CSVD and AD. Therefore, the neural mechanism of the triple-network model holds potential clinical significance for evaluating cognitive impairment and progression.

Additionally, our study demonstrated that the decreased intra-network FNC patterns within the SN and posterior DMN in patients with CSVD were significantly associated with cognitive impairment, particularly abstraction function. Moreover, the PFC is mainly associated with recognizing and leveraging abstract information of tasks, which is crucial in cognitive behavior and flexibility [46]. However, this differs from our observation and may be attributed to the damages in the regions involved in cognitive processing and control. Furthermore, previous neuroimaging studies on self-control used task-based fMRI to investigate the neurobiological basis and demonstrated that distinct brain regions are involved in cognitive control, with each region being associated with varied cognitive processes [42]. These differences in cognitive control were further shown to be associated with activity in the dlPFC that is involved in executive control and response inhibition [43,47], the insula and ACC that are implicated in performance monitoring [27], and the mPFC and PCC that are responsible for value-based decision-making [19,48,49]. In addition, Sandra et al. [50] observed that cognitive function training led to significant alterations of neural function in the dlPFC and PCC and significant associations between improvement in complex abstraction ability and an increase in cerebral blood flow in the dACC. All these aforementioned findings indicate the importance of exploring the altered modalities of the FNC in the triple-network model in patients with CSVD, which will help develop and evaluate effective treatments for CSVD via cognitive rehabilitation and other clinical interventions.

The clinical significance of abnormal FNC patterns in the triple-network model is of great importance. These aberrant patterns can serve as valuable clues for deciphering and identifying the potential underlying mechanisms of cognitive deficits associated with CSVD. By examining the disrupted interactions between the DMN, CEN, and SN, we can gain insights into how CSVD affects cognitive functions. CSVD is known to cause various cognitive impairments, including but not limited to executive dysfunction, processing speed deficits, attentional deficits, and memory problems. Understanding the specific cognitive deficits seen in patients with CSVD enables us to establish a direct link between these deficits and the abnormal FNC patterns observed in the triple-network model. This knowledge not only helps improve our understanding of CSVD pathophysiology but also provides an opportunity to develop targeted interventions and treatments for cognitive dysfunction in patients with CSVD. Furthermore, the identification of potential neuroimaging biomarkers associated with CSVD and their associations with cognitive deficits has significant clinical implications. By identifying reliable biomarkers, clinicians can improve the diagnosis and monitoring of CSVD, track disease progression, and predict individual prognosis. Additionally, neuroimaging biomarkers can be used to assess the effectiveness of therapeutic interventions and potentially guide treatment decisions for patients with CSVD. Overall, the investigation of abnormal FNC patterns in the triple-network model contributes to our understanding of CSVD-related cognitive deficits and sheds light on the underlying pathophysiological mechanisms. It also holds promise for the development of neuroimaging biomarkers that can aid in the diagnosis, prognosis, and management of CSVD, ultimately improving patient outcomes.

This study has several limitations. First, the main limitation of this paper is the small sample size. Due to the limited sample size, the reliability of the study results may be compromised, and there is a potential for missing or failing to observe small effects. An increased sample size should be prioritized to increase the statistical power for better supporting our findings. Second, the study design was cross-sectional, limiting our ability to explore the causal relationship between dysfunction of the triple-network model and cognitive impairment in patients over time. Longitudinal studies are needed in the future to answer this question. Third, in this study, only the relationship between the triple-network model and cognitive impairment in patients with CSVD was considered, while the investigation of other important brain networks was not explored. Future research should further address and improve upon this aspect. Forth, structural abnormalities play a significant role in the pathological process of CSVD, but we do not make any assumption on the particular structure of the triple-network model. Therefore, further in-depth analysis and comparison will be needed in future studies. Lastly, whether global signal regression is performed has different effects on the topological properties and connectivity patterns of the brain network [51,52]. This emphasizes the importance of considering global signal regression when studying the topological properties of the brain network in the future.

In conclusion, our study results suggest that altered FNC patterns in the triple-network model may play a crucial role in the pathophysiology of cognitive deficits in patients with CSVD. Furthermore, these findings will serve as a reference for future studies to explore the correlations between the FNC patterns in the triple-network model as well as other sensory networks, motor networks, and attention networks, which will ultimately help gain a comprehensive and nuanced understanding of the neural mechanisms underlying cognitive symptoms in patients with CSVD.

Ethics statement

This study was approved by the Ethics Committee of Jiangning Hospital, Nanjing, Jiangsu Province, China (2016YFC1300500).

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Data availability statement

The data supporting this study's findings are available from the corresponding authors upon reasonable request.

CRediT authorship contribution statement

Heng-Le Wei: Conceptualization, Formal analysis, Methodology, Software, Visualization, Writing – original draft. **Cunsheng Wei:** Conceptualization, Formal analysis, Methodology, Software, Visualization, Writing – original draft. **Yu-Sheng Yu:** Supervision, Writing – review & editing. **Xiaorong Yu:** Data curation, Investigation. **Yuan Chen:** Data curation, Investigation. **Junrong Li:** Funding acquisition, Project administration. **Hong Zhang:** Funding acquisition, Project administration. **Xuemei Chen:** Supervision, Writing – review & editing.

Declaration of competing interest

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

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