Disrupted Topological Organization of Resting-State Functional Brain Network in Subcortical Vascular Mild Cognitive Impairment

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Keywords

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SUMMARY

Aims: Neuroimaging studies have demonstrated both structural and functional abnormalities in widespread brain regions in patients with subcortical vascular mild cognitive impairment (svMCI). However, whether and how these changes alter functional brain network organization remains largely unknown. **Methods:** We recruited 21 patients with svMCI and 26 healthy control (HC) subjects who underwent resting-state functional magnetic resonance imaging scans. Graph theory-based network analyses were used to investigate alterations in the topological organization of functional brain networks. **Results:** Compared with the HC individuals, the patients with svMCI showed disrupted global network topology with significantly increased path length and modularity. Modular structure was also impaired in the svMCI patients with a notable rearrangement of the executive control module, where the parietal regions were split out and grouped as a separate module. The svMCI patients also revealed deficits in the intra- and/or intermodule connectivity of several brain regions. Specifically, the within-module degree was decreased in the middle cingulate gyrus while it was increased in the left anterior insula, medial prefrontal cortex and cuneus. Additionally, increased intermodule connectivity was observed in the inferior and superior parietal gyrus, which was associated with worse cognitive performance in the svMCI patients. **Conclusion:** Together, our results indicate that svMCI patients exhibit dysregulation of the topological organization of functional brain networks, which has important implications for understanding the pathophysiological mechanism of svMCI.

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Introduction

Subcortical vascular mild cognitive impairment (svMCI) is known to be a prodromal stage of subcortical vascular dementia (SVaD), which is an important subtype of vascular dementia (VaD) [1–4]. Patients with svMCI have been shown to exhibit cognitive impairments in executive, language, visuospatial, and memory functions [1–3,5] and have been associated with the presence of lacuna infarcts or white matter (WM) lesions that appear as periventricular white matter hyperintensity (WMH) on magnetic resonance imaging (MRI) [3,6]. These WM lesions may cause disruptions to the circuitry that connect various brain regions and induce further degeneration to even more extensive brain structures [7–9].

Neuroimaging studies have shown that svMCI is associated with extensive structural and functional abnormalities. Structurally, gray matter atrophy (volume reductions and/or cortical thickness thinning) has been observed in the frontal, parietal, and lateral temporal cortices as well as in subcortical structures such as the thalamus and basal ganglia [5,10–12]. Functionally, svMCI individuals have been shown to exhibit hypometabolism in the inferior frontal gyrus, the thalamus, and the caudate [5] and decreased spontaneous activity in default mode regions [11]. Moreover, recent studies have begun to identify svMCI-related alterations in inter-regional connectivity among frontal-subcortical circuits and the long association fibers that bridge the anterior and posterior parts of the brain [11,13,14]. This evidence of

svMCI-related abnormalities in widespread regions and connections suggests that svMCI is a complex disease associated with both local and global dysregulations across the entire brain.

Recently, graph theory has been widely applied in neuroimaging studies, offering a unique opportunity to understand the organizational principles of the brain [15–17]. The human brain has been revealed to possess nontrivial topological properties, such as the small-world properties of a high level of clustering and a short path length, that enable efficient local and global information processing and modular or community structure that allows for greater robustness and adaptivity. Brain network properties have been found to be disrupted in various brain disorders [18–20]. With respect to MCI, using magnetoencephalography (MEG) data, Buldu *et al.* [21] reported reorganization of the functional connectome in MCI patients during a memory task. Wang *et al.* [22] observed a series of topological changes of functional brain networks in the amnesic type of MCI (aMCI). However, it remains unclear whether and how the organization of brain networks are affected in svMCI patients.

Here, we employed resting-state functional MRI (rs-fMRI) to investigate topological changes of the functional connectome in patients with svMCI. In our previous report [11], we demonstrated widespread abnormalities in intrinsic functional brain activity and connectivity density. The current study focuses on disruptions of the topological architecture of the intrinsic functional brain connectome in svMCI. Specifically, we sought to determine whether svMCI affects small-worldness and modular organization and, if so, whether those topological abnormalities are associated with individual clinical and behavioral variables.

Materials and Methods

Participants

Fifty-four right-handed participants, including 26 patients with svMCI and 28 demographically matched healthy control (HC) subjects participated in this study. The recruited svMCI patients were outpatients who were registered at the neurology department of XuanWu Hospital, Capital Medical University, Beijing, China. Complete recruitment details were described in our prior work [11]. Briefly, the svMCI patients met Petersen's criteria for MCI with our previously described modifications [23–26]. We excluded patients presenting secondary causes of cognitive deficits according to the criteria [26,27] previously described in our prior work [11]. The HC subjects were community residents from Beijing who were recruited by advertisements. All of the HC subjects had no history of any neurological or psychiatric disorders, no cognitive complaints, and no abnormalities in their conventional brain MRI images. All of the participants underwent a standardized clinical evaluation protocol, which included a general and neurological examination, a global cognitive level test (i.e., Clinical Dementia Rating Scale [CDR] and Mini-Mental State Examination [MMSE]), and other cognitive assessments (i.e., Activities of Daily Living and Auditory-Verbal Learning Test [AVLT]). Data from two HC and five svMCI subjects were excluded due to excessive head motion during

the rs-fMRI scans. This study was approved by the medical research ethics committee and institutional review board of XuanWu Hospital, Capital Medical University, Beijing, China, and written informed consent was obtained from each participant.

Data Acquisition

All images were acquired using a 3.0 T Siemens scanner at XuanWu Hospital, Capital Medical University. During the scan, foam pads and headphones were used to reduce head motion and scanner noise as much as possible. Structural images were collected using a sagittal magnetization-prepared rapid gradient echo (MP-RAGE) three-dimensional T1-weighted sequence (repetition time [TR] = 1900 ms; echo time [TE] = 2.2 ms; inversion time [TI] = 900 ms; flip angle [FA] = 9°; number of slices = 176; slice thickness = 1.0 mm; data matrix = 256×256 ; field of view [FOV] = 256×256 mm²). Resting-state functional images were acquired using an echo-planar imaging sequence (TR = 2000 ms; TE = 40 ms; FA = 90°; number of slices = 28; slice thickness = 4 mm; gap = 1 mm; data matrix = 64×64 ; FOV = 256×256 mm²). The subjects were instructed to lie quietly in the scanner with their eyes closed and to remain stable as much as possible during the data acquisition. The functional scan lasted for 478 second (239 volumes) in total.

Data Preprocessing

Functional MRI data were preprocessed using Statistical Parametric Mapping (SPM5, <http://www.fil.ion.ucl.ac.uk/spm/>) and the REST toolbox (<http://resting-fmri.sourceforge.net>) [28]. The first five volumes of the functional images were discarded to equilibrate the signal and to allow participants' adaptation to the scanning noise, leaving 234 images for further analysis. After slice timing and motion correction, functional images were first co-registered to their corresponding T1-weighted anatomical images using a linear transformation. The anatomical images were subsequently segmented into grey matter (GM), WM, and cerebrospinal fluid using a new segment procedure provided in the SPM8 toolbox. The DARTEL toolbox [29] was applied on GM segments to create a group-specific template, and the GM segment from each subject was warped to the group-specific template. All of the warped GM maps were further affine transformed to Montreal Neurological Institute (MNI) space. The transformation parameters were then applied to corresponding fMRI images to bring them into MNI space with a resampled resolution of $3 \times 3 \times 3$ mm³. The normalized fMRI data were then temporally band-pass filtered (0.01–0.1 Hz) and spatially smoothed with a 6-mm full width at half maximum Gaussian kernel [30,31]. Nuisance signals of six head-motion profiles and the average signal from the WM and ventricles were regressed out from the time courses.

To moderate the effects of head motion on functional images, we first excluded one svMCI subject with excessive head movement (>3 mm maximum displacement in any of the x, y, or z directions or >3° of rotation in any direction). Moreover, given that “micro” head movements from one time point to the next can introduce systematic artifactual interindividual and group

differences in resting-fMRI metrics [32–35], we further censored the motion-contaminated fMRI volumes with framewise displacement (FD) >0.3 mm, and their one back and two forward neighbors for each subject. Subjects with <90 uncontaminated volumes (3 min) were excluded (four svMCI and two HC subjects were excluded). There were no significant differences in any of the six head motion parameters between the remaining 21 svMCI subjects and 26 HC subjects (all p s > 0.05). Furthermore, we calculated the averaged FD over all volumes as a confounding variable in the group-level analyses. There was no significant difference in the averaged FD between the two groups ($t = 0.13$, $P = 0.89$).

Network Construction

We constructed macroscale brain networks, where nodes represented brain regions and edges represented interregional resting-state functional connectivity (RSFC). Network nodes were defined by parcellating the brain into 1024 regions of interest (ROIs) according to a high-resolution, randomly generated brain atlas (H-1024) [36]. Interregional RSFC was calculated as the Pearson correlation between the averaged time courses derived from every pair of ROIs. To further de-noise spurious interregional correlations, a threshold of 20% connection density, that is, the density of the retained highest correlations, was used to set the weak correlations to zero. While we focused our analysis on networks thresholded at 20% density, we also applied a lower threshold of 10% and a higher threshold of 30% to evaluate possible thresholding effects on between-group differences in global network metrics.

Network Analysis

We studied two important topological attributes, small-world and modularity structure, in the constructed weighted brain networks.

Small-World Properties

To examine the small-world properties, we computed the clustering coefficient, C_p , and characteristic path length, L_p , of the functional brain networks [37]. The clustering coefficient quantifies the extent of local interconnectivity or cliquishness of a network, whereas the characteristic path length reflects the mean distance or routing efficiency between any given pair of nodes.

Modularity

In a network, modules refer to groups of nodes that are highly connected with each other but less connected with other nodes. The modularity Q quantifies the efficacy of partitioning a network into modules by evaluating the difference between the weight of intramodule connections and the connection weights of random networks in which connections are weighted randomly [38]. The objective of a modular detection procedure is to find a specific partition that maximizes the modularity Q . Previous studies have used other clustering methods to identify brain components or networks [39,40], such as the widely used independent component analysis (ICA). However, unlike modularity analysis, the

ICA method makes very strong statistical assumptions that the identified components are statistically independent and orthogonal with each other with no physiological justification [4]. Moreover, while ICA requires that the number of components be prespecified, modularity analysis finds modules by maximizing the modularity Q ; therefore, the number of modules is more data driven than in ICA analysis. However, there is a range of algorithms available for modular analysis, which makes it difficult for studies to compare and choose the appropriate algorithm to apply [41]. In our current study, we used the most widely accepted and used algorithm proposed by Newman [42], which was implemented using the Brain Connectivity Toolbox (BCT, <http://www.indiana.edu/~cortex/connectivity.html>). We conducted the modular detection procedure for each subject to obtain the maximal modularity Q . We also generated group brain networks by applying a threshold of 20% density after averaging the connectivity matrices over each cohort and carried out the modular detection procedure on the svMCI and control groups separately.

To evaluate interactions within and between different brain modules, we accessed two standard network metrics, the within-module degree (WD) z -score and the participation coefficient (PC) [43]. These two metrics were computed for svMCI and HC individuals based on the modular structure obtained from group-wise networks of each group. WD measures the normalized degree of connections of a node within its corresponding module:

$$z_i = \frac{k_i - \bar{k}_s}{\sigma_s},$$

where k_i is the number of intramodule connections of a node i within module s , and $\bar{k}_s$ is the average number of intramodule connections of all nodes in module s . σ_s is the standard deviation of the number of intramodule connections of all nodes in module s . Thus, z_i will be large for a node that has a large number of intramodule connections relative to other nodes in the same module. The PC for node i is defined as:

$$PC_i = 1 - \sum_{s=1}^{N_M} \left(\frac{k_{is}}{k_i} \right)^2,$$

where N_M is the number of modules, and k_{is} is the number of connections between the node i and module s . k_i is the total number of connections of node i in the network. The PC of node i will be close to one if its connections are distributed among different modules and zero if it is connected exclusively within its own module.

Null Model of Random Networks

To determine whether brain networks were topologically organized into small-world and modular architectures, we calculated the normalized clustering coefficient, characteristic path length, and modularity by dividing them by their corresponding average derived from 100 random networks. These random networks were generated with the same number of nodes, edges, and degree distributions as the real brain networks [44,45], while the weight of each edge was retained during the random rewiring procedure. Typically, a small-world network has a $C_p/C_p^{\text{rand}} > 1$ and an

$L_p/L_p^{\text{rand}} \sim 1$ [37], and these two conditions can also be summarized into a simple quantitative measurement, small-worldness, by dividing the normalized clustering coefficient by the normalized path length. A network is a small-world network if its small-worldness is >1 and is modular if it has a $Q/Q^{\text{rand}} > 1$.

Statistical Analysis

We used nonparametric permutation tests to evaluate between-group differences in topological attributes (both global and regional measures) [44,46]. Briefly, for each network metric, we first calculated the difference of the mean values between the two groups. We then generated an empirical distribution of the difference by randomly reallocating all of the values into two groups and recomputing the mean differences (10,000 permutations). The 95th percentile points of the empirical distribution were used as critical values in a one-tailed test of whether the observed group differences could occur by chance. Note that before the permutation tests, we removed the effects of age, gender, years of education, and averaged FD by multiple linear regressions. To correct for multiple comparisons across various network metrics, the false-discovery rate method was applied at a significant level of $q < 0.05$.

To assess the relationships between network metrics and clinical variables, we performed multiple linear regressions between each network measure and clinical variables (AVLT-immediate recall, AVLT-delayed recall, AVLT-recognition, and MMSE scores) in the svMCI group. Age, gender, years of education, and averaged FD were also controlled for as confounding covariates.

Results

Demographic and Clinical Characteristics

Demographic and clinical data for the svMCI patients and HCs are shown in Table 1. There were no significant differences in age,

Table 1 Demographics and clinical characteristics of the participants

	HC (26)	svMCI (21)	<i>P</i>
Gender (male/female)	12/14	9/12	0.821 ^a
Age (years)	50–79 (64.8 ± 8.1)	46–81 (65.9 ± 9.8)	0.679 ^b
Educations (years)	0–22 (12.1 ± 5.1)	0–18 (10.4 ± 4.3)	0.231 ^b
MMSE	26–30 (29.0 ± 1.2)	21–30 (25.5 ± 2.7)	$<10^{-7b}$
AVLT-immediate recall	6.3–14.7 (9.4 ± 2.3)	4.3–11.7 (6.4 ± 2.1)	$<10^{-5b}$
AVLT-delayed recall	7–15 (10.8 ± 2.7)	2–11 (6.1 ± 2.8)	$<10^{-7b}$
AVLT-recognition	9–15 (12.7 ± 1.8)	4–14 (10.0 ± 3.0)	$<10^{-3b}$

HC, healthy controls; svMCI, subcortical vascular mild cognitive impairment; MMSE, Mini Mental State Examination; AVLT, Auditory Verbal Learning Test. Data are presented as the range of min–max (mean ± SD). ^aThe *P*-value was obtained by a two-tail Pearson chi-square test. ^bThe *P*-value was obtained by a two-sample two-tail *t*-test.

gender, or years of education (all $ps > 0.05$) between the svMCI and HC groups. The svMCI group had significantly lower MMSE, AVLT-immediate recall, AVLT-delayed recall, and AVLT-recognition scores than the HC group.

Small-World Organization of the Functional Brain Networks

Using a density threshold of 20%, the functional networks in both the svMCI and HC groups exhibited small-world organization with small-world >1 . Specifically, both groups had greater clustering coefficients ($C_p/C_p^{\text{rand}} > 1$) and almost identical shortest path lengths ($L_p/L_p^{\text{rand}} \sim 1$) comparing with matched random networks (Figure 1 and Table 2). Nevertheless, between-group comparisons revealed significantly increased characteristic path lengths ($P = 0.018$) and normalized characteristic path lengths ($P = 0.016$) in the svMCI group (Figure 1 and Table 2). Similar observations were found for functional networks thresholded at 10% and 30% densities (Figure 1 and Table 2). We therefore focused our following analysis on functional brain networks constructed using the 20% density threshold.

Modular Structure of the Functional Brain Networks

Functional networks in both the svMCI and HC groups were modular, showing greater modularity than their comparable random networks (Figure 1 and Table 2). Statistical analysis revealed that compared with networks for the HC individuals, brain networks for the svMCI individuals had significantly higher modularity ($P = 0.017$). Figure 2 showed the modules detected from group-averaged functional networks for each of the two groups. In the HC group, there were five modules identified. The spatial contents of these five modules corresponded to the visual [31,40], sensorimotor [30,40], auditory [40], default mode [40,47], and fronto-parietal networks [40,48]. In the svMCI group, we identified six modules. Compared to the modular structure of the HC group, while the visual, sensorimotor, auditory, and default mode networks were relatively conserved in the svMCI group, the fronto-parietal module in the HC brain network segregated into two modules—a frontal module comprised mostly the frontal regions and a parietal module comprised the bilateral superior parietal lobe.

Intra- and Intermodule Connectivity at the Regional Level

Group comparisons revealed that compared with the HC group, the svMCI patients showed increased WD in regions including the medial prefrontal gyrus (mPFC), left insula, and cuneus but decreased WD in the middle cingulate gyrus ($P_{\text{uncorrected}} < 0.005$, Figure 3A). As for the PC, in the svMCI patients, we found increases in the left inferior parietal lobule (IPL) and superior parietal gyrus (SPL) ($P_{\text{uncorrected}} < 0.005$, Figure 3B).

Figure 1 Group differences in small-world metrics (A) and modularity metrics (B).

* $P_{corrected} < 0.05$.

Table 2 Network characteristics of the participants

Network metrics	HC	svMCI	P
Sparsity = 20%			
C_p	0.32 ± 0.06	0.29 ± 0.06	0.142
C_p/C_p^{rand}	1.76 ± 0.26	1.84 ± 0.31	0.141
L_p	3.56 ± 0.35	3.82 ± 0.45	0.018
L_p/L_p^{rand}	1.30 ± 0.05	1.35 ± 0.08	0.016
Small-worldness	1.34 ± 0.18	1.36 ± 0.20	0.34
Q	0.39 ± 0.08	0.52 ± 0.26	0.012
Q/Q^{rand}	7.36 ± 0.69	7.31 ± 0.91	0.95
Sparsity = 10%			
C_p	0.34 ± 0.06	0.32 ± 0.06	0.192
C_p/C_p^{rand}	2.49 ± 0.53	2.55 ± 0.64	0.315
L_p	3.89 ± 0.27	4.11 ± 0.38	0.023
L_p/L_p^{rand}	1.37 ± 0.06	1.40 ± 0.09	0.119
Small-worldness	1.82 ± 0.42	1.84 ± 0.48	0.43
Q	0.46 ± 0.07	0.55 ± 0.21	0.007
Q/Q^{rand}	6.39 ± 0.52	6.31 ± 0.76	0.68
Sparsity = 30%			
C_p	0.31 ± 0.06	0.28 ± 0.06	0.09
C_p/C_p^{rand}	1.45 ± 0.16	1.51 ± 0.20	0.06
L_p	3.47 ± 0.39	3.76 ± 0.49	0.024
L_p/L_p^{rand}	1.30 ± 0.05	1.35 ± 0.09	0.008
Small-worldness	1.11 ± 0.10	1.12 ± 0.10	0.32
Q	0.35 ± 0.09	0.51 ± 0.29	0.012
Q/Q^{rand}	7.88 ± 0.83	7.87 ± 0.98	0.97

HC, healthy controls; svMCI, subcortical vascular mild cognitive impairment. Data are presented as mean ± SD.

Relationship Between Network Metrics and Behavioral Measurements

In the svMCI group, AVLT-recognition score was negatively correlated with L_p ($r = -0.45$, $P = 0.04$) (Figure 4), and AVLT-delayed recall score was negatively correlated with PC in the left SPL ($r = -0.56$, $P = 0.008$) (Figure 3C).

Discussion

In this study, we investigated topological alterations of the functional brain connectome in svMCI. Although the brain networks of the svMCI patients exhibited small-world and modular structure, two critical organizational principles, we observed significant differences in global and local topological properties compared with HCs. Specifically, svMCI patients showed (1) increased path length, (2) different modular organizational structure, and (3) disrupted intra- and intermodule connectivity (WD and PC) in widespread brain regions. More importantly, the abnormal topological metrics correlated with the patients' clinical and/or behavioral performance.

Small-worldness, defined as relatively high local clustering ($C_p/C_p^{rand} > 1$) and approximately equivalent characteristic path length ($L_p/L_p^{rand} \approx 1$) compared with random networks, has been shown to be a nontrivial topological configuration in complex networks that supports high efficiency of both specialized and integrated brain processing [44,49]. Here, we found that the functional brain networks of both HC and svMCI individuals exhibit small-world architecture, which is consistent with previous findings suggesting that small-world properties exist in functional brain networks in healthy population [37] as well as in aging [50],

Figure 2 Modular architecture for both healthy controls (A) and patients with subcortical vascular mild cognitive impairment (svMCI) (B). Five modules were found in the mean functional brain network of the HCs: the motor and somatosensory module (green), the default network (blue), the fronto-parietal network (red), the visual processing module (purple), and the auditory module (yellow) (A). Six modules were detected in the mean functional brain network of patients with svMCI. As compared to the modular structure of the HC group, the visual, sensorimotor, auditory, and default mode networks were relatively conserved in the svMCI group, while the fronto-parietal module in the HC brain network segregated into two modules in the svMCI group—a frontal module comprised mostly the frontal regions and a parietal module comprised the bilateral superior parietal lobe (B). The modular architecture maps were rendered by using the BrainNet Viewer (<http://www.nitrc.org/projects/bnv/>) [76].

MCI [21], and aMCI [22] patients. Nevertheless, compared with the HC individuals, increased characteristic path length was found by quantitative analysis in the svMCI patients. This observation is compatible with previous studies, which also found increased path length in aMCI patients [22,51]. Short path length ensures a highly efficient network organization [52]. Long-range connections that are critical for keeping path lengths short in brain networks ensure that information rapidly propagates across remote brain regions [49,53]. Both structural and functional imaging studies in svMCI patients suggest abnormalities associated with long fibers, such as connections between prefrontal regions and subcortical regions [13,54]. Therefore, the increase in the average path length in the svMCI patients may be attributed to the degeneration of these long-distance fiber bundles used for information transmission. Furthermore, we observed a close negative relationship between L_p and AVLT-recognition score in the svMCI patients, which indicates that svMCI patients with functional brain networks with a longer shortest path length tend to show more severe memory deficits.

Modular analysis provides network organization patterns, which show the details of the formation and communication of subnetworks [55,56]. In the present study, both the HC and svMCI groups were found to show high global modularity, which is in good agreement with previous studies demonstrating the existence of modular structure in healthy subjects. Modularity has been suggested to be a fundamental organizational principle, which may facilitate efficient information processing both within and across modules and ensure optimal balance between functional segregation and integration. We detected five modules in the HC group and six modules in the svMCI group, most of which are associated with specific primary or cognitive functions and have been identified in previous structural and functional brain network studies. Compared with the HC group, the majority of the modules, including the visual, sensorimotor, auditory, and default mode networks, were largely preserved in the svMCI patients. Nevertheless, there was a notable rearrangement of the Executive Cognitive Network (ECN) module in the svMCI group, where the parietal regions were split from the ECN and grouped as a separate module. This is intriguing because executive dys-

function is one of the main characteristics of svMCI, and may result from lesions in the WM and the long association fibers, especially those that connect the anterior parts of the brain to the posterior parts [54,57]. Diffusion imaging studies have found reduced fractional anisotropy in frontal and parietal WM regions [58], which involve major axonal bundles that project from or to frontal and parietal regions [59]. Kim et al. [54] found that the disruption of posterior WM integrity in patients with svMCI was associated with their cognitive deficits. Recently, Schaefer et al. [52] showed reduced intrinsic functional connectivity in frontoparietal networks in patients with early small vessel disease, which is closely related to WM lesions and neuropsychological deficits. Thus, we could speculate that the separation of the parietal regions from the ECN module in the svMCI group might be related to the decline of cognitive functions (e.g., executive control) and impaired structural and functional frontoparietal connectivity in svMCI.

In addition to the modular structure reorganization, we also found increased PC, a measure of intermodule connectivity, in the ECN regions (IPL and SPL) in the svMCI patients. The parietal areas have been identified as important integrative association areas [60,61]. Studies in patients with subcortical vascular cognitive impairment (SVCI) have shown increased amyloid burden in parietal regions, which has been related to abnormal executive function as well as verbal and visual memory [62,63]. In our study, we found a negative correlation between PC in the left SPL and the AVLT-delayed recall score, which may indicate that patients with worse memory need higher intermodule connectivity in parietal regions to compensate for their abnormally configured or misbehaving functions.

The svMCI patients showed decreased within-module degree in the middle cingulate gyrus, which may be related to lesions of the cingulum bundle, which have been revealed in previous svMCI studies [64–66]. On the other hand, the left anterior insula, mPFC and cuneus showed increased within-module degree in the svMCI patients. The insula plays a role in diverse functions, including perception, motor control, self-awareness, cognitive functioning, and interpersonal experience [67]. Multimodal MRI studies [3,5,68] have found lesions in the insula associated with executive

Figure 3 (A) Group difference in within-module degree (WD) between healthy controls (HC) and subcortical vascular mild cognitive impairment (svMCI); (B) group difference in participation coefficient (PC); (C) correlation between PC of left SPL and AVLT-delayed recall in svMCI patients. AVLT, Auditory Verbal Learning Test; IPL, inferior parietal lobule; SPL, superior parietal lobule.

dysfunction in SVaD, which has been proposed as the advanced stage of svMCI [12]. Our result of increased within-module degree in the insula may reflect a compensatory mechanism, where more resources or stronger intramodule connections are needed in svMCI patients to achieve normal levels of cognition during rest. The mPFC is among the brain regions that have the highest baseline metabolic activity at rest and is a key region of the default mode network [69]. Accumulating evidence suggests that failure to suppress activity of the DMN predicts slower reaction times and momentary attentional lapses during tasks [70–72]. Thus, the increased within-module degree in the mPFC we observed during the resting state may indicate possible difficulties in suppressing its

Figure 4 Relationship between characteristic path length (L_p) and behavioral performance in svMCI patients. AVLT, Auditory Verbal Learning Test.

activity during goal-directed cognitive processes, which may lead to the prominent deficits in executive function often observed in svMCI patients. By using single photon emission computed tomography, Colloby et al. [73] found increased uptake of ^{123}I -5IA-85380, a highly selective marker for $\alpha 4\beta 2$ nicotinic acetylcholine receptors, in the cuneus in VaD patients compared with controls. Together with our observation of increased WD in svMCI patients, the abnormalities in the cuneus may be associated with the vascular etiology and need to be discussed in future studies.

Methodological Issues

Several issues need to be addressed in this study. Like numerous previous studies [22,50,74,75], in the current study, we sought to provide a summarized modular structure across groups. However, modular structure might vary slightly across individuals, especially in the svMCI population. Future work will be necessary to identify modules in individual brain networks to explore whether there is any heterogeneity in modular structure across individuals or potential bias introduced by group-level analyses. Second, as a cross-sectional study, the current data are not able to reveal the relationship between imaging characteristics and the progression of svMCI. Moreover, we used a relatively small sample size. Thus, future longitudinal studies involving larger samples will be necessary to replicate our current findings with higher statistical power and produce more fruitful insights to understand the pathology of svMCI. Third, using resting-state fMRI techniques, we focused on functional brain networks in this study. It is necessary and important to introduce multimodal imaging techniques (such as diffusion tensor imaging) to provide a more comprehensive picture of the topological alterations of both structural and functional brain networks in svMCI in future studies. Finally, in this study, only AVLT scores were used to describe the behavioral deficits of the svMCI patients. Other rating scales that reflect the cognitive dysfunction associated with svMCI etiology, especially executive function, should be employed in future studies.

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Conflict of Interest

The authors declare no conflict of interest.

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