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Structural brain network measures are superior to vascular burden scores in predicting early cognitive impairment in post stroke patients with small vessel disease

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ABSTRACT

Objectives: In this cross-sectional study, we aimed to explore the mechanisms of early cognitive impairment in a post stroke non-dementia cerebral small vessel disease (SVD) cohort by comparing the SVD score with the structural brain network measures.

Method: 127 SVD patients were recruited consecutively from a stroke clinic, comprising 76 individuals with mild cognitive impairment (MCI) and 51 with no cognitive impairment (NCI). Detailed neuropsychological assessments and multimodal MRI were performed. SVD scores were calculated on a standard scale, and structural brain network measures were analyzed by diffusion tensor imaging (DTI). Between-group differences were analyzed, and logistic regression was applied to determine the predictive value of SVD and network measures for cognitive status. Mediation analysis with structural equation modeling (SEM) was used to better understand the interactions of SVD burden, brain networks and cognitive deficits.

Results: Group difference was found on all global brain network measures. After adjustment for age, gender, education and depression, significant correlations were found between global brain network measures and diverse neuropsychological tests, including TMT-B ($r = -0.209$, $p < .05$), DSST ($r = 0.206$, $p < .05$), AVLT short term free recall ($r = 0.233$, $p < .05$), AVLT long term free recall ($r = 0.264$, $p < .05$) and Rey-O copy ($r = 0.272$, $p < .05$). SVD score showed no group difference and was not correlated with cognition tests. Network global efficiency (E_{Global}) was significantly related to cognitive state ($p < .01$) but not the SVD score. Mediation analysis showed that the standardized total effect ($p = .013$) and the standardized indirect effect ($p = .016$) of SVD score on cognition was significant, but the direct effect was not.

Conclusions: Brain network measures, but not the SVD score, are significantly correlated with cognition in post-stroke SVD patients. Mediation analysis showed that the cerebral vascular lesions produce cognitive dysfunction by interfering with the structural brain network in SVD patients. The brain network measures may be regarded as direct and independent surrogate markers of cognitive impairment in SVD.

1. Introduction

Cerebral small vessel disease (SVD) refers to a set of pathological processes affecting perforating cerebral arterioles, capillaries and venules, and is recognized as a major vascular contributor to stroke, dementia, mood disturbance and gait problems (Pantoni, 2010). SVD is the most common cause of vascular cognitive impairment (VCI) and may be responsible for up to 45% of dementia (Gorelick et al., 2011),

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secondary only to the dementia after Alzheimer's disease (AD) (Dichgans & Leys, 2017). Early detection and prevention are particularly essential since few specific treatments are available. Given that the underlying pathogenesis is still debated (Bos et al., 2018), multimodal neuroimaging techniques are usually employed to detect the lesions responsible for SVD. There are a number of recognized structural markers of SVD on MRI (Wardlaw et al., 2013), including white matter hyperintensities (WMH), lacunes, cerebral microbleeds (CMBs), and enlarged perivascular spaces (EPVS), etc. These individual imaging features of SVD are inter-related, and their respective correlations with cognition have been demonstrated (Makin et al., 2013; Prins & Scheltens, 2015; Patel et al., 2013; Arba et al., 2018) but inconsistently (Banerjee et al., 2016, 2018).

One approach to quantifying cerebral vascular brain injury (CVBI) due to SVD is to use a composite score by combining such lesion burdens in a semi-quantitative manner as proposed by Staals et al. (Huijts et al., 2013; Staals et al., 2014) The relationship of SVD score and cognitive function has not been widely examined in cohorts from different clinical settings (Staals et al., 2015). Another approach to examine the impact of SVD is to explore large-scale white matter connectivity of the brain with structural network measures using graph theoretical analysis (Bullmore & Sporns, 2009). The small world property of brain networks highlights a state of functional integration and segregation, making the brain work in a more efficient and economical way (Bullmore & Sporns, 2009; He et al., 2007). Several researchers have demonstrated that structural brain network disruption is significantly correlated with cognitive impairment in AD (Reijmer et al., 2013) and SVD (Tuladhar et al., 2016; Tuladhar et al., 2016). One group (Tuladhar et al., 2016) conducted a longitudinal study to explore if structural brain network measures could predict incident dementia, and showed that thirty-two patients who developed dementia five years later showed abnormalities in structural brain network properties at baseline.

Both SVD score and structural brain network measures were significantly correlated with cognition in previous studies (Staals et al., 2014). However, their direct comparison within one SVD cohort has not been performed, as was done in this study. As a result, we aimed to compare the SVD score and the structural brain network measures in a post-stroke SVD cohort and to provide some evidence for the underlying mechanisms of early cognitive impairment in SVD. Besides, we aimed to find a more downstream neuroimaging marker in the process of cognitive decline due to SVD.

2. Materials and methods

2.1. Participants

One hundred twenty-seven post stroke patients with SVD but without dementia were recruited consecutively from the stroke clinic at the Department of Neurology, Renji Hospital, an affiliated teaching institution of School of Medicine, Shanghai JiaoTong University from July 2015 to February 2018 (Renji Cerebral SVD Cohort Study, RCCS, http://www.clinicaltrials.gov, NCT01334749). Each subject underwent a standard baseline evaluation including neurological examination, complete sociodemographic and clinical data including vascular risk factors (VRF), neurologic examination, neuropsychological assessment and multimodal MRI examination. The recruitment criteria were as follows: (1) at least 6 years for education; (2) age 50 to 85 years; (3) at least 1 month after the clinical lacunar stroke; (4) presence of subcortical lacunar infarct(s) and WMH on MRI; (4) modified Rankin score ≤ 3 points (Quinn et al., 2009); (5) Informed consent form signed by participant.

The following exclusion criteria were applied: (1) WMH due to non-vascular dysfunction (e.g., sarcoidosis, multiple sclerosis and brain irradiation, etc.); (2) cortical and/or cortico–subcortical non-lacunar territorial infarcts and watershed infarcts; (3) other specific causes of cognitive impairments (e.g., Alzheimer's disease, Parkinson's disease, normal pressure hydrocephalus, hypothyroidism, etc.); (4) severe depression (17-item Hamilton Depression Rating Scale score ≥ 24) (Hamilton, 1960); (5) intracranial and extracranial vascular stenosis ≥ 50%; (6) cardiogenic cerebral embolism; (7) alcoholism or illicit drug use disorder or major psychiatric disorder; (8) inability to perform neuropsychological tests or contraindication to MRI; (9) dementia diagnosis by major neurocognitive disorder criteria of the Diagnostic and Statistical Manual of Mental Disorders, Fifth Edition (DSM-5) (Association, A.P, 2013).

The study was approved by the Research Ethics Committee of Renji Hospital School of Medicine, Shanghai Jiao Tong University (China).

2.2. Neuropsychological assessment

A battery of multi-domain neuropsychological tests was performed on each subject within 1 week of the MRI examination. The Montreal Cognitive Assessment (MoCA) (Pendlebury et al., 2012) and Mini Mental State Examination(MMSE) (Cockrell & Folstein, 1988) were used to assess overall cognitive performance, whereas the other neuropsychological tests were grouped into four key cognitive domains as follows: (1) attention and executive function: Trail-Making Tests A and B (Jun-Chao Lu et al., 2006), Stroop color-word test (Stroop, 1935), digit symbol substitution test (Lezak et al., 2004) and animal naming test (1 min) (Benton & Hamsher, 1983); (2) visuospatial function: Rey-Osterrieth Complex Figure Test (copy) (Shin et al., 2006); (3) language function: Boston Naming Test (30 items) (Guo et al., 2006); (4) memory: auditory verbal learning test (short and long delayed free recall) (Qihao Guo et al., 2009).

Functional status was assessed by the Katz basic activities of daily living (BADL) (Katz et al., 1963) and Lawton and Brody instrumental activities of daily living (IADL) scales (Brody, 1969) administered to the patients' primary caregivers, which include 6 basic items and 8 instrumental items respectively. The Hamilton Depression Rating Scale (HDRS) was performed for rating depressive symptoms and participants were diagnosed depression if HDRS > 7 points. The norms used were based on mean scores of each measurement from a sample of typical, elderly community members in Shanghai, China (Guo et al., 2007; Qihao et al., n.d.). We defined cognitive impairment as score of 1.5 standard deviations below the normative mean on any neuropsychological test. Because some of the patients had a degree of disability due to stroke, we carefully determined which part of the disability was cognitive and which was due to physical sequelae. All SVD patients were divided into two groups including mild cognitive impairment (MCI) and no cognitive impairment (NCI). MCI was diagnosed by mild neurocognitive disorder criteria of DSM-5 (Association, A.P, 2013).

2.3. MRI acquisition

A multimodal, whole-brain MRI protocol was acquired using a 3.0 T MRI scanner (Signa HDxt; GE HealthCare, Milwaukee, WI, USA). An eight-channel standard head coil with foam padding was used to restrict head motion. The following whole-brain sequences were obtained: (1) 3D-fast spoiled gradient recalled (SPGR) sequence images (TR = 6.1 ms, TE = 2.8 ms, TI = 450 ms, slice thickness = 1.0 mm, gap = 0, flip angle = 15°, FOV = 256 × 256 mm^2, number of slices = 166); (2) axial T2-weighted fast spin-echo sequences (TR = 3013 ms, TE = 80 ms, FOV = 256 × 256 mm^2, number of slices = 34); (3) T2-fluid attenuated inversion recovery (FLAIR) sequences:TE = 150 ms, TR = 9075 ms, TI = 2250 ms, FOV = 256 mm^2, number of slices = 66); (4) DTI sequence (TR = 17,000 ms, TE = 87.5 ms, matrix = 128 × 128, FOV = 256 mm × 256 mm, NEX = 1, slice thickness = 2 mm, gap = 0, 20 diffusion-weighted scans with b value of 1000s/mm^2 and b0 = 0); (5) Gradient Recalled Echo (GRE) T2-weighted sequence:TR = 53.58 ms, TE = 23.93 ms, flip angle = 2°, matrix = 320 × 288, FOV = 240 × 240 mm^2, slice thickness = 2 mm, NEX = 0.7, gap = 0, and slices = 72).

2.4. Rating and evaluation of SVD lesions on MRI

Individual CVBI was determined by applying the STRIVE criteria (Wardlaw et al., 2013). Periventricular and deep WMH were both

graded using the Fazekas score from 0 to 3 using T2 FLAIR sequences (Fazekas et al., 1987). Lacunes were defined as focal round or oval lesions in the subcortical white matter, thalamus, or basal ganglia, between 3 and 15 mm in diameter (cerebrospinal fluid-like low signal on T1WI and central cerebrospinal fluid-like low signal surrounded by high signals on T2 FLAIR sequence). Microbleeds were defined as small (< 5 mm), homogeneous, round foci of low signal intensity on Gradient Recalled Echo (GRE) T2*-weighted sequences in cerebellum, brainstem, basal ganglia, white matter, or cortico-subcortical junction ruling out vessel flow voids and other artifacts. The microbleed anatomical rating scale (MARS) was employed to evaluate the number of CMBs (Gregoire et al., 2009). EPVS was defined as the shape of circle, oval or linear, tubular structure with clear boundaries consistent with the perforating artery, and the signal was the same as cerebrospinal fluid on the T1WI, T2WI, and FLAIR sequences (low signal on T1WI, high signal on T2WI, low signal on FLAIR sequence), with no contrast enhancement and occupancy effects, and excluded other lesions such as tumors and lacunes. The EPVS is generally about 3 mm to 15 mm in diameter. The number of perivascular gaps in basal ganglia and centrum semiovale was recorded and scored according to the method of Maclulich (Maclullich et al., 2004). Score: 0 point: no EPVS; 1 point: 1 to 10 EPVS; 2 points: 11 to 20 EPVS; 3 points: 21 to 40 EPVS; 4 points: ≥41 EPVS. The above CVBI were rated by two experienced observers blinded to clinical data (Staals et al., 2014). We conducted a test–retest reliability analysis in 15 random samples, which yielded an intra-class correlation coefficient (ICC) of 0.779 for total Fezakas score, 0.858 for CMB numbers, 0.877 for EPVS numbers and 0.895 for Lacune numbers.

The UBO Detector (Jiang et al., 2018) was used to detect and calculate the WMH volume. It mainly contains two steps including pre-processing and WMH extraction. (1) Coregistration: register FLAIR image to T1 image; (2) T1 image segmentation: T1 image is segmented to generate individual GM(grey matter), WM(white matter) and CSF(cerebral spinal fluid) probability maps (3) DARTEL: warp each individual's T1 image the standard DARTEL space, and generate the flow field of each subject from the native space to DARTEL space;(4) Register to DARTEL: all the coregistered FLAIR images and GM, WM and CSF probability maps are brought to DARTEL space according to the flow field; (5) Non-brain tissue removal; (6) FAST Segmentation of FLAIR image; (7)WMH extraction: k-NN (k-nearest neighbors) learning algorithm was applied for the extraction of WMH, with a k of 9 and a probability threshold of 0.7.

2.5. SVD score

SVD score was computed for the presence of Lacunes, WMH, CMBs, and EPVS by an ordinal scale varying from 0 to 4 points, counting all four types of injury. The presence of Lacunes and CMBs were defined as the presence of 1 ≥ Lacune (1 point if present) or ≥ 1 CMBs (1 point if present). A point was awarded as either confluent deep WMH (Fazekas score 2 or 3) or irregular periventricular WMH extending into the deep white matter (Fazekas score 3) (1 point if present). The presence of EPVS was defined as moderate to severe (grade 2–4) in the basal ganglia (1 point if present). We conducted an inter-rater reliability analysis and the ICC for SVD score was 0.784.

2.6. Structural network construction

The DTI data was pre-processed to produce a fractional anisotropy (FA) map for each voxel and were analyzed to construct a structural network using the Pipeline for Analyzing Brain Diffusion Images toolkit (PANDA, www.nitrc.org/projects/panda) (Cui et al., 2013), a software based on FSL and MATLAB. Nodes and edges were defined as below. In a large-scale structural brain network, nodes represent automated anatomical labeling (AAL) atlas according to the parcellation of cerebral cortex into 90 anatomical regions (45 for each hemisphere with cerebellar regions excluded) and edges represent connection between two nodes if a fiber bundle was present. In brief, for the definition of nodes, T1-weighted images were nonlinearly registered to the MNI152_T1_Template and then the warping transformation was applied to transform AAL atlas to T1 native spaces. Whole brain deterministic diffusion tensor tract graph was conducted and streamlines were terminated unless the fiber turned at an angle > 45° or met a voxel with an FA < 0.2 (Basser et al., 2000). The strength of this connection was weighted by the fiber number (FN) between the two regions, resulting in a 90 × 90 FN-weighted undirected connectivity matrix for each subject at last.

2.7. Network analysis

Network analysis produces a number of global network measures using graph theoretical network analysis toolbox, a suite of MATLAB functions and MATLAB-based interface for processing (GRETNA; http://www.nitrc.org/projects/gretna) (Wang et al., 2015). Network sparsity was utilized to accomplish a thresholding procedure and this strategy helped exclude confounding effects of spurious relationships in interregional connectivity matrices. The sparsity threshold we used ranged from 0.1 to 0.3 with an interval of 0.01, which has been shown to have good small-world characteristics in previous studies (Korgaonkar et al., 2014; Xie et al., 2017). The small world properties were quantified across all selected thresholds (0.10 ≤ sparsity ≤ 0.30, in 0.01 increments), including γ (normalized clustering coefficient), λ (normalized characteristic path length) and σ (small-worldness).- Global network measures we focused on in this study quantify the integrity and integration of whole brain network, which were shown to be sensitive to structural network differences among SVD patients. Global efficiency (E_{Global}) reflects how efficiently information is exchanged over the whole network. Local efficiency (E_{Local}) measures clustering and specialization within a network and calculates how efficient communication is between the first neighbors of a given node when it is removed. Network strength measures the fiber number connecting given nodes in a weighted binary network. We also characterized the nodal property with nodal efficiency (E_{Nodal}) representing the efficiency of parallel information transfer of that node in the network. A summary statistic was calculated as the area under the curve (AUC) across all thresholds instead of using single threshold matrix (He et al., 2009).

2.8. Statistical analysis

All statistical analyses were performed on SPSS (version 22, Chicago, IL). Participant characteristics were compared between MCI and NCI individuals using independent sample *t*-test for continuous variables, the Mann–Whitney *U* test for nonparametric variables, and the $\chi 2$-test for gender and vascular risk factors. Spearman correlation analyses were used for the associations between SVD score and multi-domain cognitive scores and partial correlation was for network measures. The depression, age, gender and education levels of each subject were imported as covariates and FDR (false discovery rate) correction was performed in the statistical analysis for the large number of multiple comparisons. Binary logistic regression analysis was performed, with SVD score and network impairment as independent variables and cognitive state as dependent variable (MCI and NCI). Age, gender and education level of each subject were corrected before analysis and variance inflation factors were calculated for terms in logistic model and indicated no significant multicollinearity. Finally, estimates of direct and indirect causal mediation effects of the relationship between SVD load and cognitive function by network measures in SVD were obtained with structural equation modeling (SEM). The maximum likelihood method was used for model estimation. Bootstrap was used to examine the mediation effect (number of bootstrap sample = 2000, 95%bias-corrected confidence interval). SPSS Amos Version 24.0 software (SPSS, Chicago, IL, USA) was used for mediation analysis. A two-tailed *p*-value of < 0.05 was considered statistically significant.

Table 1
Demographic and clinical characteristics of CSVD patients.

	MCI n = 76	NCI n = 51	P-value
Demographic factors			
Male (%)	57 (75.0)	41 (80.4)	0.524
Age, mean (SD),	65.34 (7.087)	65.29 (7.322)	0.971
Education, mean (SD)	10.12 (2.723)	11.31 (2.970)	0.021
Depression (%)	11 (14.5)	6 (11.8)	0.660
Vascular risk factors			
Hypercholesterolemia (%)	8 (10.5)	5 (9.8)	0.895
Diabetes Mellitus (%)	27 (35.5)	22 (43.1)	0.388
Hypertension (%)	52 (68.4)	38 (74.5)	0.459
Smoking (%)	31 (40.8)	26 (51.0)	0.258
Neuropsychological tests			
MMSE,median (IQR)	27 (3)	29 (2)	< 0.001
MoCA, mean (SD)	21.95 (3.39)	26.02 (2.30)	< 0.001
TMT-B, mean (SD)	257.44 (111.63)	152.79 (34.45)	< 0.001
Stroop-C, mean (SD)	117.21 (46.26)	84.42 (14.81)	< 0.001
DSST, mean (SD)	26.44 (10.01)	35.67 (8.69)	< 0.001
VFT, mean (SD)	13.88 (4.30)	16.40 (3.15)	< 0.001
BNT, median (IQR)	23 (5)	26 (4)	< 0.001
AVLT-4, mean (SD)	3.49 (1.77)	6.23 (1.88)	< 0.001
AVLT-5, mean (SD)	2.79 (1.84)	5.77 (2.05)	< 0.001
Rey-O copy, median (IQR)	34 (8)	36 (2)	< 0.001

Data represent number (percentage), mean ± standard deviation (age and education); Two-sample t-tests were performed to assess group comparison for age and education, the χ2-test for gender and vascular risk factors. p-Value < .05 was considered to be statistically significant. Abbreviations: CSVD, cerebral small vessel disease; MCI, mild cognitive impairment; NCI, no cognitive impairment; MMSE, Mini Mental State Examination; MoCA, Montreal Cognitive Assessment(MoCA); TMT-B, Trail-Making Tests B; Stroop C, Stroop color-word test; DSST, digital span substitution test; VFT, verbal fluency test; BNT, Boston Naming Test; AVLT-4/5, auditory verbal learning test short and long delayed free recall; Rey-O copy, Rey-Osterrieth Complex Figure Test (copy);SD, standard deviation; IQR: interquartile range.

3. Results

3.1. Demographics

Of the cohort (n = 127), 76 SVD patients were diagnosed as MCI and the remaining 51 patients as NCI. The demographic characteristics, vascular risk factors and cognitive tests scores are listed in Table 1. MCI and NCI groups were well matched for age and sex, and there were no significant differences in risk factors between the two groups (all $p > .05$). The education level of MCI was lower than that of NCI ($p < .05$). MCI patients had lower scores in each cognitive test compared with NCI subjects.

3.2. Neuroimaging findings

Both MCI (mild cognitive impairment) group and NCI (no cognitive impairment) group showed good small world properties across all thresholds ($\gamma > 1$, $\lambda \approx 1$, $\sigma > 1$). The differences in CVBI, DTI measures and structural network measures between the two groups are shown in Table 2. MCI patients had higher WMH Fezakas scores and lacune numbers. However, the SVD score characterizing CVBI showed no significant difference between the two groups. WMH volume was significantly higher in MCI group than in NCI group. E_{Global}, E_{Local} and network strength values were significantly lower in MCI than those in NCI subjects. The nodes with impaired efficiency in MCI group compared with NCI group are shown in Fig. 1 ($p < .01$), which mainly located in the regions of frontal and temporal lobe. We performed the FDR correction and unfortunately we did not find any significant results.

3.3. Correlation analysis

Partial correlation analysis was performed between network measures and the scores of each cognitive domain with age, gender, education and depression correction. Significant correlations were observed between E_{Global} and most neuropsychological tests including TMT-B ($r = -0.209$, $p < .05$), DSST($r = 0.206$, $p < .05$), AVLT short term free recall ($r = 0.233$, $p < .05$), AVLT long term free recall ($r = 0.264$, $p < .05$) and Rey-O copy ($r = 0.272$, $p < .05$). Significant correlations were also found between E_{Local} and TMT-B($r = -0.229$, $p < .05$), and DSST($r = 0.235$, $p < .05$). For network strength, significant correlation was observed only with DSST($r = 0.255$, $p < .05$).

No significant correlation was observed between SVD score with any of neuropsychological tests. All p-values have undergone FDR correction (q = 0.05).

Significant correlation between WMH volume and cognitive scores, including TMT-B($r = 0.234$, $p < .05$), DSST ($r = -0.265$, $p < .05$), AVLT short term free recall ($r = -0.220$, $p < .05$), AVLT long term free recall ($r = -0.237$, $p < .05$), Rey-O copy($r = -0.456$, $p < .05$) and BNT ($r = -0.227$, $p < .05$).

Table 2
Neuroimaging findings of CSVD patients.

	MCI n = 76 (59.8%)	NCI n = 51 (40.2%)	P-value
CVBI lesions			
SVD score, median (IQR)	3 (2)	3 (1)	0.405
Lacunes, median (IQR)	2 (3)	2 (1)	0.044
CMBs, median (IQR)	0 (5)	0 (2)	0.334
WMH score, median (IQR)	4 (3)	2 (2)	0.040
EPVS, median (IQR)	27 (20)	23 (15)	0.109
WMH volume,mm^3, median (IQR)	17,730.56 (24,406.3)	10,108.13 (11,760.2)	0.017
Structual network measures			
E_{Global}, mean (SD)	0.10 (0.003)	0.10 (0.004)	0.004
E_{Local}, mean (SD)	0.15 (0.002)	0.15 (0.016)	0.015
Network strength, mean (SD)	80,941.19 (15,250.5)	91,553.81 (16,731.3)	0.001

Data represent mean ± standard deviation or median (interquartile range). P-value < .05 was considered to be statistically significant. Abbreviations: CSVD, cerebral small vessel disease; MCI, vascular mild cognitive impairment; NCI, no cognitive impairment; CMBs, cerebral microbleeds; WMH score, white matter hyperintensity score; EPVS, enlarged perivascular spaces; WMH volume, white matter hyperintensity volume; E_{Global}, global effect; E_{Local}, local effect, SD, standard deviation; IQR: interquartile range.

3.4. Logistic regression analysis

Binary logistic regression analysis was applied to explore if SVD score and(or) network measures could predict the cognitive state. We chose E_{Global} to represent network measure since it had the strongest correlation with cognitive functions. E_{Global} and SVD score were both entered into the regression model, while age, gender and education adjusted as potential confounders. Only E_{Global} exhibited a significant relationship with cognitive impairment ($p = .003$, OR = 0.41, 95%CI: 0.22–0.74), while SVD score showed no significant relationship ($p = .650$, OR = 1.11, 95%CI: 0.72–1.71).

3.5. Mediation analysis

The mediation analysis evaluating the network measures demonstrated goodness of fit for the data (CMIN/DF = 1.362, p = .061, goodness-of-fit index = 0.929, root mean square error of approximation = .054). The path coefficients are listed in the structural equation modeling (SEM), as shown in Fig. 2. The bootstrap statistical significance values of the direct and indirect paths are presented in the center of the diagram. The standardized total effect of SVD score to cognitive function was significant ($p = .013$), and the standardized indirect effect was also significant ($p = .016$). However, no significant standardized direct effect was observed from SVD score to cognitive

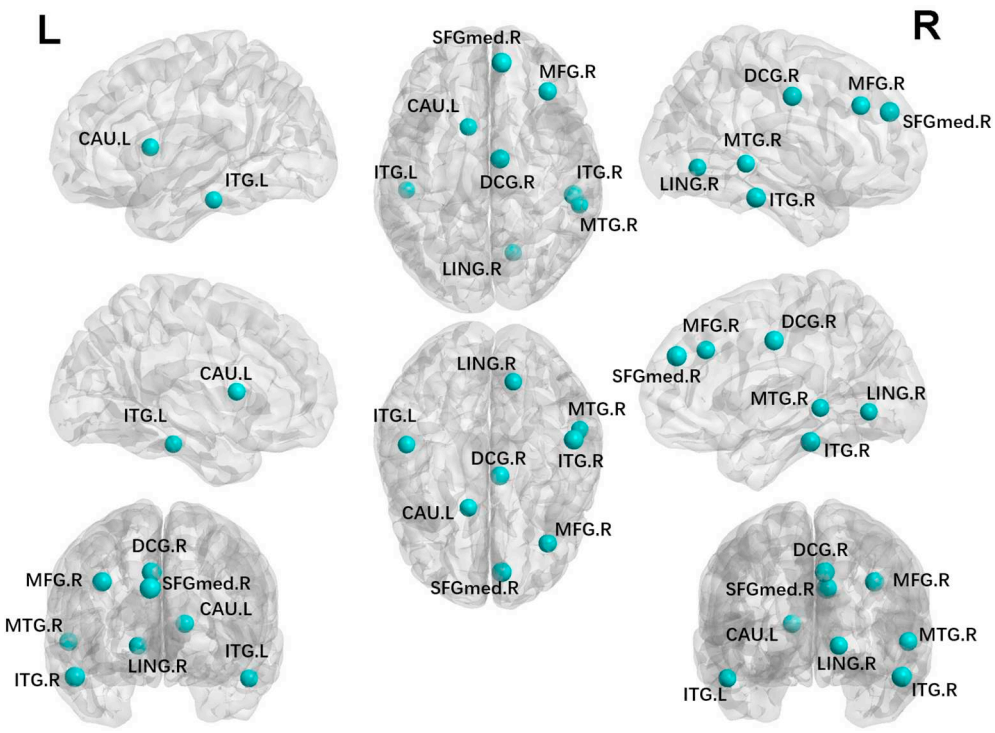

Fig. 1. Regions with impaired nodal efficiency in MCI group relative to NCI group.
The regions impaired in efficiency are shown with blue nodes, with node size representing the between-group differences in nodal efficiency ($p < .01$, uncorrected). Abbreviations: NCI = no cognitive impairment; MCI = mild cognitive impairment. MFG.R represents right middle frontal gyrus, SFGmed.R represents right superior frontal gyrus, medial, LING.R represents right lingual gyrus, PoCG.R represents right postcentral gyrus, CAU.L represents left caudate nucleus, MTG.R represents right middle temporal gyrus, ITG.L represents left inferior temporal gyrus, ITG.R represents right inferior temporal gyrus.

function ($p = .097$), which indicated that cognition impairment caused by structural lesions might be totally mediated by network disruption in this present study. The p value was still significant after FDR correction for standardized total and indirect effect.

4. Discussion

The SVD score, which comprises multiple CVBI measures as a composite, is gaining much attention recently. Its clinical relevance has been examined in community-dwelling older adults, participants with high vascular risks and stroke patients (Huijts et al., 2013; Staals et al., 2015; Del Brutto et al., 2018; Hatate et al., 2016) especially in relation to cognitive functions (Staals et al., 2015). In this study, the correlation between SVD score and cognitive functions was not significant. The construction of an SVD score acknowledges the diversity of CVBI in patient populations, but does not give consideration to the location and extent of the damage, especially for lacunes and CMBs. In our study, even though lacune numbers were higher in MCI than NCI, SVD scores did not differ. In relation to CMBs, 42.5% of the patients were positive, and 22% had 5 or more CMBs, but there were no group differences on CMB counts. Since the SVD scores did not differ between groups and did not correlate with individual cognitive test scores, it is not surprising that the SVD score emerged as a poor discriminator between the groups, even though the groups had significant cognitive differences.

Three determinants are important for the cognitive discriminating power of a neuroimaging score: are the individual lesions being quantified adequately, do they have independent relationships with cognition, and how should the composite score be calculated to reflect the relationship accurately? Although four CVBI measures that make up the SVD score in this paper are currently the most commonly used neuroimaging markers for SVD, some other potential measures such as cerebral microinfarcts and cortical superficial siderosis (cSS) were not included. Some previous studies have attempted to combine other lesions with the SVD score to improve its relationship with cognition or other clinical measure (Boulouis et al., 2017; Valenti et al., 2017). Moreover , the relationship between individual CVBI measures with cognitive outcome is not consistently reported. Of these, lacunes and WMHs have been more consistently associated with cognition (Pantoni, 2010) unlike CMBs and EPVS. CMBs are considered to have a threshold effect that only a high microbleed count (5 or more) being associated with an increased risk of cognitive deterioration (Patel et al., 2013; Akoudad et al., 2016). A meta-analysis of 5 population-based studies

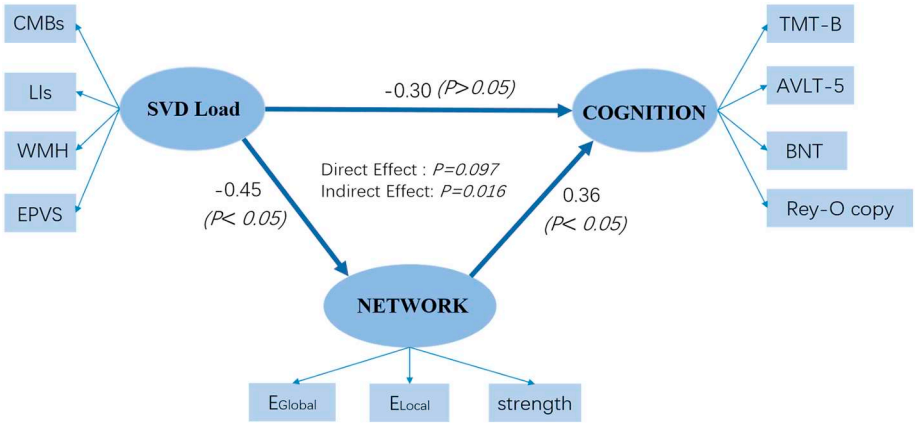

Fig. 2. Mediation analysis.
Path diagram for SVD load, network measures and cognitive function in a causal mediation framework. Numbers on the paths are standardized coefficients. The bootstrap statistical significance of the direct and indirect paths is presented in the center of the diagram. P-value < .05 was considered to be statistically significant. CMBs, cerebral microbleeds; WMH, white matter hyperintensity; EPVS, enlarged perivascular spaces; TMT-B, Trail-Making Tests B; AVLT-5, auditory verbal learning test long delayed free recall; BNT, Boston Naming Test; Rey-O copy, Rey-Osterrieth Complex Figure Test (copy); E_{Global}, global efficiency; E_{Local}, local efficiency.

investigating the association of EPVS with cognition in elderly without dementia showed no significant results (Hilal et al., 2018) A recent longitudinal study also did not find an association of EVPS with cognition during 5 years of follow-up (Benjamin et al., 2018).

While the composite SVD score is arguably more representative of the total SVD burden than a single measure, it combines the various measures on the basis of simple summation of the number rather than weight the lesions for their relative contributions. As shown in this study, the Fazakes score was not significant correlated with any cognitive scores but WMH volume was significantly related to multiple cognitive domains. In our study, the majority of the cohort had high SVD scores (i.e., 60% scored ≥3points). This may have led to a ceiling effect, thereby reducing the differentiating power of SVD score on cognition. Furthermore, the score does not take lesion location into account, which may be an important factor for cognition. Future attempts at composite measures should take the contribution of each lesion type, lesion location and other novel measures into consideration. It would also be important to examine the applicability of the composite measure in different clinical situations.

The salient finding of this study is that structural network characteristics correlated well with cognitive dysfunction, in accordance with previous literature (Lawrence et al., 2014). Global structural network connectivity was significantly higher in NCI group than in MCI group. E_{Global}, E_{Local} and network strength exhibited good correlations with multiple cognitive tests of different domains, and E_{Global} was an independent predictor of cognitive group membership. A longitudinal 5-year study supported the finding that structural network disruption plays a vital role in cognitive decline (Tuladhar et al., 2016). Consistent with our results, individual lesions were not independently associated with cognition in that study. Various pathological processes leading to demyelination, reduction in axonal number, and density are likely to affect white matter tract integrity directly or indirectly (Thomalla et al., 2004; de Laat et al., 2011). Since structural brain network represents the integrity of white matter connectivity, it is arguably more reflective of the mechanisms that underlie cognitive dysfunction than any other measures. Since cognitive function depends on the interconnection and integration of multiple cortical regions, individual lesion in focal regions may not accurately reflect the functional disturbance at the core of cognitive decline. The greater sensitivity of brain network measures may be due to the their continuous, quantitative property with high sensitivity to detecting subtle disruptions of microstructures in tissues (Smith & Beaudin, 2018). This is supported by the results of the mediation analysis which suggested that structural lesions intrinsically disrupt network efficiency, leading to cognitive impairment. Interestingly, the NCI group showed significantly higher E_{Nodal} than MCI group in several regions, including frontal and temporal lobes. These regions are parts of the default mode network (DMN) in functional network analysis. DMN is a distinct network comprised of two subsystems including the medial temporal lobe subsystem and the medial prefrontal subsystem (Buckner et al., 2008) and several studies have found that the functional connectivity is gradually interrupted mainly in the frontal, parietal and temporal cortex with the cognitive decline, (Yi et al., 2012; Papma et al., 2012; Sang et al., 2018) which may be attributed to the disruption of white matter fibers.

SVD usually presents with the insidious onset of minor stroke(s) but it may gradually lead to cognitive impairment in a long time with various stages and a progressive course. Therefore, it is particularly important to find a surrogate neuroimaging marker to assess and track the progress of cognitive status. The network measures exhibited more reliable correlation with cognitive impairment than SVD score in this cohort. Besides, the mediation analysis may implicate that network measures may be a downstream indicator for the cognitive decline.

Our study had some limitation. First, our sample size is relatively small, although we consider the study to be adequately powered for the analyses being presented. Second, it is a cross-sectional study and causal inference should not be drawn from such a study, for which longitudinal data with repeat measurements are necessary. Third, deterministic fiber tracking has several limitations, such as failure to track crossing fibers and low signal-to- noise ratio. Future technical advances are likely to improve this. Fourth, this study focuses on the structural brain network measures but without functional brain network information. In the future, structural and functional brain networks analyses conducted in large samples from multiple centers in longitudinal studies may help further clarify the underlying mechanisms of cognitive dysfunction in SVD.

5. Conclusion

Our study provides some evidence for the underlying mechanisms of early cognitive impairment in SVD, by comparing the relationship of the SVD score and structural brain network measures with cognitive test measures. We found that brain network measures served as mediators between conventional CVBI, and were independent surrogate markers of cognitive function. Our work suggests that the study of brain networks may be more informative than examining individual lesions in understanding the impact of SVD on cognition.

Conflict of interest

None.

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