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Research paper

Structural network connectivity impairment and depressive symptoms in cerebral small vessel disease

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ABSTRACT

Background: Cerebral small vessel disease (SVD) can disrupt mood regulation circuits and cause depressive symptoms which may occur prior to onset of other symptoms. However, the topological network alterations in SVD with depressive symptoms remained unclear. We aim to investigate how these changes in structural network were related to depressive symptoms in SVD.

Methods: We recruited 20 SVD with depressive symptoms (SVD + D), 20 SVD without depressive symptoms (SVD-D) and 16 healthy control (HC) individuals. Graph theory and diffusion tensor imaging (DTI) were applied to construct a structural network. We compared networks between groups, and examined the relationships between network properties, conventional measures of MRI, and depressive symptoms.

Results: The structural network was significantly disrupted in global and regional levels in both SVD groups. SVD + D group showed more severe impairment of global network efficiency, and lower nodal efficiency and less connections within multiple regions like hippocampus, amygdala and several cortical structures. The disruption of network connectivity was associated with depressive symptoms and MRI measures of SVD, however, no mediation effect of network efficiency was detected between MRI measures and depressive symptoms.

Limitation: The relatively small sample size and lower spatial resolution of DTI-based network limited our power of investigation.

Conclusions: The brain structural network is significantly disrupted in SVD + D and the impairment is related to severity of vascular damages and depressive symptoms. The study provides evidence for the role of structural network damage in SVD-related depressive symptoms and might be a potential novel disease marker for SVD and comorbid depression.

1. Introduction

Cerebral small vessel disease (SVD), characterized by white matter hyperintensities (WMH), lacunar infarcts, microbleeds and global atrophy, is the most common type of cerebral vascular disease (Pantoni, 2010) and known to be associated with cognitive and motor dysfunction in the elderly (O'Brien, 2006; Pantoni, 2010). Depressive symptoms are also a major clinical feature of SVD, about 10% of which suffer these symptoms, however, they are largely under-researched (van Sloten et al., 2015).

The vascular depression hypothesis proposed that cerebrovascular disease, including SVD, may increase the risk of developing depressive symptoms (Sneed et al., 2008; Taylor et al., 2013). Recent findings showed that WMH, lacunar infarcts and microbleeds were associated with more severe depressive symptoms (Direk et al., 2016), especially when SVD damages located in cortical-subcortical circuits which mediate mood regulation and emotion perception (Fu et al., 2010; Grool et al., 2012; van Uden et al., 2015; Wu et al., 2011). SVD patients with depressive symptoms showed lower white matter integrity on diffusion tensor imaging (DTI) (Brookes et al., 2014; Pasi et al., 2016). To get a better understanding of the "disconnection syndrome" (O'Sullivan et al., 2001) which involves damages in multiple domains that regulate emotional and cognitive function , magnetic resonance imaging (MRI) and graph theory have been applied in many connectome studies, recently.

Graph theoretic and DTI approaches have made it possible to quantify the topological structural organization of complex neural networks across the entire brain (Bullmore and Sporns, 2009; Gong et al., 2009). Topological architectures of brain networks are usually evaluated from multiple aspects: global properties (e.g., local efficiency, and global efficiency), edge connectivity and nodal properties (e.g., efficiency, degree, and betweenness) (Bullmore and Sporns, 2009; Fornito et al., 2013). SVD showed significant changes of network properties, which are related to conventional MRI measures of SVD

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and to clinical symptoms, especially cognitive impairment (Kim et al., 2015; Lawrence et al., 2014; Reijmer et al., 2016; Tuladhar et al., 2016). However, it remains unclear as to how the topological organization of anatomical brain networks change in SVD patients with depressive symptoms.

In this study, we sought to investigate changes of structural network topological properties in SVD patients with depressive symptoms and how the alteration of networks effects SVD-related depressive symptoms.

2. Methods

2.1. Participants

We prospectively recruited a total of 56 participants (Han Chinese and right-handed), including 20 SVD with depressive symptoms (SVD + D), 20 SVD without depressive symptoms (SVD-D) and 16 healthy control (HC) individuals. All the SVD patients were enrolled from Zhongnan Hospital of Wuhan University, whereas the healthy participants were from local community. Participants provided prior written informed consent. Study protocols were approved by the Zhongnan Hospital Research Ethics Committee (Table 1).

Participants of the study received a series of neuropsychological assessments including Montreal Cognitive Assessment (MoCA), 15-item Geriatric Depression Scale (GDS), Hamilton Anxiety Scale. The SVD patients were recruited based on most common signs of SVD on neuroimaging (WMH and/or lacunes) (Pantoni, 2010; Tuladhar et al., 2016). Depressive symptoms were assessed by 15-item GDS with a cut-off score 6 (Friedman et al., 2005). All SVD + D patients were drug-naïve and diagnosed with their first episode of depression. Exclusion criteria included a history of major neurological or psychiatric disorders (e.g., stroke, dementia, Parkinson's disease, multiple sclerosis, seizure, bipolar disorders or psychotic), head injury with loss of consciousness and the inability to undergo an MRI.

2.2. Image acquisition

The participants were scanned using a 3.0 T MRI scanner (Magneto Trio, Siemens Erlangen, Germany), laying supine with the head snugly fixed by a belt and foam pads to minimize head motion. 3D T1-weighted MPRAGE axial images: Repetition time/ echo time (TR/TE) = 1900/2.1 ms, thickness/gap = 1.0/0 mm, flip angle = 9°, inversion time = 900 ms, matrix = 256 × 256, field of view (FOV) = 240 mm × 240 mm. Diffusion tensor imaging : Diffusion was measured along 60 noncollinear directions (b value = 1000 s/mm^2), and an additional image without diffusion weighting (b = 0), TR/TE = 6000 ms/90 ms, matrix = 128 × 128, FOV = 240 mm × 240 mm, number of excitations = 3, slice thickness = 3 mm with no gap.

Table 1
Demographic, vascular risk factors and conventional MRI measures.

	HC (n = 16)	SVD-D (n = 20)	SVD + D (n = 20)	F/χ^2 value (p value)
Age, y, mean (SD)	61.56 (5.60)	62.50 (5.96)	62.65 (6.75)	0.16 (0.855)
Gender, male, n (%)	7 (43.8)	11 (55.0)	9 (45.0)	0.58 (0.749) [d]
GDS, mean (SD)	2.06 (1.39)	3.00 (1.69)	8.80 (2.24)	75.08 (< 0.001) [b, c]
MoCA, mean (SD)	26.19 (1.64)	25.05 (1.61)	24.45 (2.01)	4.34 (0.018) [b]
Hypertension, n (%)	7 (43.8)	17 (85.0)	18 (90.0)	11.8 (0.003) [d]
Diabetes, n (%)	1 (6.3)	5 (25.0)	5 (25.0)	2.55 (0.280) [d]
Hyperlipidemia, n (%)	3 (18.9)	6 (30.0)	7 (35.0)	1.18 (0.554) [d]
WMH, %, mean (SD)	0.026 (0.019)	0.465 (0.197)	0.496 (0.246)	33.29 (< 0.001) [a, b]
Lacunes, n, (%)	2 (12.5)	6 (30.0)	5 (25.0)	1.58 (0.453) [d]

ANOVA showed significant difference in GDS, MoCA scores and percentage of WMH volumes in total intracranial volume. χ^2 test showed significant difference in hypertension. [a, b, c]: *Post hoc* analysis revealed the source of ANOVA, Bonferroni-corrected ([a]: HC vs SVD-D; [b]: HC vs SVD + D; [c]: SVD-D vs SVD + D), [d]: χ^2 test was performed.
Abbreviations: HC = Healthy controls; SVD-D = Small vessel disease without depressive symptoms; SVD + D = Small vessel disease with depressive symptoms; GDS = Geriatric Depression Scale; MoCA = Montreal Cognitive Assessment; WMH = White matter hyperintensities; SD = Standard deviation.

2.3. Data preprocessing

DTI data were preprocessed and analyzed using the Pipeline for Analyzing Brain Diffusion Images toolkit (PANDA, www.nitrc.org/projects/panda) (Cui et al., 2013), which is a MATLAB toolbox that utilized FMRIB Software Library (FSL) (Behrens et al., 2003), Pipeline System for Octave and Matlab (PSOM), Diffusion Toolkit, and MRIcron. In brief, raw DTI data were corrected for head motion and eddy-current distortions by realigning all diffusion-weighted images to b = 0 image. Subsequently, the diffusion tensor elements were calculated by the Stejskal and Tanner equation and then were diagonalized to obtain three eigenvalues and eigenvectors. The fractional anisotropy (FA) map was then generated.

2.4. Measurement of WMH and lacunes

WMH segmentation and volume calculation was processed by the lesion growth algorithm (Schmidt et al., 2012) as implemented in the Lesion Segmentation Toolbox version 2.0.1 (LST, www.statisticalmodelling.de/lst.html) for SPM. The threshold for the algorithm was set at 0.30 after visually comparing WMH probability lesion maps derived by threshold ranging from 0.05 to 1.0. WMH volume was adjusted for head size by calculating its percentage relative to total intracranial volume. Lacunes were segmented manually using 3D T1-weighted images by 2 trained raters. Sharp delineated cerebrospinal-fluid-like hypointensities with diameter between 2 and 15 mm on T1-weighted images and were carefully distinguished from perivascular spaces (Wardlaw et al., 2013).

2.5. Structural network construction

The network nodes and edges were defined by the following procedures.

2.6. Network node definition

The nodes of DTI-based structural network were defined by automated anatomical labeling (AAL) atlas (Tzourio-Mazoyer et al., 2002), which was used to parcellate the cerebral cortex into 90 anatomical regions (45 for each hemisphere; Table s1) without cerebellum. The detailed procedure of parcellation has been previously described (Gong et al., 2009). Specifically, the individual 3D-T1 images were coregistered to b = 0 images, and then, normalized the 3D-T1 images to the Montreal Neurologic Institute (MNI) space. Finally, the inverse transformations were applied to the AAL atlas, resulting in DTI native-space cortex parcellations for each one.

2.7. Network edge definition

Deterministic fiber assignment with the continuous tracking (FACT) algorithm was used to track the white matter fibers. The tracking continued to one of the defined nodes unless the fiber made a turn greater than 45° or met a voxel with an FA less than 0.2 (Mori et al., 1999). The weights of a network edge were defined as the fiber number (FN) between two connected nodes. At last, a 90 × 90 matrix was generated, representing the FN-weighted structural network of each subject.