Type 2 diabetes mellitus (T2DM) is associated with cognitive dysfunction and may even progress to dementia. However, the underlying mechanism of altered functional topological organization and cognitive impairments remains unclear. This study explored the topological properties of functional whole brain networks in T2DM patients with graph theoretical analysis using a resting-state functional magnetic resonance imaging (rs-fMRI) technique. Thirty T2DM patients (aged 51.77 ± 1.42 years) and 30 sex-, age-, and education-matched healthy controls (HCs) (aged 48.87 ± 0.98 years) underwent resting-state functional imaging in a 3.0 T MR scanner in addition to detailed neuropsychological and laboratory tests. Then, graph theoretical network analysis was performed to explore the global and nodal topological alterations in the functional whole brain networks of the T2DM patients. Finally, correlation analyses were performed to investigate the relationship between the altered topological parameters, cognitive performances and clinical variables. Compared to HCs, we found that T2DM patients displayed worse performances in general cognitive function and several cognitive domains, including episodic memory, attention and executive function. In addition, T2DM patients showed a higher small-worldness ($\sigma$), a higher normalized clustering coefficient ($\gamma$) and a higher local efficiency ($E_{loc}$). Moreover, decreased nodal topological properties were mainly distributed in the occipital lobes, frontal lobes, left median cingulate and paracingulate gyri, and left amygdala, while increased nodal topological properties were mainly distributed in the right gyrus rectus, right anterior cingulate and paracingulate gyri, right posterior cingulate gyrus, bilateral caudate nucleus, bilateral cerebellum 3, bilateral cerebellum crus 1, vermis (1, 2) and vermis 3. Some disrupted nodal topological properties were correlated with cognitive performance and HbA1c levels in T2DM patients. This study shows altered functional topological organization in T2DM patients, mainly suggesting a compensation mechanism of the functional whole brain network in the relatively early stage to counteract cognitive impairments.

Keywords: type 2 diabetes mellitus, cognitive function, resting-state functional magnetic resonance imaging, topological organization, graph theoretical analysis
INTRODUCTION

With the growth of the aging population and changes in people’s living habits, the prevalence of diabetes has been increasing year by year worldwide (1, 2). Type 2 diabetes mellitus (T2DM) is the most common type, accounting for more than 90% of all diabetes. Multiple studies have shown that T2DM can increase the risk of cognitive dysfunction and may even progress to dementia, including vascular dementia and Alzheimer’s disease (AD) (3–5). However, the underlying mechanism of T2DM-induced cognitive dysfunction is still unclear.

Resting-state functional magnetic resonance imaging (rs-fMRI) has become an important neuroimaging research method to understand the neurophysiological mechanisms of T2DM-induced cognitive dysfunction. Recently, many studies have focused on the functional changes of T2DM patients in a resting state. Some previous studies reported altered regional homogeneity (ReHo) values or amplitude low-frequency fluctuations (ALFF) values in the occipital lobes, temporal lobes, frontal lobes, cingulate gyrus, and cerebellum (6–8). And functional connectivity (FC) measures the similarity of the time series of two relatively remote brain regions (9). Previous studies have mainly shown impaired FC in the default mode network (DMN), ventral attention network (VAN), and dorsal attention network (DAN) (10–13). Besides, these disrupted regional brain activity and FC were associated with multiple cognitive impairments in T2DM patients, including visual processing, memory, attention, and executive function. Specifically, these methods focused only on local spontaneous brain activity using ReHo and ALFF values or concentrated their investigations within specific brain networks using seed-based approaches or independent component analysis (ICA). However, T2DM-related abnormal brain areas are extensively distributed, and cognitive dysfunction involves comprehensive interactions between different brain areas. In this context, building the functional whole brain network is necessary to comprehensively understand the underlying mechanisms of T2DM-related cognitive impairments.

The human brain is a complex network that works in a small-world network model efficiently and optimally (14). Graph theoretical analysis can effectively reflect altered topological properties of complex human brain networks. In recent years, this method has been widely used in studies of various neuropsychiatric diseases, such as AD, epilepsy and schizophrenia (15–17), while T2DM-related research was rarely reported. In the studies of functional brain network, Chen et al. (18) found that the global topological properties of the T2DM patients without cognitive dysfunction were lower than those of HCs, however, van Bussel et al. (19) revealed that the global topological properties of the T2DM patient group and the prediabetic patient group were significantly higher than those of the healthy control group and associated with lower processing speed. It can be summarized that the definite alterations of topological properties existing in the functional brain networks of T2DM patients remain unclear and the relationship between altered topological property and cognitive function is unknown. In addition, the currently studies focused only on the cerebrum networks, however, the structure and function of the cerebellum was changed in T2DM patients (7, 20). Thence, we also need to include the cerebellum to comprehensively explore the topological properties of the whole brain network.

Therefore, in the present study, we used rs-fMRI with graph theoretical analysis to explore the characteristic changes of functional whole brain network topological properties in T2DM patients. We also analyzed the correlation among the altered topological parameters, cognitive performance and related clinical variables. We hope to provide some potential imaging biomarkers of T2DM-related cognitive deficits.

MATERIALS AND METHODS

Participants

A total of 34 right-handed T2DM patients and 33 sex-, age-, and education-matched healthy controls (HCs) were recruited from the First Affiliated Hospital of Guangzhou University of Chinese Medicine. All participants received a detailed medical history interview and neurological examination. Clinical and demographic information were collected for all subjects, including biological test, blood pressure, body mass indicator (BMI), education level, alcohol consumption, smoking status, and duration of the disease (for T2DM patients only). The inclusion criteria were as follows: (1) All participants were between the ages of 40 and 65 years; (2) A standardized diagnosis of T2DM was confirmed based on medical history, medications used, fasting plasma glucose (FPG) levels (≥7.0 mmol/L) or 2-h OGTT glucose levels (≥11.1 mmol/L), which was in accordance with the diagnostic and classification criteria published by the American Diabetes Association (ADA) in 2014 (21); (3) HCs with FPG levels ≤6.1 mmol/L were included to this study. The exclusion criteria were as follows: (1) with clinically obvious complications, for example, the third or higher stages of diabetic retinopathy (based on the International Clinical Disease Severity Scale for diabetic retinopathy) (22), accompanying abnormal urin ary microalbumin of nephropathy and with symptoms of peripheral neuropathy; (2) any history of severe hypoglycemia; (3) impaired glucose tolerance or impaired fasting glucose; (4) hypertension; (5) history of brain lesions such as tumor or stroke; (6) unrelated psychiatric or neurological disorder(s); (7) history of alcohol, smoke or drug abuse; (8) systemic diseases such as severe anemia, thyroid dysfunction, or acquired immune deficiency syndrome; and (9) MRI contraindications. This study was approved by the ethics committee of First Affiliated Hospital of Guangzhou University of Chinese Medicine. The current study was carried out in accordance with the principles of the Declaration of Helsinki and the approved guidelines. All participants signed informed consent before participating in the study.

Neuropsychological Test

All participants completed detailed standardized cognitive assessment, which covered multiple cognitive domains. General cognitive function was assessed by the Chinese version of the Montréal Cognitive Assessment Scale-B (MoCA-B). Episodic verbal memory was measured by the Auditory Verbal Learning
First, all participants underwent routine whole-brain axial T1WI (TR/TE = 550/24 ms), T2WI (TR/TE = 5,100/130 ms), and T2 FLAIR (TR/TE = 9,000/120 ms) to rule out intracranial organic diseases, e.g., infarction, malformation, and tumor. Resting-state fMRI data were collected using a gradient-echo EPI sequence sensitive to blood oxygen level-dependent contrast with the following parameters: TR = 2,000 ms, TE = 30 ms, flip angle = 90°, thickness = 3 mm, gap = 1 mm, FOV = 220 × 220 mm, matrix = 64 × 64, slices = 36, 185 volumes. Sagittal high-resolution T1WI whole-brain images were acquired using 3D FSPGR sequences (TR = 8.15 ms, TE = 3.17 ms, Prep Time = 450 ms, flip angle = 12°, slice thickness = 1 mm, no gap, NEX = 1, FOV = 256 × 256 mm, matrix = 256 × 256, 188 sagittal slices). Earplugs and foam pads were used to reduce equipment noise and head motion during scanning. All participants were told to lay quietly in the scanner with their eyes closed, avoiding strong ideological activities but keeping awake.

Cerebral small vascular disease, mainly including white matter hyperintensities (WMHs) and lacunar infarction, may have an impact on brain function and cognitive function (23). In this study, these changes were assessed on T2WI and T2 FLAIR images according to the age-related white matter changes (ARWMC) scale (24). Two experienced radiologists who are blinded to group status separately performed the ratings and then reached a consensus through discussion. All participants with lacunar infarcts or a rating score > 2 were excluded. Consequently, 2 T2DM patients and 1 healthy control subject were excluded from this study.

Image Acquisition
For each participant, whole-brain MRI data were acquired using a 3T scanner (Signa HDxt GE Medical Systems, USA) with an 8-channel head coil. The scan time was within 1 week after medical history interview, neurological examination and biological tests, and the same day after neuropsychological tests. First, all participants underwent routine whole-brain axial T1WI (TR/TE = 2,500/24 ms), T2WI (TR/TE = 5,100/130 ms), and T2 FLAIR (TR/TE = 9,000/120 ms) to rule out intracranial organic diseases, e.g., infarction, malformation, and tumor. Resting-state fMRI data were collected using a gradient-echo EPI sequence sensitive to blood oxygen level-dependent contrast with the following parameters: TR = 2,000 ms, TE = 30 ms, flip angle = 90°, thickness = 3 mm, gap = 1 mm, FOV = 220 × 220 mm, matrix = 64 × 64, slices = 36, 185 volumes. Sagittal high-resolution T1WI whole-brain images were acquired using 3D FSPGR sequences (TR = 8.15 ms, TE = 3.17 ms, Prep Time = 450 ms, flip angle = 12°, slice thickness = 1 mm, no gap, NEX = 1, FOV = 256 × 256 mm, matrix = 256 × 256, 188 sagittal slices). Earplugs and foam pads were used to reduce equipment noise and head motion during scanning. All participants were told to lay quietly in the scanner with their eyes closed, avoiding strong ideological activities but keeping awake.

Threshold Selection and Network Analysis
In this study, whole brain functional networks were constructed based on an undirected and unweighted method. For all participants, the brain functional networks should be thresholded by a sparsity value to ensure that all resultant networks have the same number of edges and that the number of spurious edges is minimized (28, 29). However, no golden criteria are available for which sparsity value is currently the most biologically meaningful. According to previous studies (30, 31), a sparsity range of 0.05–0.5 with an interval of 0.01 was chosen, and the remaining fraction of edges was calculated in the functional network for each participant. For each sparsity threshold, eight global and nodal network parameters were computed. The global network measures included five parameters (the normalized clustering coefficient γ, the normalized characteristic path length λ, the small-worldness σ, local efficiency $E_{\text{loc}}$ and global efficiency $E_{\text{glob}}$). The nodal network measures included three parameters (nodal degree, nodal efficiency and nodal betweenness). In addition, for each participant, to assess whether the network had small-world property, the network measures were normalized to comparable values from random networks ($N = 100$). Furthermore, the area under curves (AUCs), which are sensitive at detecting topological alterations of brain disorders (32), were calculated for each parameter over the entire sparsity range ($0.05 \leq Sp \leq 0.5$).
Statistical Analysis
The demographic and clinical characteristics plus neuropsychological assessment of the T2DM patients and HCs were analyzed using the IBM Statistical Package for the Social Sciences 20.0 software (IBM SPSS Inc., Chicago, IL, USA). For continuous variables, independent two-sample t-tests or Mann-Whitney non-parametric tests were used, according to whether they met the normal distribution and variance homogeneity. The chi-square test was used to evaluate the differences in results between the genders within the groups. With gender, age, education years, and BMI as covariates, the between-group differences in the global parameters (γ, λ, σ, E_loc, and E_glob), nodal parameters (nodal degree, nodal efficiency, and nodal betweenness) and the AUC values of each parameter were compared using two-sample t-tests (P = 0.05) over the entire sparsity range (0.05 ≤ Sp ≤ 0.5). The Bonferroni method was applied at a p-value of 0.05 to correct for multiple comparisons. In addition, with the same indicators as covariates, the correlation between the altered functional network topological parameters and neuropsychological tests and clinical variables were analyzed using partial correlation analysis. P < 0.05 was considered statistically significant.

RESULTS
Clinical and Neuropsychological Results
Four T2DM patients and 3 HCs with obvious head motion or ARWMC scale rating scores > 2 were excluded, and 30 T2DM patients and 30 HCs were eventually included in the present study. The clinical and neuropsychological results of the T2DM patients and HCs are summarized in Table 1. The two groups were matched on age, sex, and education, and the BMI and blood lipid level were similar (P > 0.05), but both systolic blood pressure (SBP) (P = 0.013) and diastolic blood pressure (DBP) (P = 0.035) were higher in the T2DM patients. Compared with the HCs, the T2DM patients scored poorer on the MoCA-B (P = 0.010) and AVLT immediate recall tests (P = 0.016), spent much more time on the TMT-A (P = 0.018) and Grooved Pegboard Tests (P_F = 0.009, P_t = 0.025) and had no significant decreases in the other neuropsychological tests (P > 0.05).

Small-World Properties of Resting-State Functional Networks
Compared to random networks, the functional brain networks of the two groups had relatively higher normalized clustering coefficients (γ > 1), similar characteristic path lengths (λ ≈ 1), and small-worldness σ (σ = γ/λ) > 1, that is, demonstrated small-world property (Figures 1A–C).

Altered Small-World Property and Network Efficiency in T2DM Patients
Compared to HCs, T2DM patients showed increased γ values over the entire sparsity range (0.05 ≤ Sp ≤ 0.5), increased σ and E_loc values for a range of sparsity values (σ: 0.13 ≤ Sp ≤ 0.5 and E_loc: 0.09 ≤ Sp ≤ 0.31) (Figures 1A,C,D). Moreover, T2DM patients showed the AUC values of γ (P = 0.019), σ (P = 0.032), and E_loc (P = 0.034) were significantly higher than HCs (Figure 2). However, λ and E_glob values were similar between T2DM patients and HCs (P > 0.05) (Figures 1B, E, 2).

Altered Nodal Topological Metrics in T2DM Patients
We identified 26 brain regions with altered nodal parameters between the T2DM patients and the HCs in at least one of the three nodal characteristics, which are reported in Table 2. Compared to the HCs, the T2DM patients showed decreased nodal parameters in frontal lobes [right precentral

| TABLE 1 | Clinical and neuropsychological results of T2DM patients and HCs. |
|---|---|---|
| **Clinical characteristics** | **T2DM patients (n = 30)** | **HCs (n = 30)** | **P-value** |
| Age (years) | 51.77 ± 1.42 | 48.87 ± 0.98 | 0.009 |
| Sex (M/F) | 18/12 | 18/12 | 1.000 |
| Education (years) | 10.70 ± 0.69 | 10.23 ± 0.61 | 0.614 |
| BMI (kg/m²) | 24.82 ± 0.56 | 24.18 ± 0.52 | 0.409 |
| SBP (mmHg) | 127.20 ± 2.35 | 120.03 ± 1.51 | 0.013* |
| DBP (mmHg) | 82.80 ± 1.67 | 78.70 ± 0.88 | 0.035* |
| Total cholesterol (mmol/L) | 4.71 ± 1.78 | 4.27 ± 0.96 | 0.240 |
| Triglyceride (mmol/L) | 1.54 ± 0.92 | 1.48 ± 0.50 | 0.755 |
| LDL cholesterol (mmol/L) | 3.34 ± 1.19 | 2.93 ± 0.45 | 0.084 |
| HDL cholesterol (mmol/L) | 1.07 ± 0.29 | 1.15 ± 0.46 | 0.424 |
| Alcohol consumption (%) | | | |
| None/Low/High | 83.3/16.7/0 | 90.0/10.0/0 | – |
| Smoking status (%) | | | |
| Never/Former/Current | 80.0/13.3/6.7 | 86.7/10.0/3.3 | – |
| Duration of diabetes (years) | 5.04 ± 4.46 | – | – |
| Fasting blood glucose (mmol/L) | 8.62 ± 3.44 | 5.03 ± 0.48 | <0.001* |
| 2h OGTT glucose (mmol/L) | 18.53 ± 5.46 | – | – |
| HbA1C (%) | 8.54 ± 2.09 | – | – |
| Type 2 diabetes medication, yes (%) | | | |
| Oral medication | 50.0 | – | – |
| Insulin medication | 16.7 | – | – |
| Insulin and oral medication | 20.0 | – | – |
| None (newly diagnosed) | 13.3 | – | – |

Data are mean ± SD. BMI, body mass index; SBP, systolic blood pressure; DBP, diastolic blood pressure; MoCA-B, Montreal cognitive assessment-B; AVLT, Auditory verbal learning test; TMT-A, Trail making test-A; DST, digit span test; CDT, Clock drawing test. *P < 0.05, which was considered statistically significant.
Small-world property and network efficiency measures of the whole brain network over the defined wide range of sparsity values of T2DM patients and healthy controls. Compared to random networks, graphs display that both the two groups had relatively higher normalized clustering coefficients ($\gamma > 1$), similar normalized characteristic path lengths ($\lambda \approx 1$), and small-worldness ($\sigma = \gamma / \lambda > 1$, that is, demonstrated small-world property (A–C). Moreover, T2DM patients had higher local efficiency and similar global efficiency than HCs (D,E).

Altered small-world property and network efficiency measures of the whole brain network over the defined wide range of sparsity values between T2DM patients and healthy controls. Compared to HCs, T2DM patients showed the AUC values of $\gamma$ ($p = 0.019$), $\sigma$ ($p = 0.032$), and $\Eloc$ ($p = 0.034$) were significantly higher than HCs. However, $\lambda$ and $\Eglob$ values were similar between T2DM patients and HCs.

Correlation Analyses Among Altered Network Parameters, Cognitive Function and Clinical Variables

In T2DM patients, MoCA-B scores were positively correlated with the nodal degree ($r = 0.400, p = 0.043$) and nodal efficiency ($r = 0.452, p = 0.021$) of the REC.R. AVLT immediate recall scores were positively correlated with the nodal betweenness of the AMYG.L ($r = 0.457, p = 0.019$), and AVLT short-term recall scores were positively correlated with the nodal degree of the MOG.R ($r = 0.431, p = 0.028$). Both the Grooved Pegboard-R ($r = -0.461, p = 0.018$) and Grooved Pegboard-L ($r = -0.436, p = 0.026$) were negatively correlated with the nodal betweenness of the MOG.R. HbA1c was negatively correlated with the nodal betweenness of the PCG.R ($r = -0.388, p = 0.034$) and AVLT immediate recall scores ($r = -0.458, p = 0.019$). Correlation analyses were illustrated in Figure 3. No relationship was found in altered global network parameters.
TABLE 2 | Brain regions with altered nodal parameters in T2DM patients.

| AAL no. | Regions Abbreviation | Nodal degree | Nodal efficiency | Nodal betweenness |
|---------|----------------------|--------------|-----------------|------------------|
| 2       | Right precentral gyrus PreCG.R | 0.052 | 0.034 | 0.036 |
| 3       | Left superior frontal gyrus (dorsolateral) SFGdor.L | 0.519 | 0.196 | 0.005 |
| 20      | Right supplementary motor area SMA.R | 0.141 | 0.156 | 0.044 |
| 23      | Left superior frontal gyrus (medial) SFGmed.L | 0.335 | 0.183 | 0.012 |
| 33      | Left median cingulate and paracingulate gyri DCG.L | 0.059 | 0.037 | 0.652 |
| 41      | Left amygdala AMYG.L | 0.499 | 0.385 | 0.026 |
| 46      | Right cuneus CUN.R | 0.054 | 0.039 | 0.652 |
| 47      | Left lingual gyrus LING.L | 0.008 | 0.009 | 0.340 |
| 48      | Right lingual gyrus LING.R | 0.008 | 0.012 | 0.531 |
| 49      | Left superior occipital gyrus SOG.L | 0.004 | 0.010 | 0.135 |
| 50      | Right superior occipital gyrus SOG.R | 0.016 | 0.017 | 0.656 |
| 51      | Left middle occipital gyrus MOG.L | 0.058 | 0.045 | 0.010 |
| 52      | Right middle occipital gyrus MOG.R | 0.039 | 0.015 | 0.047 |
| 63      | Left supramarginal gyrus SMG.L | 0.058 | 0.037 | 0.024 |
| 28      | Right gyrus rectus REC.R | 0.048 | 0.034 | 0.252 |
| 32      | Right anterior cingulate and paracingulate gyri ACQ.R | 0.930 | 0.597 | 0.040 |
| 36      | Right posterior cingulate gyrus PCG.R | 0.488 | 0.903 | 0.033 |
| 65      | Left angular gyrus ANG.L | 0.865 | 0.552 | 0.040 |
| 71      | Left caudate nucleus CAU.L | 0.001 | 0.004 | 0.005 |
| 72      | Right caudate nucleus CAU.R | 0.030 | 0.030 | 0.084 |
| 91      | Left cerebellum crus1 CRBLCrus1.L | 0.150 | 0.374 | 0.049 |
| 92      | Right cerebellum crus1 CRBLCrus1.R | 0.182 | 0.504 | 0.025 |
| 95      | Left cerebellum 3 CRBL3.L | 0.010 | 0.011 | 0.532 |
| 96      | Right cerebellum 3 CRBL3.R | 0.004 | 0.001 | 0.208 |
| 109     | Vermis (1, 2) Vermis(1, 2) | 0.015 | 0.140 | 0.616 |
| 110     | Vermis 3 Vermis 3 | 0.003 | 0.141 | 0.023 |

AAL No., number of automated anatomical labeling. Note: Brain regions were considered abnormal in T2DM patients if they showed p < 0.05 compared to HCs in at least one of the three nodal parameters and boldface p-values were statistically significant.

DISCUSSION

In this cross-sectional study, we focused on the topological organization of rs-fMRI whole brain network of middle-aged T2DM patients without obvious complications using graph-based theoretical approaches. The results displayed that both the two groups exhibited small-world organization of their functional networks, but compared to HCs, T2DM patients showed (1) a higher normalized clustering coefficient ($\gamma$), a higher small-worldness ($\sigma$) and a higher local efficiency ($E_{loc}$); (2) both decreased and increased nodal network parameters; (3) altered nodal network parameters of some brain regions were related to cognitive impairments and HbA1c. These findings provide new insight into the underlying functional neuropathological effects of T2DM-related cognitive impairments.

**Increased Global Network Measures**

The small-world network, with a similar characteristic shortest path length and a higher clustering coefficient compared to the random network, is a highly integrated and optimized network model that can maximize efficiency and minimize information processing. Small-world networks were found not only in real-world networks, for example, social, traffic, and genetic networks, but also in functional, structural, and EEG human brain networks. In this study, the functional whole brain networks of both T2DM patients and HCs exhibited small-world organization, which was consistent with previous studies (18, 19, 32, 33).

As far as we know, normal human brain networks that combine a high $\sigma$, a high $\gamma$, and a high $E_{loc}$ indicate a highly integrated and optimized network, a high local effectiveness in processing information and a high fault tolerance of the network. Our investigation showed this combination in T2DM patients, implying that the whole brain networks were better organized than those in HCs. The result seems unreasonable and converse because the networks of T2DM patients should be less, instead of better, organized. However, in the research of the rs-fMRI network among T2DM patients, prediabetes patients and healthy controls, van Bussel et al. (19) found...
results similar to our study. They held the view that before the appearance of clinically manifested cognitive decrements, the brain functional network may have already reorganized as a compensatory mechanism to counterwork the slight cognitive decrements. Once the functional reorganization fails, there will be a disrupted functional network and clinically manifested cognitive decrements will be discovered in T2DM patients. MoCA-B is widely used to assess general cognitive function and is more sensitive than MMSE. The mean MoCA-B score was 25.23 ± 0.66 in the T2DM patients in our study, which was slightly lower than the normal score 26, suggesting a stage of slight cognitive decrements. Besides, the included T2DM patients are middle-aged, with a short diabetes duration and well-controlled glucose levels, and without obviously complications, thus they may be relatively “healthy” patients. Therefore, the better organized whole brain networks in the T2DM patients of our study also supported the compensatory mechanism put forward by van Bussel et al. However, Chen et al. (18) showed longer path length and lower global efficiency but similar clustering coefficient and local efficiency in T2DM patients without mild cognitive impairment (MCI), indicating a less rather than better organized functional network, which is not consistent with our findings. These differences may be attributed to the severity of the disease condition or the sensitivity of the different neuropsychological tests and need to be discussed through longitudinal, large sample, long-term investigations in the future. Moreover, disrupted structural networks have already been reported via graph theoretical network analysis in T2DM patients (32, 33), but the relationship between the brain structural network and the functional network is still unknown. We believe that it is meaningful to combine structural networks with functional networks using theoretical network analysis to explore the underlying mechanism of T2DM-related cognitive function in the future.
Decreased Nodal Network Measures

Nodal network parameters (nodal degree, nodal efficiency and nodal betweenness) can detect the activity, importance and influence of a region in network communication. In our study, reduced nodal parameters were observed in the occipital lobes, frontal lobes, left median cingulate and paracingulate gyri, left amygdala and supramarginal gyrus. And the decreased nodal parameters of occipital lobes existed in CUN.R, bilateral LING, SOG, and MOG. Recently, a study found that the degree centrality of the LING was significantly reduced in T2DM patients and the connectivity within the LING-related visual network was diffusely decreased (34). Moreover, they found positive correlations of the occipital connectivity with visual memory and executive performance. In addition, in the earlier studies, T2DM patients showed not only decreased volume and brain metabolites (35, 36) but also decreased ReHo and ALFF values of the occipital lobes, especially in CUN, LING, SOG, MOG and calcarine gyrus (CAL) (6, 8, 37). In our study, the nodal degree of the MOG.R was negatively correlated with the consumed time of the Grooved Pegboard Test (a scale reflecting execution function), suggesting that a decreased nodal degree of the MOG.R may be attributed to reduced performance in executive function.

The cingulate gyrus is the core node in the DMN and acts as a transportation hub during information transmission processing and participates in various cognitive functions. To the best of our knowledge, only one study showed that the increased degree centrality of the dorsal anterior cingulate cortex (dACC) and the increased connectivity of the dACC was related to higher FPG levels and better TMT-B performance in T2DM patients (34). But impaired functional activity of DMN has been widely reported in previous studies using ReHo, ALFF, seed-based approaches or independent component analysis (12, 38, 39). Our study found that the nodal parameters in the DCG.L and SMG.L were reduced, while the nodal parameters in the ACG.R and PCG.R were increased. These findings may be interpreted as the fact that the left hemisphere of the recruited right-handed participants are more active than the right hemisphere and more sensitive to pathological changes caused by hyperglycemia, thus, compensatory increases of the right cingulate gyrus will be made to maintain the brain function activities of the whole brain. Furthermore, the nodal betweenness of the PCG.R was negatively correlated with HbA1c, suggesting that controlling and monitoring the HbA1c value is of great significance for the development of diabetic encephalopathy.

The frontal lobe is the latest and most advanced part of brain development. It is widely accepted that the frontal lobes, especially prefrontal lobes, are primarily responsible for high-order cognitive control (40, 41), and appear to be vulnerable regions in T2DM patients by using functional connectivity and graph theoretical network analysis (13, 19, 32). In this study, as shown in Table 2, several frontal lobes (PreCG.R, SMA.R, SFGdor.L, and SFGmed.L) showed decreased nodal parameters, while the REC.R showed increased nodal parameters. In addition, increased nodal degree and nodal efficiency of the REC.R were related to higher MoCA-B scores. These results suggest that disrupted frontal topological properties may further explain the damaged neural mechanism and declined cognitive function in T2DM patients. The AMYG is located in the medial temporal lobe and is mainly involved in mood and memory. The AMYG.L performed decreased nodal betweenness and was related to worse performance in the AVLT immediate recall test, suggesting that its ability to participate in network information transmission was reduced and may partially explain the reason for memory loss in T2DM patients. Recently, Xia et al. (42) reported that T2DM patients may be accompanied by depressive mood, and depressed T2DM patients showed decreased AMYG FC when compared to non-depressed T2DM patients. However, our study did not assess depression-related scales, and this needs to be further discussed in future studies.

Increased Nodal Network Measures

Finally, to the best of our knowledge, this study is the first to explore the topological properties of whole-brain (including cerebellum) functional networks using graph theoretical analysis in T2DM patients. In the previous studies of resting state functional MRI, increased ReHo or ALFF values and functional connectivity of the cerebellum posterior lobe and cerebellum culmen were reported in T2DM patients (7, 8, 43). They hold the view that cerebellum, especially the cerebellum posterior lobe, may play a role of compensation. And this study demonstrated increased nodal parameters in the bilateral cerebellum 3, bilateral cerebellum crus 1, vermis (1, 2) and vermis 3, which was partly consistent with the previous studies. Moreover, in the previous studies of structural MRI, decreased FA values of vermis (44) and increased MD values of bilateral cerebellum anterior and posterior lobes (45) were reported, and some decreased connections in cerebellar and cerebro-cerebellar circuit were found (20). These studies displayed that the cerebellum was both damaged in function and structure, but there was no report about the definite relationship between cerebellum and cognitive function in T2DM patients. The cerebellum not only plays an important role in motor control and coordination but also relates to some advanced cognitive functions, such as language, emotional modulation, episodic and working memory (46–48). In the present study, the nodal degree of the right cerebellum 3 was positively correlated with the AVLT short-term delayed recall score, suggesting a close relationship between the cerebellum and memory. Therefore, we speculate that in the relatively early stage, the elevated brain functional activity of the cerebellum, especially the cerebellum posterior lobe, can recruit more nerve resources as a compensation mechanism to slow the process of cognitive decline. This may also explain why the local efficiency of T2DM patients is higher than that of HCs from another expect, which may be due to the compensation mechanism of the increased nodal properties in the these brain regions mentioned above.

LIMITATIONS

This study had some limitations. First, it was a cross-sectional study that did not assess the progression of functional network changes and had a relatively small sample size. Second, the medication of T2DM patients was not completely identical,
so medication confounding effects may exist. Therefore, the
effect of medication needs to be investigated in future studies.
Third, previous studies reported that T2DM patients may have
depression, but our study did not assess the patient’s mood state
with a detailed depression scale. Moreover, according to the
presence depression, we can divide these T2DM patients into
different subgroups and further explore the differences between
them. Finally, we only explored the relationship between the
brain functional network and cognitive performance in T2DM.
The incorporation of a structural network allowed us to examine
whether the functional changes underlying cognitive dysfunction
in T2DM are associated with structural network alterations.
Further studies that combine multimodal imaging techniques
will be helpful to interpret this issue.

CONCLUSION

In summary, this study displayed disrupted functional networks
in middle-aged T2DM patients with mild cognitive impairments,
demonstrating a more efficient global topological organization
and showing both decreased and increased nodal parameters.
This may suggest a compensation mechanism for cognitive
decline in terms of functional reorganization of the whole
brain networks. Furthermore, the study demonstrated that graph
theoretical network analysis provided novel insight and the
results may serve as potential imaging biomarkers for subtle
whole brain alterations of T2DM-related cognitive decline.

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ETHICS STATEMENT

This study was approved by the ethics committee of First
Affiliated Hospital of Guangzhou University of Chinese
Medicine. The current study was carried out in accordance with
the principles of the Declaration of Helsinki and the approved
guidelines. All participants signed informed consent before
participating in the study.

AUTHOR CONTRIBUTIONS

CQ carried out the data collection, analysis and interpretation,
and drafted the initial article.YL, XT, HZ, JY, YLL, and YZ
participated in the data collection and interpretation.XL, HL, CZ
and SQ contributed to the conception and design of the study,
interpretation of data, and manuscript revision. All authors read
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49. Conflict of Interest Statement: The authors declare that the research was conducted in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest.

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