



Aberrant Brain Triple-Network Effective Connectivity Patterns in Type 2 Diabetes Mellitus

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ABSTRACT

Introduction: Aberrant brain functional connectivity network is thought to be related to cognitive impairment in patients with type 2 diabetes mellitus (T2DM). This study aims to investigate the triple-network effective connectivity patterns in patients with T2DM within and between the default mode network (DMN), salience network (SN), and executive control network (ECN) and their associations with cognitive declines.

Methods: In total, 92 patients with T2DM and 98 matched healthy controls (HCs) were

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recruited and underwent resting-state functional magnetic resonance imaging (rs-fMRI). Spectral dynamic causal modeling (spDCM) was used for effective connectivity analysis within the triple network. The posterior cingulate cortex (PCC), medial prefrontal cortex (mPFC), lateral prefrontal cortex (LPFC), supramarginal gyrus (SMG), and anterior insula (AINS) were selected as the regions of interest. Group comparisons were performed for effective connectivity calculated using the fully connected model, and the relationships between effective connectivity alterations and cognitive impairment as well as clinical parameters were detected.

Results: Compared to HCs, patients with T2DM exhibited increased or decreased effective connectivity patterns within the triple network. Furthermore, diabetes duration was significantly negatively correlated with increased effective connectivity from the r-LPFC to the mPFC, while body mass index (BMI) was significantly positively correlated with increased effective connectivity from the l-LPFC to the l-AINS ($r = -0.353$, $p = 0.001$; $r = 0.377$, $p = 0.004$).

Conclusion: These results indicate abnormal effective connectivity patterns within the triple network model in patients with T2DM and provide new insight into the neurological mechanisms of T2DM and related cognitive dysfunction.

Keywords: Type 2 diabetes mellitus; Triple network model; Effective connectivity; Resting-state functional magnetic resonance imaging

Key Summary Points

Why carry out the study?

Type 2 diabetes mellitus (T2DM) may increase the risk of cognitive decline and dementia; however, the underlying neuropathological mechanisms are not clear. Changes in functional connections and functional networks among brain regions in patients with T2DM have indeed been detected. To further determine the directionality of changes, we explored using effective connectivity (EC) analysis based on spectral dynamic causality model (spDCM).

The triple network model (TPN) includes the default mode network (DMN), executive control network (ECN), and salience network (SN). The disruption of the interactions within and between these three core networks may cause neuropsychiatric disorders. Abnormal communication among brain networks may exist in type 2 diabetes, but it is unknown whether the effective connection among the triple networks has changed.

This study used spDCM based on fMRI to detect directed connectivity changes in the DMN, SN, and ECN in patients with T2DM.

What was learned from the study?

There are abnormal EC patterns among the TPN in patients with T2DM. Decreased EC from the SN to the ECN may be related to poorer visuospatial recall ability as well as islet function.

rising production of glucose are the characteristics of T2DM [1]. The changing lifestyle and global ageing of populations contribute to the high incidence of T2DM [2]. Clinical research suggests that T2DM increases the risk of cognitive decline and dementia [3]. T2DM-related cognitive dysfunction is a cerebral comorbidity involving a wide spectrum of various functions, including executive, motor, psychomotor, verbal memory, and visual memory [4]. This cognitive impairment not only impacts personal health but also diabetes management. Moreover, it is associated with complications related to diabetes treatment [1, 5].

Intrinsically, the human brain is composed of distinct brain networks. Each network consists of a different set of cortical and subcortical regions linked by temporally synchronized neural activity [6]. An extensive body of resting-state functional connectivity (rs-FC) research has established that abnormal communication among large-scale brain networks may exist in type 2 diabetes [7, 8]. Seed-based functional connectivity analyses have shown that patients with T2DM exhibit increased or decreased connectivity between the left hippocampus and the inferior parietal lobule in the executive control network (ECN) and the medial prefrontal cortex (mPFC) in the default mode network (DMN) [9]. Meta-analysis revealed hypoconnectivity between ECN seeds and the salience network (SN) regions, especially in the left insula. Moreover, hypoconnectivity was found within DMN regions between the left anterior cingulate cortex (ACC) and the left medial prefrontal cortex (mPFC) [7]. Our previous study revealed that patients with T2DM exhibited decreased rsFC between dorsal attention network (DAN) seeds and ventral attention network (VAN) regions with independent component analysis of resting-state functional magnetic resonance imaging (rs-fMRI) data [10].

The triple network model (TPN), first described by Menon in 2011, includes the DMN, ECN, and SN [11]. The DMN, which controls internal thought and autobiographical memory, is characterized by increased activity during the resting state. The ECN is responsible for enhancing stimulus-related cognitive control functions such as working memory or directed attention.

INTRODUCTION

Type 2 diabetes mellitus (T2DM) is a complex metabolic disorder with an increasing prevalence worldwide. Varying degrees of insulin resistance, impairment of insulin secretion function, and

The SN acts as a mediator, regulating activities between the DMN and the ECN. The TPN model posits that the SN plays a central role in abnormal mapping of external stimuli and self-referential psychological events [12]. Inappropriate allocation of these networks to external tasks or internal events may contribute to neuropathological conditions. Numerous fMRI studies have shown that disruption of the interactions within and between these three core networks represents an important feature of the nervous system and neuropsychiatric disorders. Li et al. used static network analysis and reported that patients with amnesic mild cognitive impairment had significantly decreased functional connectivity strength between the DMN and ECN, as well as between the SN and DMN [13]. Meng et al. reported that the dynamic dysfunction of these three core networks occurred in patients with Alzheimer's disease (AD) and may contribute to AD [14].

As mentioned previously, changes in functional connections and functional networks between brain regions in patients with T2DM have indeed been detected. Alterations in network connectivity associated with cognitive impairment in various domains have also been elucidated using rs-fMRI. However, rsFC makes it difficult to infer the directionality of coupling between these multiple distributed systems. Therefore, the effective connectivity (EC) approach is the best way to investigate the directionality of regional coupling within and between networks and the causal influence exerted by one node on another. Friston et al. first proposed the spectral dynamic causal model (spDCM) to estimate the causal influence of one neuronal subpopulation relative to another neuronal subpopulation to characterize the causal organization of the brain [15]. Spectral DCM has been successfully used in the study of different diseases, such as schizophrenia and depressive disorder [16, 17]. Therefore, the application of ECs to a priori-defined networks of interest, such as the TPN, is attractive because it may help identify T2DM-related connectivity abnormalities that explain global and TPN-specific cognitive deficits.

Here we performed data-driven DCM analysis in patients with T2DM to investigate alterations

of effective connectivity patterns in the TPN. We hypothesized that patients with T2DM may have abnormal EC patterns in TPN which might contribute to the cognitive decline. This study provides new insights into early brain network changes in T2DM and contribute to develop new imaging biomarkers for early prediction of T2DM-related cognitive dysfunction.

METHODS

Participants

The study was conducted in accordance with the Declaration of Helsinki, and approved by Ethics Committee of Nanjing First Hospital (protocol code KY20220124-02 and date of approval 24 January 2022). A total of 190 individuals aged between 40 and 70 years, including 92 patients with T2DM and 98 healthy controls (HCs), were recruited from the Department of Endocrinology, Nanjing First Hospital (public hospital), between February 2022 and December 2023. The study sample size was calculated by G*Power software (version 3.1.9.7). All participants were right-handed and educated for at least 8 years; all participants have health insurance. All patients with T2DM were diagnosed according to the criteria of the American Diabetes Association [18]. The regimen for patients with T2DM included oral hypoglycemic drugs ($n=71$), insulin ($n=48$), glucagon-like peptide 1 receptor agonist (GLP-1RA) ($n=19$). Sex, age, and education-matched HCs were recruited through community health inspections or online advertising during the same period. We measured the fasting glucose levels and postprandial glucose levels and excluded individuals with a fasting glucose level greater than 6.1 mmol/l or postprandial glucose level greater than 7.8 mmol/l. Participants were not excluded from the fMRI analysis because of excessive head motion during the scan.

In order to minimize the impact of potential confounding variables on the main measures of the study, participants were excluded from the study if they had head injury, Parkinson's disease, epilepsy, stroke, alcoholism, major

depression or other neurological or psychiatric illness, severe vision or hearing loss, or other major medical illness.

Clinical Data and Neuropsychological Testing

Demographic data were recorded including sex, age, education levels, weight, height, and body mass index (BMI) [weight in kg/(height in m)²]. Two separate assessments were employed to determine the average value. Blood samples were obtained through venipuncture at 8 A.M. following an overnight fast of a minimum of 10 h. Fasting blood glucose, fasting serum C-peptide, HbA1c, triglycerides, total cholesterol, low-density lipoprotein cholesterol (LDL-C), and high-density lipoprotein cholesterol (HDL-C) levels were measured.

Classical neuropsychological assessments were executed to evaluate affective and cognitive symptoms in all participants. The Montreal Cognitive Assessment (MoCA) [19] and Mini Mental State Exam (MMSE) [20] are routine cognitive screening tests that assess possible dementia and MCI. The Auditory Verbal Learning Test (AVLT) and AVLT-delay [21] are commonly used methods for assessing episodic verbal learning. The Complex Figure Test (CFT) and CFT-delay [22] assess visual perception, visuomotor integration, and visuospatial recall. The Digit Symbol Substitution Test (DSST) [23] is commonly used to assess the ability to switch attention and information processing. The Digital Span Test (DST) [24] is a measurement of attention and short-term memory. The Trail-Making Test A and B (TMT-A and B) are employed to evaluate executive control, which includes structured visual search, focused attention, and cognitive adaptability. The Clock Drawing Test (CDT) is utilized to appraise executive function and visual-spatial ability. All neuropsychological tests were conducted by two trained and experienced physicians.

MRI Acquisition

All subjects were scanned using a 3.0-T MRI scanner (Ingenia, Philips Medical Systems,

Netherlands) with an 8-channel phased-array head coil. Foam padding and earplugs were used to minimize involuntary head motion and reduce noise. Participants were directed to remain motionless with their eyes shut, endeavoring not to focus on any specific thoughts and to prevent head movement throughout the scanning process.

Functional images were obtained with a gradient echo-planar imaging (EPI) sequence with the following parameters: TR/TE, 2000 ms/30 ms; slices, 36; flip angle (FA), 90°; thickness, 4 mm; gap, 0 mm; field of view (FOV), 240 mm × 240 mm; matrix size, 64 × 64; and voxel size, 3.75 mm × 3.75 mm × 4.0 mm. The scan lasted for 8 min and 8 s. Structural images were obtained with a high-resolution T1-weighted (T1W) sequence, namely three-dimensional turbo fast echo (3D-TFE), with the following scan parameters: TR/TE, 8.1 ms/3.7 ms; FA, 8°; FOV, 256 mm × 256 mm; slice, 170; thickness, 1 mm; gap, 0 mm; and matrix size, 256 × 256. In addition, both scans were acquired utilizing sensitivity encoding (SENSE) technology for parallel imaging with a SENSE factor of 2.

The rs-fMRI data were pre-processed using GRETNA software on the MATLAB 2013b platform. The DICOM images were first converted to NIFTI files, and the first ten time points were removed for signal equilibrium. In the subsequent step, 220 remaining volumes underwent correction to calculate the time delay in data acquisition between slices (slice timing) and to adjust for any head movement during scanning (realignment).

The spDCM analysis was conducted using the DCM toolbox integrated within SPM12 to identify the effective connectivity among brain regions during the resting state. First, a first-level analysis was performed, and a general linear model with six rigid body motion parameters, WM signal, and CSF signal as interference covariates was applied to the time series. In order to calculate the DCM model from the preprocessed fMRI data, the next we defined the region of interest (ROI) and extract the time series.

Eight ROIs were selected as seeds matching the 6-mm spherical ROIs used in prior research examining the seed-to-voxel functional

connectivity (FC) of these networks [25–27]. The DMN hubs were the PCC (1, –61, 38) and mPFC (1, 55, –3); the SN hubs were the left anterior insula (l-AINS) (–44, 13, 1), right anterior insula (r-AINS) (47, 14, 0), left supramarginal gyrus (l-SMG) (–60, –39, 31), and right supramarginal gyrus (r-SMG) (62, –39, 31); and the ECN hubs were the left lateral prefrontal cortex (l-LPFC) (–43, 33, 28) and right lateral prefrontal cortex (r-LPFC) (41, 38, 30).

The primary eigenvariates of the time series were derived from the aforementioned ROIs. A gray matter (GM) mask, set at a threshold of 0.5, was applied to the time series data within the standard MNI space in order to exclude any extraneous contributions from white matter (WM) and cerebrospinal fluid (CSF).

Dynamic causal modeling analysis was conducted on the specified ROIs, wherein each subject had bidirectional connections established between every pair of ROIs, resulting in a fully interconnected model with each node linked to all others. Subsequently, the parameters for this comprehensively connected model were estimated. The process of model estimation relied on the parametric empirical Bayes (PEB) framework [28]. Instead of estimating each individually, a single spDCM model was jointly estimated and then underwent Bayesian model reduction. Finally, the inherent connectivity strength was extracted from the estimation results, i.e., the effective connectivity value.

Statistical Analysis

Differences in demographic characteristics, clinical data, and neuropsychological variables between HCs and patients with T2DM were analyzed with two-sample *t* tests for means and χ^2 tests for proportions (statistically significant difference was set at $p < 0.05$). For the spDCM analysis, to compare the difference in mean connection strength between the two groups, an independent two-sample *t* test was performed after adjusting for the effects of age, sex, and education, with the significance level set at $p < 0.05$ (FDR correction). Additionally, to examine the correlation between abnormal causal connectivity strength and clinical variables in

individuals with T2DM, Pearson's or Spearman's correlation coefficients were calculated utilizing the SPSS 26.0 software package. Furthermore, correlation analyses using Spearman's or Pearson's methods were conducted to assess the relationships between neuropsychological assessment scores and effective connectivity strength, with a *p* value less than 0.05 deemed to signify statistical significance.

RESULTS

Demographic and Clinical Data

The demographic and clinical data of all the subjects are summarized in Table 1. No significant differences were observed in age, sex, education level, BMI, or LDL-C between the T2DM group and HCs. Fasting glucose, HbA1c, triglyceride, and total cholesterol levels were greater in the patients with T2DM compared to the control group; conversely, the HDL-C level was lower in the T2DM group. The subjects' neuropsychological data are summarized in Table 2. We found inferior outcomes on the CFT-delay, as well as TMT-A and B, in the patient cohort relative to the control subjects.

Effective Connectivity Strength of Each Group

We employed one-sample *t* tests to discern significant effective connections that deviated from zero in both the patients with T2DM and the HCs. Furthermore, we interpreted positive correlation coefficients, as derived from DCM, as representing excitatory connections, signaling an augmentation in the level of effective connectivity. Conversely, negative correlation coefficients represented inhibitory connections, indicating a decrease in the level of effective connectivity (for brevity, self-connections are omitted from our results). In the T2DM group, inhibitory connections existed from the l-LPFC to the mPFC and the r-LPFC to the l-AINS (Fig. 1a, c). More nodes had coupling strengths that differed from zero in the HC group. We found that the r-LPFC and mPFC exhibited excitatory connections to

Table 1 Demographic and clinical characteristics of patients with T2DM and healthy controls

	T2DM (<i>n</i> = 92)	Healthy controls (<i>n</i> = 98)	<i>P</i> value
Age (year)	58.090 ± 7.563	56.360 ± 7.134	0.106
Gender (male/female)	51/41	57/41	0.704
Education levels (years)	11.680 ± 2.173	11.320 ± 1.967	0.222
Diabetes duration (years)	9.252 ± 4.588	–	–
BMI (kg/m ²)	24.793 ± 2.911	24.311 ± 2.070	0.189
HbA1c (%)	8.332 ± 1.699	5.496 ± 0.168	< 0.001**
Fasting glucose (mmol/L)	8.062 ± 2.845	5.404 ± 0.307	< 0.001**
Triglycerides (mmol/L)	1.878 ± 1.088	1.390 ± 1.040	0.002*
Total cholesterol (mmol/L)	4.937 ± 1.171	4.557 ± 1.081	0.021*
LDL-C (mmol/L)	2.727 ± 0.895	2.647 ± 0.827	0.519
HDL-C (mmol/L)	1.217 ± 0.317	1.340 ± 0.352	0.016*
C-peptide	1.874 ± 1.227	–	–

Data are represented as mean ± SD, *n* (%), or median (range)

LDL-C low-density lipoprotein cholesterol, *HDL-C* high-density lipoprotein cholesterol

**p* < 0.05

the PCC and that the PCC exhibited excitatory connections to the mPFC. An inhibitory connection was detected from the PCC to the r-LPFC (Fig. 1b, d).

Difference in Effective Connectivity Strength Between Groups

In order to ascertain the disparities between the two groups, we utilized an independent samples *t* test to compare the mean connectivity strength. Group differences in effective connectivity strengths between patients with T2DM and HCs within the triple network are shown in Table 3, Figs. 2 and 3. Compared to HCs, patients with T2DM exhibited increased effective connectivity from the r-LPFC to the mPFC, from the mPFC to the r-SMG, from the l-LPFC to the l-AINS, and from the l-AINS to the r-AINS. Decreased effective connectivity was exhibited from the PCC to the mPFC, mPFC to the l-LPFC, from the r-SMG to the l-SMG/l-LPFC, and from the r-AINS to the l-LPFC in the T2DM group.

Correlations Between Altered EC and Neuropsychological Characteristics

Within the T2DM patient group, there was a positive correlation between the CFT-delay score and reduced effective connectivity from the r-AINS (SN) to the l-LPFC (ECN) ($r=0.452$, $p<0.001$) (Fig. 4). Diabetes duration was significantly negatively correlated with increased effective connectivity from the r-LPFC to the mPFC, and BMI was significantly positively correlated with increased effective connectivity from the l-LPFC to the l-AINS ($r=-0.353$, $p=0.001$; $r=0.377$, $p=0.004$) (Fig. 5a, b). Furthermore, the diminished effective connectivity from the r-SMG to the l-LPFC exhibited a significant positive correlation with C-peptide levels ($r=0.472$, $p<0.001$), as depicted in Fig. 5c. The observed correlations were adjusted for covariates such as age, sex, and education level.

Table 2 Neuropsychological test information of patients with T2DM and healthy controls

	T2DM (<i>n</i> = 92)	Healthy controls (<i>n</i> = 98)	<i>P</i> value
MMSE	28.794 ± 0.806	29.061 ± 1.138	0.064
MoCA	26.888 ± 1.692	27.207 ± 1.681	0.195
AVLT	34.967 ± 7.036	35.602 ± 6.452	0.517
AVLT-delay	6.967 ± 2.226	6.867 ± 2.260	0.759
CFT	34.098 ± 1.897	34.495 ± 1.780	0.138
CFT-delay	18.962 ± 4.621	21.755 ± 5.947	< 0.001**
TMT-A	71.207 ± 23.223	64.612 ± 17.141	0.027*
TMT-B	199.272 ± 53.393	166.704 ± 48.673	< 0.001**
CDT	3.544 ± 0.543	3.459 ± 0.540	0.285
DST	11.304 ± 1.790	11.643 ± 1.701	0.183
VFT	14.141 ± 3.541	14.724 ± 3.224	0.236
DSST	69.239 ± 7.947	69.602 ± 8.991	0.769

Data are represented as mean ± SD

MMSE Mini Mental State Exam, *MoCA* Montreal Cognitive Assessment, *AVLT* auditory verbal learning test, *CFT* complex figure test, *TMT* trail making test, *CDT* clock drawing test, *DST* digit span test, *VFT* verbal fluency test, *DSST* Digit Symbol Substitution Test

p* < 0.05; *p* < 0.001

DISCUSSION

To our knowledge, this is the first study to investigate causal interactions in patients with T2DM in the TPN using spDCM. Among the triple networks, self-inhibition was detected within the DMN and SN, whereas self-excitation was detected only in the SN. Furthermore, we found a relationship between abnormal effective connectivity and visuospatial recall ability as well as islet function.

The mPFC and PCC are crucial components of the DMN, a network of brain areas that are activated during self-referential and introspective tasks [29]. The mPFC and PCC are highly interconnected and are thought to play complementary roles in these processes. The mPFC is involved in higher-order cognitive functions such as decision-making, planning, and social cognition, while the PCC is involved in the processing of self-relevant information,

episodic memory retrieval, and mind wandering. The strong connection between these two regions is believed to allow for the coordination of information processing and the integration of self-referential information with higher-order cognitive functions. A previous rs-fMRI study of patients with T2DM indicated weaker functional connections between the PCC and numerous brain regions (like the frontal lobes, the temporal lobes, and the thalami) [30]. Our previous research in patients with T2DM with insulin resistance demonstrated that significantly decreased EC from the PCC to the left hippocampus was negatively associated with the insulin resistance score [31]. We found bidirectional excitatory effective connectivity between the PCC and mPFC in HCs; however, these enhanced connections were absent in the T2DM group. Conversely, the T2DM group showed reduced connections from the PCC to the mPFC, which suggests that individuals with T2DM may experience difficulties in self-awareness,

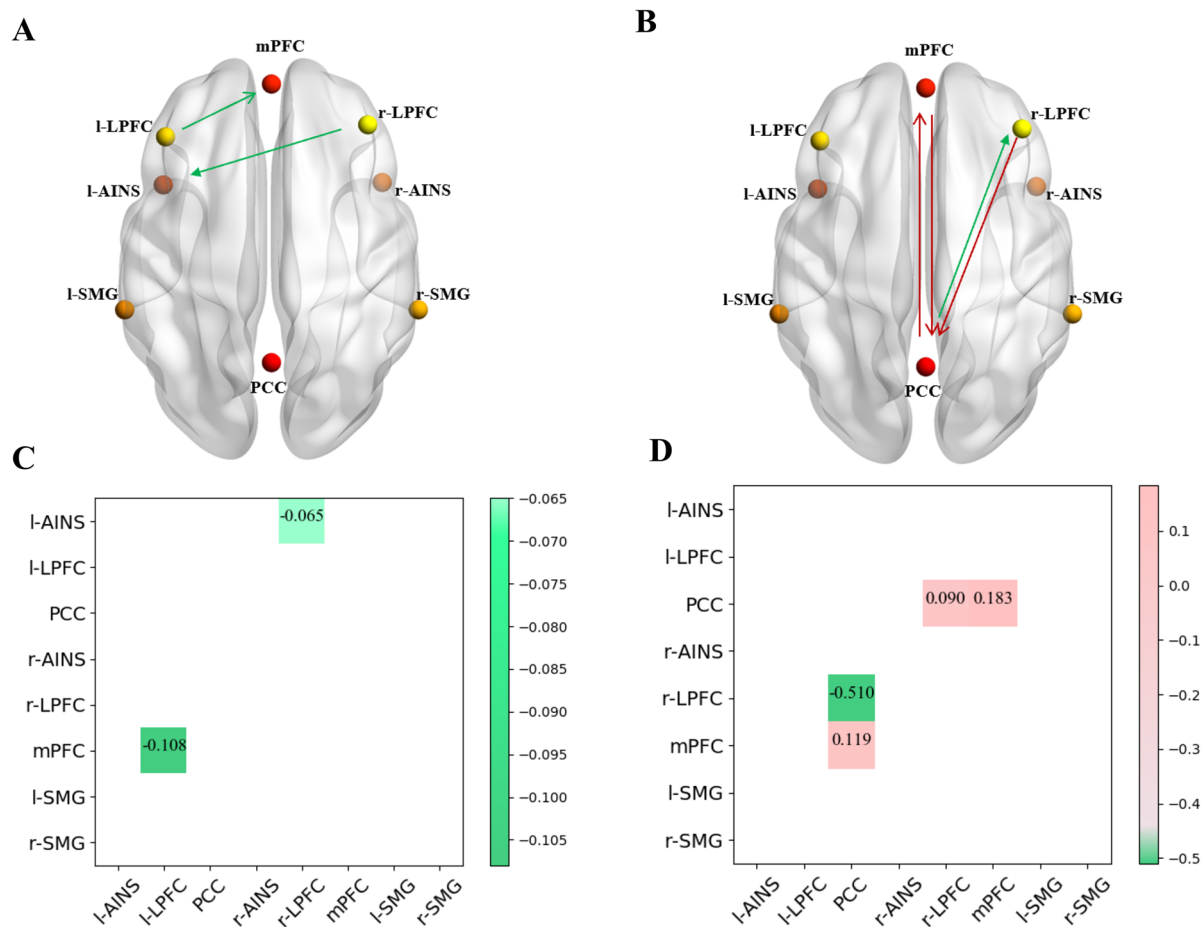


Fig. 1 Intra- and internetwork effective connectivity patterns in both groups and the color matrix of one-sample t tests. **a** Effective connections that are significantly different from zero in patients with T2DM. **b** Effective connections that are significantly different from zero in HCs. In both HCs and patients with T2DM, connections found to be significant within each group on the basis of paramet-

ric empirical Bayesian analysis are depicted as red arrows for excitatory connections and green arrows for inhibitory connections. Group mean effective connectivity in the patients with T2DM (**c**) and HCs (**d**). *mPFC* medial prefrontal cortex, *PCC* posterior cingulate cortex, *LPFC* lateral prefrontal cortex, *SMG* bilateral supramarginal gyrus, *AINS* anterior insula

emotional regulation, and decision-making. Another study examined the DMN connectivity in patients with T2DM with different durations of diabetes, especially from the perspective of T2DM development and the severity of diabetes. They observed that connectivity increased when diabetes duration was less than 10 years [32]. Because the average duration of diabetes in the patients with T2DM included in our study was approximately 9 years, our results are consistent with these studies. Nevertheless, we further identified a specific effective connection

direction, namely excitatory connections outflowing from the mPFC to the r-SMG and inflowing from the r-LPFC to the mPFC. In addition, the significantly enhanced connectivity strength from the r-LPFC to the mPFC was negatively associated with diabetes duration. These results further indicated that with the prolongation of the course of diabetes, this compensatory positive connection gradually decreases.

The SN is thought to switch between the DMN (when internal attention is required) and the ECN (when goal-directed attention is required)

Table 3 Group differences in mean effective connectivity strength for region of interests

Connection		Connectivity strength (mean ± SD)		<i>p</i> value	<i>t</i>
		T2DM	HC		
PCC to mPFC	DMN to DMN	0.033 ± 0.168	0.119 ± 0.244	0.005	2.809
mPFC to l-LPFC	DMN to ECN	-0.040 ± 0.168	0.024 ± 0.178	0.012	2.539
mPFC to r-SMG	DMN to SN	0.032 ± 0.183	-0.035 ± 0.174	0.010	-2.597
r-SMG to l-SMG	SN to SN	-0.036 ± 0.202	0.049 ± 0.243	0.009	2.638
r-SMG to l-LPFC	SN to ECN	-0.019 ± 0.214	0.072 ± 0.193	0.002	3.079
r-AINS to l-LPFC	SN to ECN	-0.194 ± 0.244	0.081 ± 0.196	0.002	3.144
l-AINS to r-AINS	SN to SN	0.061 ± 0.290	-0.036 ± 0.220	0.010	-2.615
r-LPFC to mPFC	ECN to DMN	0.065 ± 0.344	-0.058 ± 0.326	0.012	-2.526
l-LPFC to l-AINS	ECN to SN	0.059 ± 0.194	-0.020 ± 0.200	0.007	-2.748

Results of an independent sample *t* test with FDR-corrected *p* values

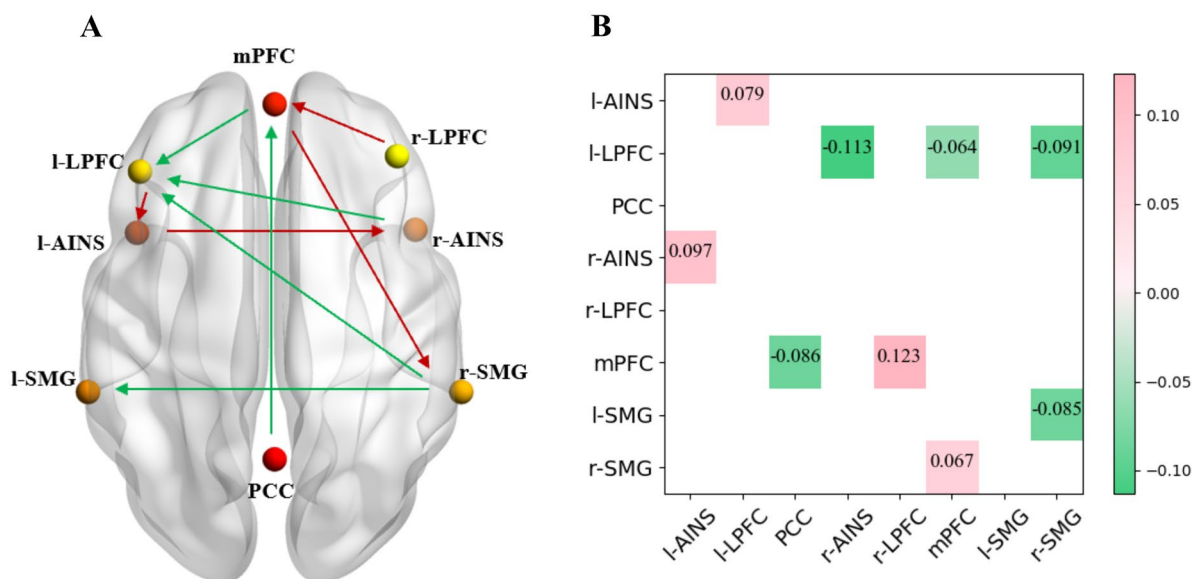


Fig. 2 Effective connectivity with significant differences between HCs and patients with T2DM (a). The red arrows indicate that the T2DM group had a significantly positive difference from the HC group; the green arrows indicate that the T2DM group had a significantly negative differ-

ence from the HC group. **b** Color matrix of independent two-sample *t* tests. Results of an independent sample *t* test with FDR-corrected *p* values (*p* < 0.05). Pink, HC < T2DM; green, HC > T2DM

and play an important role in mediating interactions between large-scale functional networks. Multiple studies involving a wide range of cognitive control tasks have shown evidence for a

causal role of the SN [33, 34]. The anterior insula belongs to SN, which is proposed to play a key role in discerning pertinent stimuli from the expansive and relentless flow of sensory inputs

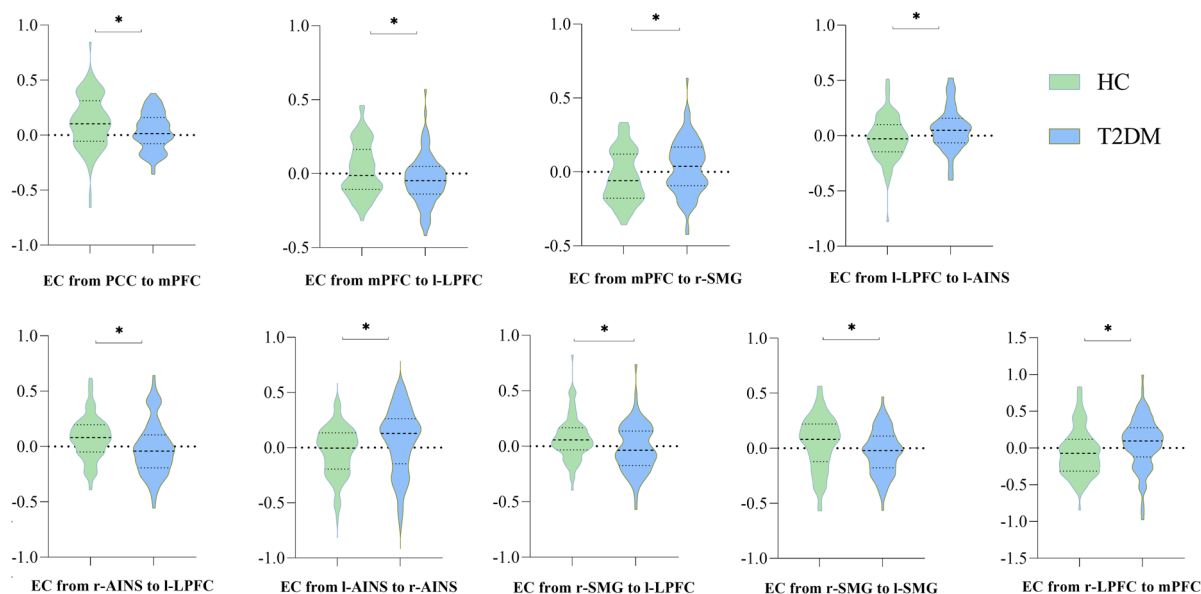


Fig. 3 Violin plots showing the effective connectivity strengths of brain regions with significant group differences. * $P < 0.05$

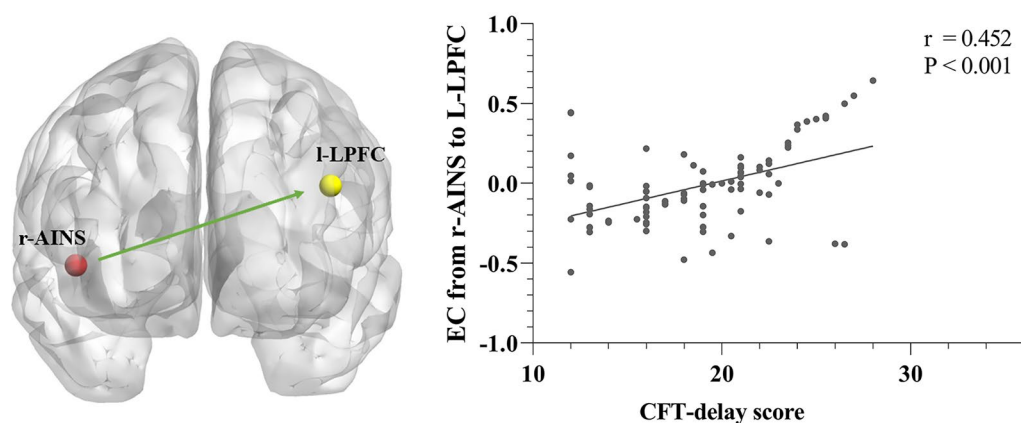


Fig. 4 Significant correlations between effective connectivity strengths and neuropsychological scores. The effective connectivity from the r-AINS to the l-LPFC was strongly correlated linearly with the CFT-delay score

that influence the senses. For these reasons, we selected the bilateral anterior insula, located in the anterior part of the SN, and the bilateral supramarginal gyrus, which is located in the posterior part of the SN, as ROIs for evaluating effective connectivity, similar to the findings of previous studies on the triple network in patients with AD and other neuropsychiatric disorders [30, 35]. The anterior insula is a key hub within the broader central-insular “salience network,” coordinating and driving the activity

of other major functional brain networks. The microanatomy and large-scale connectivity of the insular cortex make it essential for sorting and integrating multiple sensory stimuli from both internal and external sources to initiate higher-order control functions [11].

Wang et al. explored functional connectivity between the r-insula and the DMN and ECN in patients with T2DM. The findings showed decreased functional connectivity between the right AINS and the mPFC. Moreover, the reduced

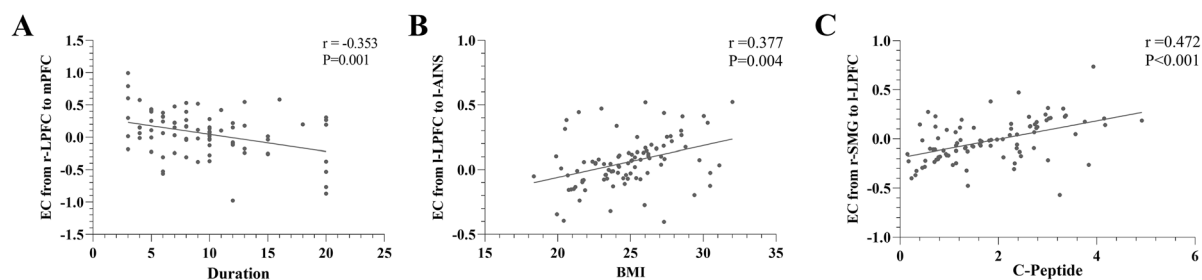


Fig. 5 Spearman's correlation between differences in effective connectivity strengths and clinical characteristics of patients. **a** Correlations between effective connectivity

strengths and diabetes duration; **b** effective connectivity strengths and BMI; and **c** effective connectivity strengths and C-peptide levels

functional connectivity between the posterior cingulate and inferior frontal gyrus (IFG) was detected. Furthermore, the diminished functional connectivity observed between the right AINS and the right IFG might be associated with attentional deficiencies in patients [36]. In another rsFC study, Zhang et al. stated that patients with T2DM exhibited reduced functional connectivity between the AINS and both the supramarginal gyrus and the LPFC compared to healthy individuals [37]. The decreased EC from the r-AINS to the l-LPFC in our study aligned with prior research outcomes. Furthermore, our results indicated the decreased EC was positively correlated with the CFT-delay score. These results may confirm that the decrease in visuospatial recall capability in patients with T2DM could be related to abnormal transhemispheric EC from the SN to the ECN. Moreover, increased effective connectivity within the SN from the l-AINS to the r-AINS was also detected. This atypical excitatory connection across hemispheres may compensate for abnormal directed connection barriers between the default and execution networks.

A multimodal meta-analysis indicated that patients with T2DM had decreased gray matter volume (GMV) mainly in the bilateral supramarginal gyrus [38]. The SMG is important in cortical speech and language, especially in the right hemisphere, and is essential for visuospatial awareness. The variability of anomia is associated with the involvement of the posterior middle SMG, while stimulation of the anterior SMG results in semantic paraphasias [12, 39]. Studies have revealed that neural populations in the

right hemisphere's supramarginal gyrus (SMG) were responsible for processing subjective time perception, particularly due to their sensitivity to specific temporal durations [40]. Our study showed that the right supramarginal gyrus is an important effective connection node. There are two effective outflow connections from the r-SMG to the l-SMG and l-LPFC. This atypically reduced connectivity across hemispheres was absent in HCs. Therefore, we concluded from these results that the r-SMG might be a sensitive region for exploring TPN network switching barriers and visuospatial awareness. Moreover, the decreased EC from the r-SMG to the l-LPFC was positively correlated with fasting C-peptide levels, which are an important indicator of insulin secretion in the body. In the diabetes population included in this study, low fasting C-peptide levels indicated impaired insulin secretion. Insulin imbalance may lead to neurodegeneration, and previous studies revealed that a relative deficiency of insulin secretion was negatively correlated with GMV in the mPFC and temporal and parietal regions in patients with AD [41]. We focused more on changes in brain functional connections and found that decreased islet function might induce inhibitory EC from the SN to the ECN, thus contributing to clinical symptoms in patients with T2DM.

The LPFC is strongly implicated in executive control, encompassing functions such as working memory, attention to the characteristics of stimuli, and the choosing of responses that are appropriate to the context [42]. The LPFC is specifically involved in tasks that require self-regulation, such as inhibiting responses

or switching between tasks. It coordinates the activity of other brain regions to ensure that appropriate actions are taken on the basis of current goals and the environmental context [6]. Xu et al. conducted a comprehensive mapping of the cortical connectome in the LPFC using electrical microstimulation combined with fMRI in primate plays. These results indicated that connections with the LPFC fell within six cortical domains: the temporal cortex, PPC, orbitofrontal and insular cortices, mPFC, posteromedial cortex, and within the LPFC itself [43]. In another multi-tissue epigenetic analysis, Sarnowski et al. identified potentially distinct epigenetic regulatory mechanisms in peripheral blood and lateral prefrontal cortex tissues that underlie insulin resistance and AD at the carnitine palmitoyltransferase 1A (CPT1A) genetic locus [44]. On the basis of these results, we suspected that the LPFC is an important node associated with cognitive impairment and insulin resistance.

A functional connectivity study indicated increased FC between the bilateral lateral prefrontal cortex and the PCC in patients with T2DM with early cognitive decline [45]. We observed that there were multiple reduced effective connections that extended into the l-LPFC without any excitatory inflow. These results suggest that the LPFC in the executive network exhibits weaker synergistic conversion within the TPN in patients with T2DM than in healthy controls. We also found only one excitatory outflow from the l-LPFC, which was significantly positively correlated with BMI. Since the early 1990s, BMI has been extensively utilized for categorizing overweight and obesity, as well as investigating risks associated with obesity, and offering dependable data regarding excessive body weight. Research on the brain mechanisms of obesity has shown that BMI is positively associated with hypothalamic rs-FC with the insula. Additionally, a positive relationship between hypothalamic GMV and hypothalamus–insula connectivity has been observed [46]. An obesity spDCM study indicated that BMI was linked to decreased inhibitory control from the ventromedial prefrontal cortex to the anterior insula, increased excitatory connections

from the anterior insula to the hypothalamus, and heightened self-inhibition of the ventromedial prefrontal cortex in the hunger state [47]. These results indicated that BMI may be related to the circuits between the hypothalamus and insula and to the LPFC; however, contrary to our results, how diabetes status and whether the patient is in a hunger state may affect the functional connection direction of the three nodes need further study.

This study has several limitations. First, although we selected eight ROIs in the triple network, this complex network contains more nodes. More detailed studies should be performed in the future to elucidate the specific effects of additional nuclei. Given the complexity of this network, the relevance of these associations between cognition and EC abnormalities may not be restricted to mutual causality. Finally, treatment options for patients with T2DM are variable, so we were unable to control for the potential effects of medication on outcome variables. Future studies with different therapeutic regimens are necessary to further validate these initial findings.

CONCLUSION

Our study used spDCM based on fMRI to detect directed connectivity changes in the DMN, SN, and ECN in patients with T2DM. The current findings emphasized the significance of connectivity within the triple network as a potential imaging marker for cognitive impairment in patients with T2DM. This finding could enhance our comprehension of the neurological mechanisms underlying T2DM and offer valuable insights into the associated cognitive decline.

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Data Availability. The datasets generated during and/or analyzed during the current study are available from the corresponding author on reasonable request.

Declarations

Conflict of Interest. Yujie Zhang, Xiao Yin, Yu-Chen Chen, Huiyou Chen, Mingxu Jin, Yuehu Ma, Wei Yong, Vijaya Prakash Krishnan Muthaiah, Wenqing Xia and Xindao Yin have nothing to disclose.

Ethical Approval. The study was conducted in accordance with the Declaration of Helsinki, and approved by Ethics Committee of Nanjing First Hospital (protocol code KY20220124-02 and date of approval 24 January 2022).

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