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Network topology and machine learning analyses reveal microstructural white matter changes underlying Chinese medicine Dengzhan Shengmai treatment on patients with vascular cognitive impairment

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ABSTRACT

With the increasing incidence of cerebrovascular diseases and dementia, considerable efforts have been made to develop effective treatments on vascular cognitive impairment (VCI), among which accumulating practice-based evidence has shown great potential of the traditional Chinese medicine (TCM). Current randomized double-blind controlled trial has been designed to evaluate the 6-month treatment effects of Dengzhan Shengmai (DZSM) capsules, one TCM herbal preparations on VCI, and to explore the underlying neural mechanisms with graph theory-based analysis and machine learning method based on diffusion tensor imaging (DTI) data. A total of 82 VCI patients were recruited and randomly assigned to drug (45 with DZSM) and placebo (37 with placebo) groups, and neuropsychological and neuroimaging data were acquired at baseline and after 6-month treatment. A total of 82 VCI patients were recruited and randomly assigned to drug (45 with DZSM) and placebo (37 with placebo) groups, and neuropsychological and neuroimaging data were acquired at baseline and after 6-month treatment. After treatment, compared to the placebo group, the drug groups showed significantly improved performance in Alzheimer's Disease Assessment Scale-Cognitive subscale (ADAS-cog) score ($p < 0.001$) and the other cognitive domains. And with the reconstruction of white matter structural network, there were more streamlines connecting the left thalamus and right hippocampus in the drug groups ($p < 0.001$ uncorrected), with decreasing nodal efficiency of the right olfactory associated with slower decline in the general cognition ($r = -0.364$, $p = 0.048$). Moreover, support vector machine classification analyses revealed significant white matter network alterations after treatment in the drug groups (accuracy of baseline vs. 6-month later, 68.18 %). Taking together, the present study showed significant efficacy of DZSM treatment on VCI, which might result from white matter microstructure alterations and the topological changes in brain structural network.

1. Introduction

With the aging of the global society, incidence of cerebrovascular diseases and dementia has been rapidly increasing. It is estimated that the total number of dementia patients will reach 152 million in 2050, and 25 % of them will be Chinese [1]. Vascular cognitive impairment (VCI) is considered to be the second most common form of dementia after Alzheimer's disease [2,3]. And it not only has a huge impact on the life quality of patients, but also poses a heavy burden on families and society [4,5].

VCI refers to a wide variety of medical conditions caused by cerebrovascular risk factors and cerebrovascular diseases, and it varies from

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mild cognitive impairment to dementia [3,6,7]. The revision of the VCI definition [8] not only broadened the range, distinguished the degree of severity, and improved the consistency and standardization of the disease, but also revealed the practical implications of early prevention and intervention towards VCI risk factors. As VCI is drawing rapidly increasing attention because of its high prevalence and potential reversibility [9], the earliest stages of VCI are the critical periods for preventing or changing the course of cerebrovascular diseases, retarding the progress of VCI, and incorporating dementia drugs into a therapeutic plan.

At present, the primary treatment for VCI is prevention by treating vascular diseases and other risk factors linked to VCI [10]. Although studies have suggested that patients with VCI can benefit from donepezil and other medications [11], there is still dispute over the intervention effects of those medications in clinical trials. Traditional Chinese medicine (TCM) has shown effects with regard to the prevention and treatment of VCI [12–17], and has been widely used in clinical practice and has demonstrated good curative effects [18,19]. Dengzhan Shengmai (DZSM) capsule is a patented traditional Chinese medicine for the secondary prevention of stroke and its use is supported by evidence-based medicine. In the Chinese Pharmacopoeia 2015 edition, DZSM are composed of four prepared slices of Chinese crude drugs: Erigerontis Herba (EH), Ginseng Radix et Rhizoma (GR), Schisandrae Chinensis Fructus (SCF), and Ophiopogonis Radix (OR) [20]. The assay indicators of DZSM are scutellarin and 4,5-DiCQA [20]. Scutellarin is an herbal flavonoid glucuronide with multiple pharmacological activities and has multiple beneficial effects, such as anti-oxidant, anti-inflammation, vascular relaxation, anti-platelet, anti-coagulation, and myocardial protection [21]. Scutellarin, through binding to Aβ42, efficiently inhibits oligomerization as well as fibril formation and reduces Aβ oligomer-induced neuronal toxicity in cell line SH-SY5Y, which has the beneficial effects on intervention on development or progression of AD-like neuropathology [22]. DZSM protected against cognitive defects of AD through accelerating the scutellarin-mediated aggregation of Aβ into fibrils or protofibrils and reduction of soluble Aβ oligomers [23]. There was a meta-analyse showing that DZSM capsule appeared to improve neurological function and quality of life based on conventional therapy for ischemic stroke and DZSM capsule seemed generally safe for clinical application [24]. As the incidence of cognitive impairment-related diseases has increased, DZSM capsules have been widely used in the prevention of high-risk factors for dementia and the clinical treatment of cognitive impairment-related diseases in recent years.

At present, most of the evaluation methods regarding TCM in the treatment of VCI are neuropsychological tests, which are greatly influenced by education level. Recent work has suggested that the effects of vascular lesions on cognitive function were mediated through alterations in structural and functional connectivity [25]. Further promotion and more extensive use of TCM are limited by the lack of objective evaluation methods examining their effects on improving cognitive injury. Therefore, it is of great clinical significance for the use of TCM in the prevention and treatment of VCI to identify scientific methods to evaluate the effectiveness of clinical interventions.

Advanced neuroimaging techniques such as diffusion tensor imaging (DTI) can explore micro changes in white matter integrity and even the complex structural networks in patients with dementia or cognitive impairment [26,27], creating great opportunities for the discovery and efficacy evaluation of potential medications. Brain imaging could be incorporated in the design for any trial of VCI, with MRI being the complementary method for phase III studies [9]. As neuroimaging provides in vivo evidence that VCI may be a disease of the brain network, graph theoretical analysis (GTA) using DTI data can facilitate examination of large-scale white matter (WM) connectivity of the human brain from a network perspective [28]. With GTA quantifying the nature of network structures, recent results have shown that changes in network structures will explain the association between lesions of small vessel diseases observed on neuroimages and cognitive deficits [29,30].

By employing a dual outcome strategy (cognitive and brain global structural measures) [31], this double-blind placebo-controlled study aims to evaluate VCI patients' changes in behaviors and brain white matter after 6 month intervention with DZSM capsules, and to explore the structural mechanisms of TCM on VCI by DTI-based network construction and GTA, along with neuropsychological tests. This study might not only be of significance for explanations on the pathological mechanisms of VCI, but also serve as a methodological reference for future researches on evaluating the curative effects of TCM.

2. Methods

2.1. Study design and participants

This clinical trial was registered in the Chinese Clinical Trial Registry (ChiCTR-IPR-16009289), and the study's content was approved by China-Japan Friendship Hospital, and was a random double-blind controlled trial containing treatment (with DZSM capsules) and placebo (with placebo capsules), with the patients, caregivers, and site investigators blinded to the treatment allocations. The DZSM capsule is a widely used compound Chinese medicine that was approved by the China Food and Drug Administration (CFDA) in 2002, and the drugs used in this study were supplied by the sponsor and were provided to the participants at baseline. The components of the placebo were corn starch 80.57 %, caramel pigment 19.34 %, milk chocolate brown 0.04 %, lemon yellow 0.03 %, bitter agent 0.02 %. The patients were randomly assigned in a 1:1 ratio to orally administer 2 capsules of DZSM or placebo, which were identical in appearance, three times daily for 6 months. All participants received a neuropsychological assessment and MRI scanning by professional imaging staff at baseline and after 6 months of treatment.

To ensure the quality of the cognitive tests, the investigators were trained before the study began. All the patients were from China-Japan Friendship Hospital, and were diagnosed as VCI by at least two neurologists, and another neurologist performed all the recheck. We enrolled a total of 100 patients, 50 in the DZSM capsule group and 50 in the placebo group. 18 patients were dropped out, of which 7 for loss to follow-up, 5 for poor compliance, 6 for withdrawal, nobody for adverse reactions. Finally, 82 patients (45 in the drug group and 37 in the placebo group) completed the neuropsychological tests at baseline and after 6 months of treatment. These 82 participants were eventually included in the results analysis (demographic details in Table 1).

The trial inclusion criteria were as follows: (1) more than 45 years of age; (2) more than 6 years of education; (3) neither normal nor demented according to the criteria of the Diagnostic and Statistical Manual of Mental Disorders, Fourth Edition [32,33]; (4) objective evidence for cognitive impairment or cognitive decline, i.e., at least 1.5 standard deviations from norms adjusted for age and education in any cognitive domain [9]; (5) normal activities of daily living; (6) absence of a history of taking cholinesterase inhibitor medications. The MRI inclusion criteria were as follows [19]: (1) multiple (>3) supratentorial subcortical small infarcts (3–20 mm in diameter), with/without white matter lesions (WML) of any degree; or moderate to severe WML (score ≥ 2 according to the Fazekas rating scale) [34], with/without small infarct; or one or more strategically located subcortical small infarcts in the caudate nucleus, globus pallidus, or thalamus; (2) absence of cortical and watershed infarcts, hemorrhages, hydrocephalus, and WMLs with specific causes (e.g., multiple sclerosis).

The exclusion criteria included: (1) severe aphasia, physical disabilities, or any other factor that might have precluded completion of neuropsychological testing; (2) disorders other than subcortical vascular cognitive impairment without dementia that might have affected cognition; (3) diseases such as schizophrenia, inherited or inflammatory small vessel disease, serious bone and joint, liver, kidney, hematopoietic system and endocrine system disease as well as cancer; (4)

Table 1
Baseline characteristics of participants.

	Drug group n = 45	Placebo group n = 37	T/κ^2	P
Age	65.56 ± 8.32	65.97 ± 7.89	0.231	0.818
Gender (M/F)	22/23	20/17	0.051	0.641
Edu	11.56 ± 3.93	11.55 ± 4.62	0.003	0.998
Hypertension	27/18	17/20	1.613	0.204
Diabetes	16/29	9/28	1.209	0.272
Hypercholesteremia	25/20	27/10	2.655	0.103
Stroke History	26/19	21/16	0.009	0.926
CHD	5/40	5/32	0.109	0.741
ADAS-cog	10.89 ± 4.37	8.73 ± 6.67	1.758	0.083
MMSE	25.53 ± 3.70	26.27 ± 4.05	0.859	0.393
Episodic memory				
AVLT N5	3.44 ± 2.44	5.22 ± 5.69	1.893	0.062
AVLT N1-N5	22.38 ± 8.41	24.53 ± 12.28	0.933	0.354
R-O recall	13.26 ± 6.88	14.27 ± 7.44	0.616	0.540
Visual-spatial				
R-O copy	32.86 ± 6.63	32.51 ± 5.37	0.253	0.801
CDT	22.08 ± 6.50	22.41 ± 6.49	0.215	0.830
Working memory				
Digit span, back	3.89 ± 1.01	4.34 ± 3.69	0.789	0.432
Executive function				
TMT BA	117.19 ± 62.18	112.09 ± 98.77	0.278	0.782
Stroop CB	62.52 ± 33.59	44.59 ± 74.96	1.389	0.169
Attention				
SDMT	28.31 ± 11.43	29.35 ± 15.13	0.342	0.733
Reasoning				
Similarity	13.24 ± 4.78	13.92 ± 6.32	0.545	0.587
Language				
CVFT	40.11 ± 9.14	38.27 ± 8.89	0.885	0.379
BNT	23.67 ± 4.61	24.40 ± 3.94	0.751	0.455

Abbreviation: CHD = Coronary Heart Disease; ADAS-cog = Alzheimer's Disease Assessment Scale-Cognitive section; MMSE = Mini-Mental Status Examination; AVLT = Auditory Verbal Learning Test; ROCF = Rey-Osterrieth Complex Figure test; CDT = Clock-Drawing Test; CVFT = Category Verbal Fluency Test; BNT = Boston Naming Test; SDMT = Symbol Digit Modalities Test; TMT = Trail Making Test.
The values of hypertension, diabetes, hypercholesteremia, stroke history and coronary heart disease in the lines of drug group and placebo group were the number with certain disease/without certain disease.

alcohol or drug abuse disorder, or other medications that might have affected cognitive functioning, including tranquilizers, anxiolytics, hypnotics, nootropics, and cholinomimetic agents; (5) inability to undergo a brain MRI.

2.2. Neuropsychological testing

The primary outcome was the Alzheimer's Disease Assessment Scale-Cognitive subscale (ADAS-Cog) [35,36], which covered four domains (general, mental cognitive state, activities of daily living, and behavior). ADAS-Cog is considered as the gold standard for assessing the efficacy of antidementia treatments [37]. The secondary outcomes included the Mini-Mental Status Examination (MMSE) [38] scores and performance in seven cognition domains: (1) episodic memory: Auditory Verbal Learning test (AVLT) [39,40] and Rey-Osterrieth Complex Figure (ROCF)-Delay Recall test; (2) visual-spatial ability: Rey-Osterrieth Complex Figure (ROCF)-Copy [41] and Clock Drawing test (CDT) [42]; (3) working memory: digit span test backward [43]; (4) executive function: Stroop Color Word test (C-B time) [44,45] and Trail Making test (TMT) (B-A time) [46]; (5) attention: Symbol Digit Modalities test (SDMT) [47]; (6) reasoning: similarity test; and (7) language tests: Category Verbal Fluency test (CVFT) [48] and Boston Naming test (BNT) [49].

2.3. Data acquisition

Patients underwent MRI scans on a 3-T scanner (SIEMENS MAGNETOM Prisma syngo MR D13D) at Beijing Tiantan Hospital affiliated with the Captain Medical University. In all subjects, we acquired T1-weighted MR images and DTI scans. The T1-weighted images were acquired by using a magnetization-prepared rapid gradient echo (MPRAGE) sequence: 192 sagittal slices, slice thickness = 0.90 mm, repetition time (TR) = 2300 ms, echo time (TE) = 2.32 ms, field of view (FOV) = 240 × 240 mm^2, and acquisition matrix = 256 × 256. The diffusion tensor images were acquired by a single-shot EPI sequence: 75 axial slices, slice thickness = 2.0 mm, no gap, 30 diffusion directions with b = 1000s/mm^2, and b_0 = 0, TR = 8000 ms, TE = 60 ms, FOV = 282 × 282 mm^2, acquisition matrix = 128 × 128. Six subjects were excluded because of poor image quality.

2.4. Imaging data preprocessing

The preprocessing of the DTI data was performed following the steps of PANDA toolbox (http://www.nitrc.org/projects/panda/) [50], including eddy current and motion artifact correction, estimation of the diffusion tensor, diffusion metrics calculation, and diffusion tensor tractography. The fractional anisotropy (FA) value of each voxel was calculated. Tractography was performed to generate three-dimensional streamlines defining fiber tract connectivity, and tractography was terminated if it turned an angle greater than 45 degrees or reached a voxel with an FA less than 0.2.

2.5. Network construction and graph theoretical analysis

The WM connectivity network was modeled as an unweighted network comprising 90 nodes, defined by the automated anatomic labeling (AAL) template [51]. The workflow of the network construction is summarized in Fig. 1. For each participant, individual T1 images were co-registered to the b0 images in the DTI space and then nonlinearly transformed to the ICBM152 T1 template in the MNI space. We used inverse transformations to warp the AAL atlas from the MNI space to the DTI native space. After this step, we obtained 90 cortical and subcortical ROIs. Each ROI represented a distinct gray matter region and was considered as one network node. The threshold for the streamline was selected as 3 to define the edges of the binary network, which we considered that they were structurally connected when there were at least three fiber streamlines between two brain regions. The network edges were set to 1 as structurally connected and 0 for less than 3 streamlines. Therefore, a binary 90 × 90 WM structural network was constructed for each participant. And subsequent binary graph theory-based network analyses were performed in GRETNA (http://www.nitrc.org/projects/gretna/) [52]. To characterize the topological organization of the WM structural networks, several key graph measures were calculated, including global efficiency (GloE), shortest path length (Lp), clustering coefficient (Cp), and small-world parameters (Gamma and Lambda) [53], as well as regional measures including nodal efficiency and nodal LocE for local efficiency [54,55].

2.6. Statistical analysis

All statistical analyses were performed in SPSS version 22.0. A two-sample *t*-test or chi-square test was used to compare the group differences in age, sex, years of education and all neuropsychological tests at baseline. For the neuropsychological assessments and the structural network characteristics before and after treatments, repeated measures analysis of covariance (ANCOVA) was performed to evaluate the interaction and main effects (with age, sex, and education controlled). For each group separately, we also performed a two-sample *t*-test between the baseline and the second visit network matrix at each edge to test for significant differences in structural connectivity. Partial correlation analyses were conducted to explore the relationship between the changed cognitive performances and the significantly changed structural network characteristics, while controlling for age, sex, and

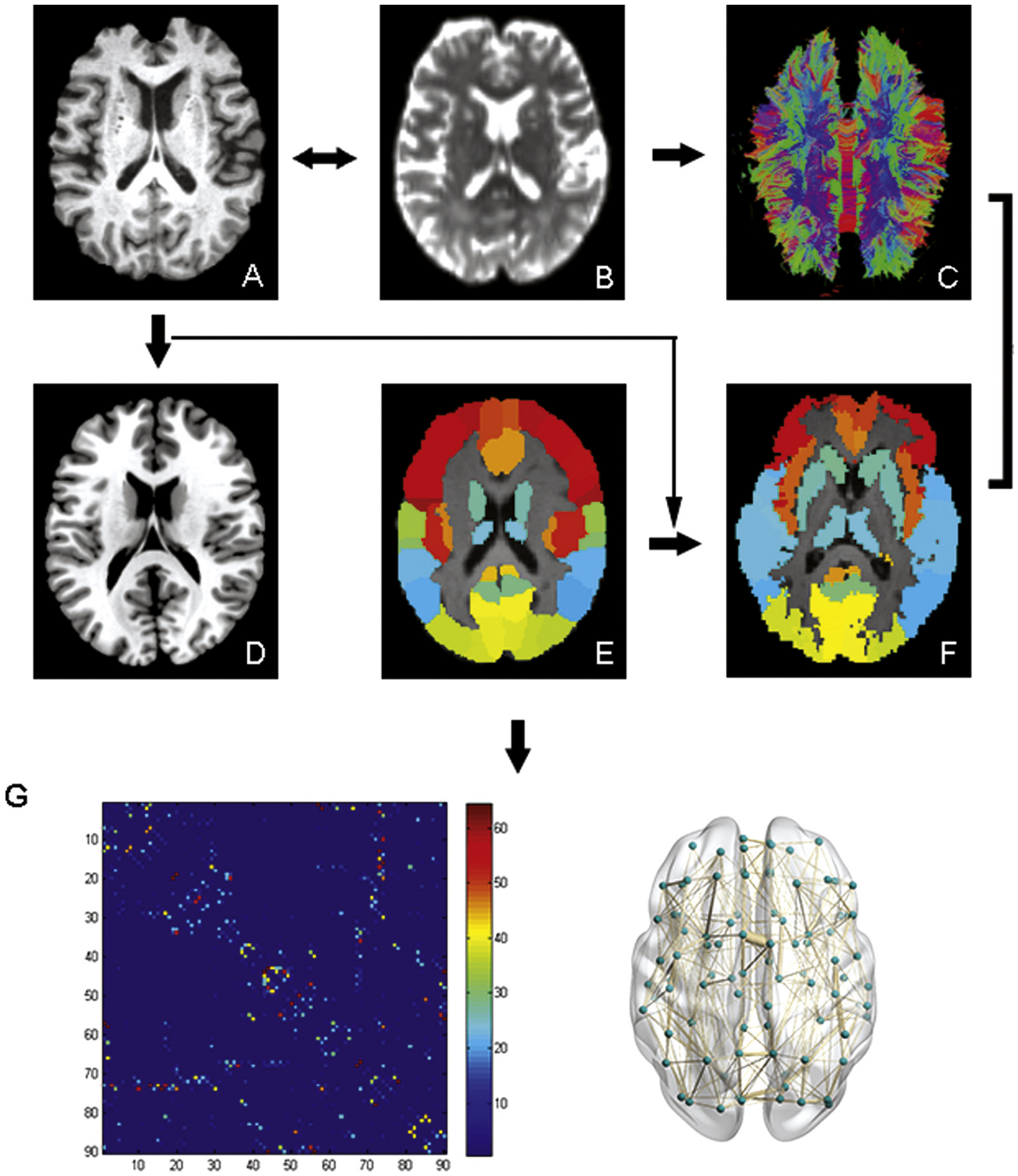

Fig. 1. The workflow of network construction.

education. All hypothesis tests were two-tailed, and P values ≤.05 were considered significant.

2.7. Network classification

Furthermore, we used a binary support vector machine (SVM) to determine whether classifiers based on machine learning technology could classify the structural network matrix into the at baseline and after treatment groups. A leave-one-subject-out cross validation and 1000 permutation tests were performed, and the classification performance was evaluated by the accuracy (ACC) and the area under the receiver operating characteristic (ROC) curve.

3. Results

3.1. Demographics and neuropsychological testing

There were no significant differences in age, sex, education, hypertension, diabetes, hypercholesteremia, stroke history, or coronary heart disease between the drug and placebo groups (Table 1). At

Table 2
Neuropsychological testing at two time points for both drug and placebo groups.

	Drug group (n = 45)		Placebo group (n = 37)		Main effect of time		Main effect of group		Interactions	
	Baseline	6 months later	Baseline	6 months later	F value	P value	F value	P value	F value	P value
ADAS-cog	10.89 ± 4.37	6.24 ± 3.54	8.73 ± 6.67	11.43 ± 7.21	7.155	0.009	1.424	0.236	73.158	< 0.001
MMSE	25.53 ± 3.70	27.18 ± 2.93	26.27 ± 4.05	24.35 ± 7.62	0.044	0.834	2.139	0.148	10.210	0.002
Episodic memory										
AVLT N5	3.44 ± 2.44	4.36 ± 2.52	5.22 ± 5.69	4.27 ± 3.29	0.030	0.864	1.298	0.258	6.420	0.013
AVLT N1-N5	22.38 ± 8.41	24.91 ± 8.77	24.53 ± 12.28	23.24 ± 12.10	1.704	0.196	0.034	0.854	4.709	0.033
R-O recall	13.26 ± 6.88	11.02 ± 6.98	14.27 ± 7.44	13.40 ± 10.65	2.572	0.113	1.108	0.296	0.729	0.396
Visual-spatial										
R-O copy	32.86 ± 6.63	32.22 ± 7.38	32.51 ± 5.37	30.19 ± 11.36	0.456	0.501	0.830	0.365	0.015	0.904
CDT	22.08 ± 6.50	23.89 ± 4.73	22.41 ± 6.49	20.68 ± 7.27	0.411	0.524	1.218	0.274	6.362	0.014
Working memory										
Digit span, backward	3.89 ± 1.01	4.09 ± 1.08	4.34 ± 3.69	4.05 ± 1.20	0.005	0.947	0.544	0.463	0.315	0.576
Executive function										
TMT BA	117.19 ± 62.18	128.33 ± 77.07	112.09 ± 98.77	95.14 ± 81.94	0.013	0.908	0.398	0.530	0.951	0.332
Stroop CB	62.52 ± 33.59	46.18 ± 36.45	44.59 ± 74.96	26.27 ± 57.63	2.322	0.132	4.553	0.036	0.111	0.740
Attention										
SDMT	28.31 ± 11.43	33.73 ± 13.72	29.35 ± 15.13	31.56 ± 17.25	12.204	0.001	0.008	0.929	0.511	0.477
Reasoning										
Similarity	13.24 ± 4.78	14.73 ± 5.12	13.92 ± 6.32	15.19 ± 5.09	6.183	0.015	0.066	0.797	0.245	0.622
Language										
CVFT	40.11 ± 9.14	40.84 ± 8.82	38.27 ± 8.89	38.16 ± 12.34	4.086	0.047	0.642	0.426	0.466	0.497
BNT	23.67 ± 4.61	22.42 ± 7.86	24.40 ± 3.94	21.65 ± 8.84	4.472	0.038	0.115	0.735	0.258	0.613

Abbreviation: ADAS-cog = Alzheimer's Disease Assessment Scale-Cognitive subscale; MMSE = Mini-Mental Status Examination; AVLT = Auditory Verbal Learning Test; ROCF = Rey-Osterrieth Complex Figure test; CDT = Clock-Drawing Test; CVFT = Category Verbal Fluency Test; BNT = Boston Naming Test; SDMT = Symbol Digit Modalities Test; TMT = Trail Making Test. The comparisons of the neuropsychological scores between the two groups (drug and placebo) within two time points were performed with the repeated ANCOVA (2 × 2).

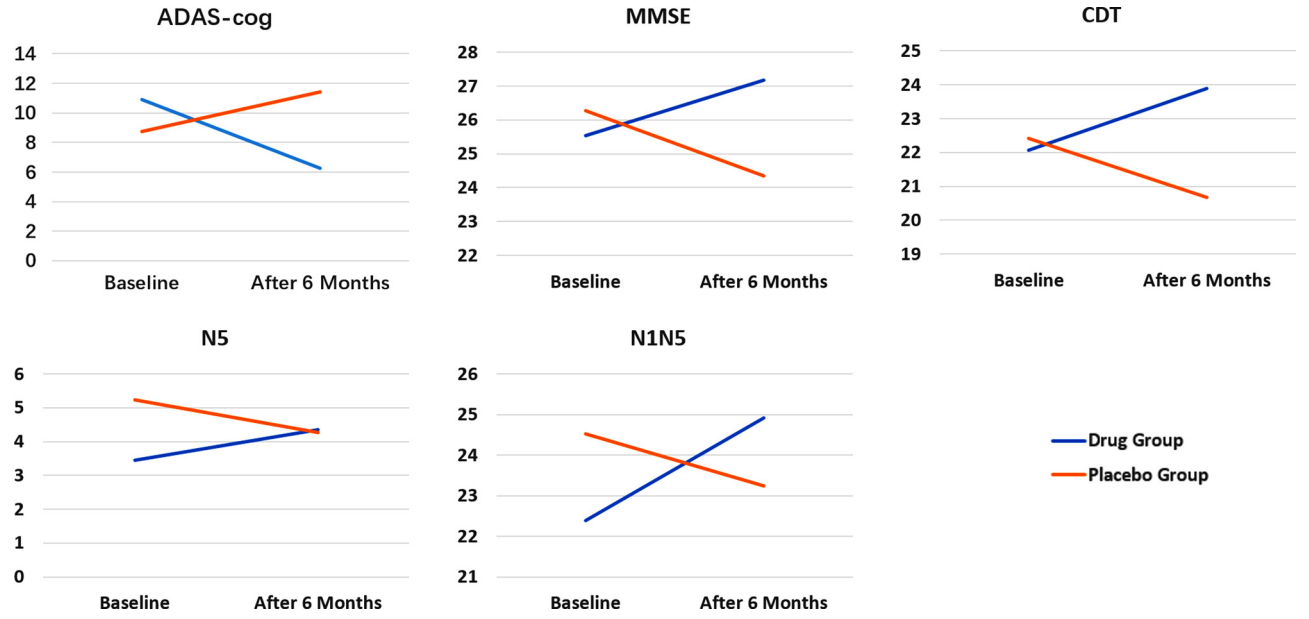

Fig. 2. The repeated ANCOVA on the neuropsychological testing scores. Significant group × time interactive effects were found in the ADAS-cog ($p < 0.001$), MMSE ($p = 0.002$), AVLT N5 ($p = 0.013$), AVLT N1-N5 ($p = 0.033$), and CDT ($p = 0.014$). The post-hoc analyses on time reveled that after treatment, the drug group presented better performance on ADAS-cog ($p < 0.001$), MMSE ($p = 0.031$), AVLT N1-N5 ($p = 0.011$) and CDT ($p = 0.019$), with worse performance in the placebo group on MMSE ($p = 0.023$).

baseline, no significant differences were found in the neuropsychological testing scores between the two groups ($p > 0.05$) (Table 1). For the repeated ANCOVA on cognitive scores, significant group × time interactive effects were found in the ADAS-cog ($p < 0.001$), MMSE ($p = 0.002$), AVLT N5 ($p = 0.013$), AVLT N1-N5 ($p = 0.033$), and CDT ($p = 0.014$) (Table 2). The interactive effects of ADAS-cog and MMSE were still significant after Bonferroni Multiple comparison correction, but group × time interactive effects of AVLT N5, AVLT N1-N5, and CDT were no longer significant. The post-hoc analyses on time reveled that after treatment, the drug group presented better performance on ADAS-cog ($p < 0.001$), MMSE ($p = 0.031$), AVLT N1-N5 ($p = 0.011$) and CDT ($p = 0.019$), with worse performance in the placebo group on MMSE ($p = 0.023$) (Fig. 2).

3.2. Network-level differences in structural connectivity

While there were more streamlines connecting the left thalamus and right hippocampus (part of the corpus callosum) after treatment in the drug group ($p < 0.001$, uncorrected, Fig. 3A), the placebo group showed remarkable decrease in structural connectivity, with no

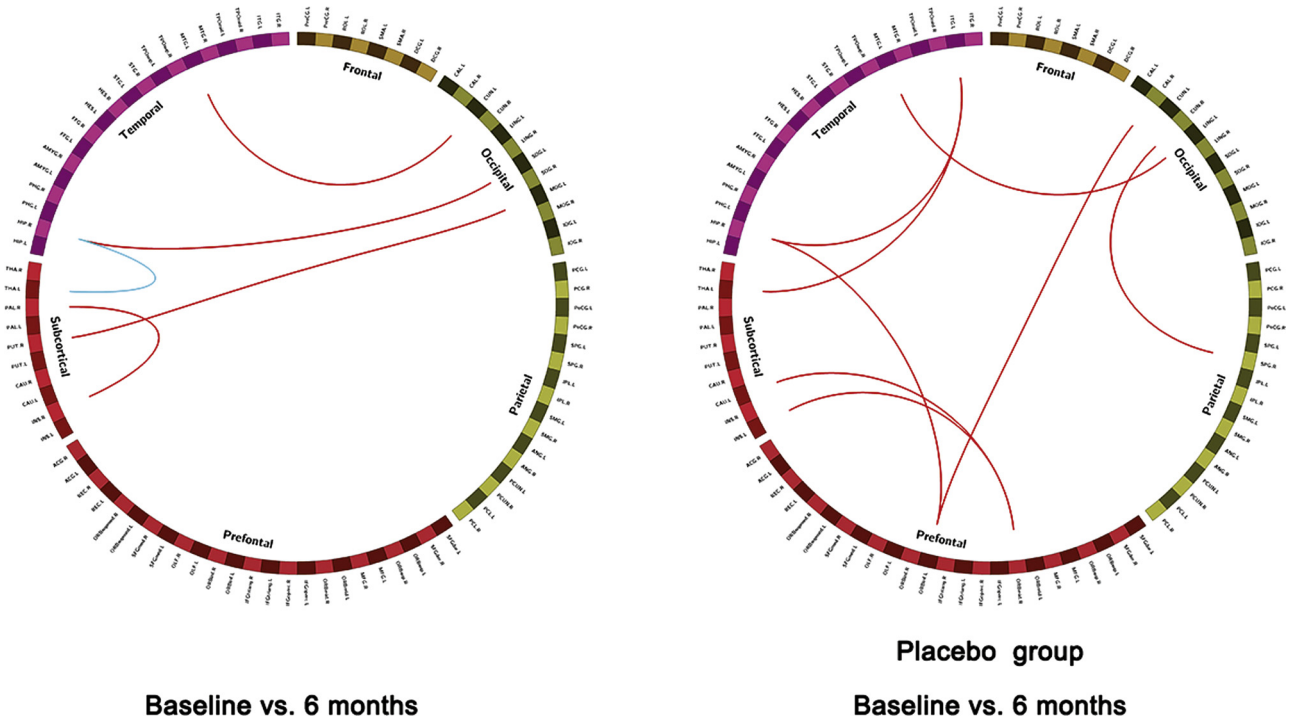

Fig. 3. The changed structural connectivity. (A) Changed white matter networks in the drug group after treatment (P < 0.001 uncorrected). (B) Changed white matter networks in the placebo group after follow-up (P < 0.001 uncorrected). (Blue: increased; red: decreased).

streamline increases found at the six-month follow-up (Fig. 3B).

3.3. Graph theoretical results

Both the drug and placebo groups showed typical small-world organization (Lambda ~ 1, Gamma > 1) of the WM structural networks. A significant group × time interaction effect was found for Lambda (p = 0.029), which indicated trend of changes in the drug group (Table 3). For the nodal characteristics, we found significant interaction effects for the nodal efficiency of the left olfactory gyrus (p = 0.050) and left superior parietal gyrus (p = 0.006), as well as for the nodal local efficiency of the right olfactory gyrus (p = 0.003) and left cuneus (p = 0.040). We also found a significant main effect of group in the right cuneus (p = 0.021) (Fig. 4, Table 3), and further simple effects analyses of group and time revealed that, after 6 months of treatment, the nodal efficiency of the left olfactory gyrus (p = 0.053) and left superior parietal gyrus (p = 0.063) showed decreasing trends in the drug group. No such trends were found in the placebo group. The results in graph theoretical results were not corrected for multiple comparisons.

3.4. Relationship between structural network characteristics and cognitive performance

The changes in the right olfactory local efficiency were negatively correlated with changes in MMSE scores (r = −0.364, p = 0.048) in the drug group, which suggested that decreased local efficiency may attenuate the cognitive decline (Fig. 5). None of the other global or local topological metrics showed a significant correlation with the cognitive scores.

Table 3
The interaction and main effects of network topological properties.

	Drug group		Placebo group		Main effect of time		Main effect of group		Interaction	
	Baseline	6 months later	Baseline	6 months later	F value	P value	F value	P value	F value	P value
Cp	0.42 ± 0.04	0.42 ± 0.06	0.40 ± 0.05	0.41 ± 0.06	0.638	0.428	1.129	0.292	0.005	0.943
Lp	2.53 ± 0.43	2.73 ± 1.34	2.67 ± 0.65	2.88 ± 1.70	1.019	0.317	0.458	0.501	0.001	0.979
Gamma	3.41 ± 0.74	3.28 ± 0.83	3.27 ± 0.79	3.26 ± 0.81	0.310	0.580	0.233	0.631	0.209	0.649
Lambda	1.10 ± 0.02	1.09 ± 0.02	1.09 ± 0.03	1.09 ± 0.02	0.006	0.940	0.149	0.701	5.037	0.029
Sigma	3.10 ± 0.64	2.30 ± 0.72	2.30 ± 0.68	2.97 ± 0.70	0.335	0.565	0.233	0.631	0.103	0.750
Global efficiency	0.40 ± 0.05	0.40 ± 0.07	0.39 ± 0.06	0.39 ± 0.08	0.155	0.695	0.818	0.370	0.051	0.822
Nodal efficiency										
Olfactory_L	0.35 ± 0.12	0.33 ± 0.15	0.29 ± 0.16	0.35 ± 0.12	1.083	0.302	0.424	0.518	4.008	0.050
Parietal_Sup_L	0.44 ± 0.05	0.44 ± 0.06	0.46 ± 0.05	0.40 ± 0.09	9.772	0.003	0.544	0.464	7.985	0.006
Nodal local efficiency										
Olfactory_R	0.58 ± 0.38	0.39 ± 0.39	0.45 ± 0.35	0.58 ± 0.34	0.311	0.579	0.109	0.743	9.326	0.003
Cuneus_L	0.73 ± 0.08	0.67 ± 0.20	0.70 ± 0.14	0.74 ± 0.11	0.257	0.614	0.251	0.618	4.432	0.040
Cuneus_R	0.70 ± 0.09	0.72 ± 0.08	0.75 ± 0.11	0.76 ± 0.09	0.590	0.446	5.585	0.021	0.077	0.783

For nodal efficiency and nodal local efficiency, only nodes with significant main effects or interactive effects were presented.

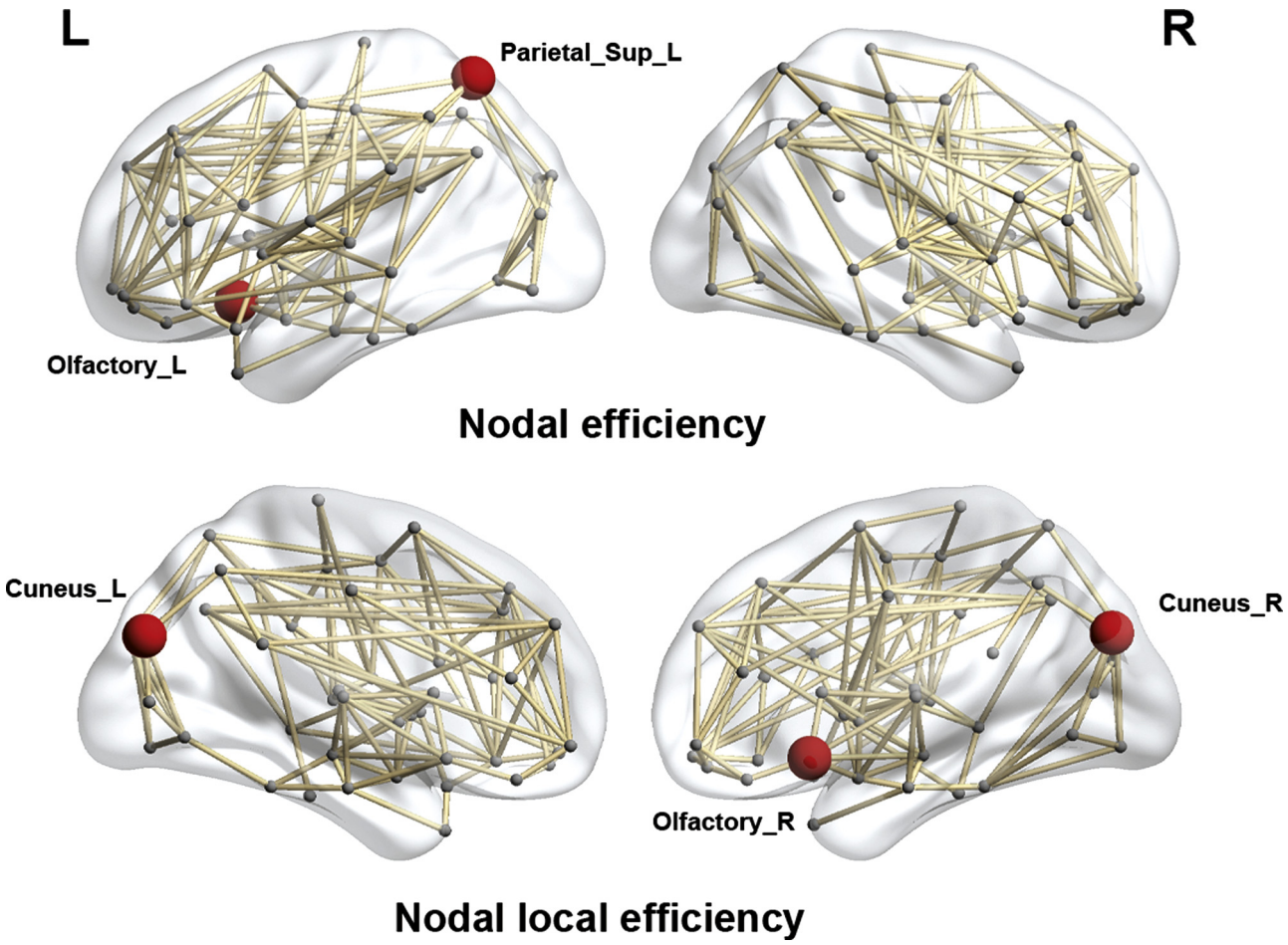

Fig. 4. The nodes shown significant interactions or main effects in efficiency.

3.5. Results of SVM classification

Fig. 6A showed that the SVM classified the network matrix of the drug group at baseline vs. after treatment with an accuracy of 68.18 %. However, this classification accuracy in the placebo group was only 48.15 %. ROC curves of these classifiers are displayed in Fig. 6B.

4. Discussion

This study suggested that DZSM capsule treatment for 6 months was effective in improving cognitive status and increasing white matter connectivity and may have improved the degree of small-world attribute in patients with VCI. These results indicated that the drugs could treat VCI efficiently and showed the value of using neuroimaging techniques and machine learning analyses in clinical trials to assess biomarkers and to understand the underlying brain mechanisms.

After 6 months of treatment, the drug group showed significant group and time interaction effects on the cognitive scores of the ADAS-cog, MMSE, AVLT, CDT, etc. The ADAS-Cog was able to measure impairments in multiple cognitive domains [56]. The minimal clinically relevant change on the ADAS-Cog often used in clinical studies to define responders varied between 3 and 5 points, with a change of ≥ 4 being recommended by a consensus committee of the FDA [57]. In this study, the ADAS-cog decreased by > 4 points after treatment in DZSM group, indicating that the treatment was effective. The MMSE can be used as an effective tool for easily detecting the basic cognitive status of patients with high sensitivity [58,59]. The AVLT, including the immediate memory, delayed memory and recognition tests, can comprehensively assess types of memory impairment [39]. The CDT mainly reflected visuospatial function [60,61]. The above results suggested that DZSM capsules could improve general cognitive function, episodic memory and visuospatial function of VCI patients. Our results suggested that ADAS-cog, MMSE, AVLT and CDT had been improved by 6 months of DZSM capsules treatment. The aggregation of Aβ can induce oxidative stress, inflammation and neurotoxicity, which further leading to cognitive dysfunction. Scutellarin, one of the Essential ingredients of DZSM

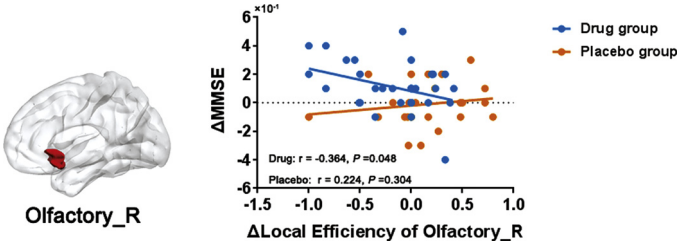

Fig. 5. The correlation between the nodal local efficiency and changed cognition.

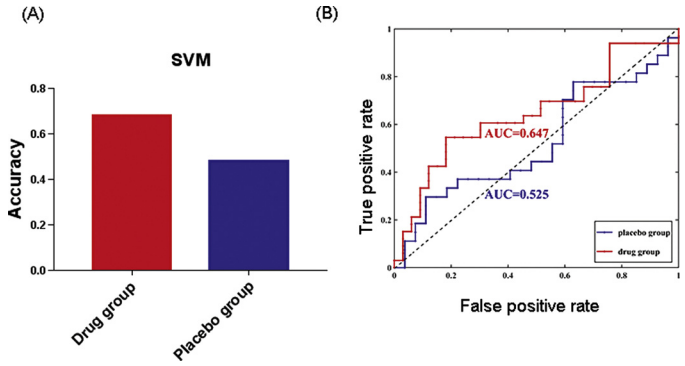

Fig. 6. The classifying accuracy and ROC curves of the SVM classifiers in drug and placebo group separately.

capsules, has been reported to reduce the aggregation of Aβ [1,2]. Therefore, we suspected that DZSM capsules may improve its general cognitive ability, situational memory and visual spatial ability by reducing the aggregation of Aβ.

This study found that the structural connections between the left thalamus and the right hippocampus in the drug group were strengthened after the intervention, and the white matter fiber bundle may have been located in the callosum ($P < 0.001$, uncorrected) [62]. The thalamus, as a location for strategic infarcts in vascular dementia, is involved in cognition [63]. With its dense cortical and subcortical connections, the thalamus is a vital subcortical region that supports cognitive functions that are known to be reduced in VCI, including executive/attention functions and memory, among others [64]. Lesions in the thalamus not only affect declarative memory but also interfere with nondeclarative motor skill learning [65]. The hippocampus has extensive connections with the cerebral cortex and is involved in memory. Li et al. suggested that increased GABAergic neurotransmission and reduced activity of extracellular regulated protein kinase existed in the bilateral hippocampi and thus contributed to cognitive impairment after ischemic stroke [66]. The brain connectivity network was progressively disrupted as cognitive impairment worsened, with an increased number of decreased connections between brain regions [67]. In this study, the placebo group showed more decreased structural connectivity than the drug group, and no enhanced white matter connectivity was observed at 6 months of follow-up.

Both the drug and placebo groups demonstrated small-world architectures (Gamma/Lambda > 1) in our study. Large-scale networks could reveal attributes that accommodate and promote the segregation and integration of neural information [68]. The small-world properties, which represented the network information transmission efficiency, are were usually disrupted in many neuropsychological diseases [69,70], including vascular diseases [71,72]. Our results found that the drug group showed an increased trend in small-worldness after treatment, which may suggest an improvement in network efficiency. Graph theoretical methods recently provided valuable tools to explore the underlying therapeutic mechanisms of drugs on a more global level [73,74]. To our best knowledge, this current study is one of the first ten researches to apply graph theory to evaluate the impact of TCM on structural neuronal networks.

Many reports showed that the white matter network efficiency could be considered as the good index for the brain structure [75]. Small vessel disease (SVD), which has extensive effects on the microstructures of the brain, is the most common and most homogeneous form of VCI [76]. Measures of network disruption were associated with MRI markers of SVD and cognitive function [77]. Network efficiency was found to mediate the effects of SVD-related MRI lesions on cognitive function [78]. Global network efficiency is sensitive to the cumulative effect of multiple manifestations of SVD on brain connectivity and may therefore serve as a useful marker for functionally relevant disease progression in clinical trials [79]. We found a significant group-by-time interaction in nodal efficiency, where the left olfactory cortex and cuneus in the drug group showed a downward trend and the placebo group showed no such trend after 6 months of treatment. Nodal efficiency expressed the importance of the nodes for information communication within the network. Lawrence and colleagues found that 85 out of 90 nodes showed significantly decreased nodal efficiency in SVD; there were 5 regions, including the bilateral olfactory cortex [80], that did not show this effect. Another study also found an increased nodal local efficiency in the olfactory cortex in SVD patients [72]. Gong et al. found that 14 regions localized in the frontal and temporal cortex showed increased regional efficiency in aging, which may indicate a putative compensatory mechanism of the cortical network [81].

In our study, we found significant group × time interaction effects for the nodal efficiency of the left olfactory gyrus and left superior parietal gyrus, as well as for the nodal local efficiency of the right olfactory gyrus and left cuneus. We further investigated the relationships between the network measures and cognition, and the results suggested that the change in nodal efficiency in the right olfactory cortex in the drug group was significantly correlated with the improvements in MMSE scores. However, the placebo group showed no such correlation. The structure and function of the olfactory cortex are usually involved in the pathology of dementia [82]. A previous study showed that the olfactory bulb and tract volume were significantly correlated with global cognitive performance in dementia [83]. The correlation between behavioral performance and the white matter structural network indicated that the changes in the connectivity attributes of the olfactory cortex were correlated with the improvement in cognitive ability. Thus, we speculated that the DZSM capsule may play an important role in increasing network efficiency in some key brain regions.

In recent years, SVM has been successfully applied in the context of disease diagnosis, transition prediction and treatment prognosis, using both structural and functional neuroimaging data [84]. In our study, we found the SVM classified the network matrix of the drug group at baseline vs. after treatment with an accuracy of 68.18 %. However, this classification accuracy in the placebo group was only 48.15 %, basically at the random level (50 %). These results clearly showed that the DZSM capsule had caused obvious, at least above the random level, brain structural network connectome changes. And more importantly, these kinds of change were accompanied by improvements in cognition, represented by significant reduction of ADAS-cog as well as increase of MMSE.

This study demonstrated the efficacy of DZSM capsules on VCI through the white matter structural network method, which was feasible and innovative. The strengths of the study lie in the combination of neuropsychological tests, MRI DTI technical network construction and GTA methods, which has not been used in past clinical trials assessing TCM treatment of VCI.

Neuroimaging is critically important in the diagnosis and management of VCI [3]. The use of MRI is a surrogate marker for small vessel

disease, which was supported by natural history data that showed progression of these lesions [85]. The structural network based on diffusion MRI data could more intuitively depict the authentic structural connections of encephalic regions. DTI is useful in the assessment of surrogates for microarchitectural integrity in normal-appearing and lesioned white matter, in the determination of structural connectivity of white matter, and in tractography [86]. Structural brain imaging, especially MRI, remains the imaging method of choice for vivo assessment of cerebrovascular diseases [9].

For the past few years, substantial research on the prevention and treatment of VCI with TCM has been performed. DZSM capsules have received approval from the China Food and Drug Administration for treating apoplexy sequelae caused by deficiency of *Qi* and *Yin* and blood stasis in cerebrovascular diseases. Attempts to develop new treatments for cognitive impairment associated with VCI have been fraught with lengthy time requirements, expensive costs, and high failure rates. Repurposing older drugs to new indications might provide a lower-risk alternative [87]. Chinese doctors treat VCI with DZSM capsules, which has good efficacy.

In the future, we can further extend this study in the following aspects. Our study has shown good efficacy within 6 months. An adequately designed study lasting for 1–3 years will be necessary to fully explore the symptomatic efficacy of DZSM capsules in this disorder as well as its efficacy in the prevention of VCI. In addition, blood-brain barrier (BBB) breakdown is an early biomarker of human cognitive dysfunction [88] and is initially compromised in VCID, leading to a chronic hypoxic state and hypoperfusion [89]. Chronic hypoperfusion has long been implicated in VCI pathogenesis [90]. In the future, we can further combine DTI and cerebral atrophy to comprehensively analyze the influence of vascular lesions on the distal connecting regions of the brain [91], assess perfusion alterations in patients with VCI by arterial spin labeling (ASL) [92], and quantify the permeability of the partial BBB of the human brain by dynamic contrast-enhanced (DCE)-MRI [88,93].

5. Conclusion

In conclusion, this study preliminarily suggested that DZSM capsule treatment for 6 months is effective for the cognitive and global function of VCI patients, providing a promising choice for early intervention in the disease. Current TCM clinical studies have not used DTI brain network methods to evaluate the efficacy, but our results revealed the regulatory effect of DZSM capsules on the white matter structural network from the perspective of human brain connectivity, providing a visual, quantifiable and noninvasive evaluation method for the treatment of VCI with TCM.

Declaration of Competing Interest

The authors declare no conflict of interest.

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Appendix A. Supplementary data

Supplementary material related to this article can be found, in the online version, at doi:https://doi.org/10.1016/j.phrs.2020.104773.

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