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ORIGINAL RESEARCH

Aberrant Modular Segregation of Brain Networks in Patients with Diabetic Retinopathy

Heng-Hui Li[1,*], Yan-Ni Su[2,*], Xin Huang[3]

[1]Department of Ophthalmology, Gaoxin Branch of the First Affiliated Hospital of Nanchang University, Nanchang, Jiangxi, 330006, People's Republic of China; [2]The First Clinical Medical College, Jiangxi Medical College, Nanchang University, Nanchang, Jiangxi, 330006, People's Republic of China; [3]Department of Ophthalmology, Jiangxi Provincial People's Hospital, The First Affiliated Hospital of Nanchang Medical College, Nanchang, Jiangxi, 330006, People's Republic of China

*These authors contributed equally to this work

Correspondence: Xin Huang, Department of Ophthalmology, Jiangxi Provincial People's Hospital, No. 152, Ai Guo Road, Dong Hu District, Nanchang, 330006, Jiangxi, People's Republic of China, Tel +86 15879215294, Email 334966891@qq.com

Background: Diabetic retinopathy (DR) is a prevalent ocular manifestation of diabetic microvascular complications and a primary driver of irreversible blindness. Existing studies have illuminated the presence of aberrant brain activity in individuals affected by DR. However, the alterations in the modular segregation of brain networks among DR patients remain inadequately understood. The study aims to explore the modular segregation of brain networks in patients with DR.

Methods: We examined the blood oxygen levels dependent (BOLD) signals using resting-state functional magnetic resonance imaging (R-fMRI) in a cohort of 46 DRpatients and 43 age-matched healthy controls (HC). Subsequently, Modular analysis utilizing graph theory method was applied to quantify the degree of brain network segregation by computing the participation coefficient (PC). Deviations from typical PC values were further elucidated through intra- and inter-module connectivity analyses.

Results: The DR group demonstrated significantly lower mean PC in the frontoparietal network (FPN), sensorimotor network (SMN), and visual network (VN) compared to the HCgroup. Moreover, increased inter-module connections were observed between the default-mode network (DMN) and SMN, as well as between FPN and VN within the DR group. In terms of nodal analysis, higher PC values were detected in the left thalamus, right frontal lobe, and right precentral gyrus in the DR group compared to the HC group.

Conclusion: Patients with DR show impairments in primary sensory networks and higher cognitive networks within their functional brain networks. These changes may provide essential insights into the neurobiological mechanisms of DR by identifying alterations in the brain networks of DR patients and pinpointing sensitive neurobiological markers that could serve as vital imaging references for future treatments of diabetic retinopathy.

Keywords: diabetic retinopathy, brain functional networks, functional connectivity, fMRI

Introduction

Diabetic retinopathy (DR) is a serious complication of long-term diabetes mellitus (DM),[1] is primarily characterized by retinal microangiomas, retinal hemorrhage, macular edema, and retinal neovascularization.[2] Diabetic retinopathy, as the primary microvascular complication of diabetes mellitus, stands as the leading cause of visual impairment in patients with diabetes mellitus.[3] It is strongly linked to prolonged diabetes duration and inadequate control of glycemic and blood pressure levels.[4] With the prolonged duration of diabetes, around 50% of patients develop diabetic retinopathy within 10 years of diabetes diagnosis, and this percentage may increase to 90% after 25 years.[5] Epidemiological projections indicate that by 2030, the global population affected by diabetic retinopathy will escalate to 191 million individuals.[6] Previous neuroimaging studies have demonstrated functional and structural alterations in the brains of individuals with diabetes.[7,8] Furthermore, these functional alterations in individuals with diabetic retinopathy may contribute to the advancement of visual impairment.[9] Currently, the precise neurophysiological mechanisms underlying visual loss and cognitive decline in patients with diabetic retinopathy remain elusive. Recent studies using amplitude of low-frequency

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fluctuations of resting-state BOLD imaging have revealed abnormal spontaneous brain activity across various brain regions in individuals with DR.[10] An extensive study conducted over multiple years revealed a correlation between the severity of retinopathy in diabetic patients and a reduction in grey matter volume in specific brain regions, namely the right inferior frontal gyrus and right occipital lobe.[11] There is a suggestion that the functional and structural alterations in the brains.[9] Individuals with DR are at a heightened risk of developing neurodegenerative diseases.[12] In a separate study, it was found that patients with proliferative diabetic retinopathy exhibited elevated apparent diffusion coefficient values in areas.[13] A corresponding fMRI-based investigation demonstrated disrupted network module balance in the brains of patients with diabetic retinopathy, including alterations in the nodal centers of the default mode network (DMN) and the visual network (VN), alongside abnormal functional connectivity among the VN, DMN, salience network (SN), and sensorimotor network (SMN).[14] Previous studies have illustrated the existence of atypical alterations in brain networks among DR patients. However, further research is warranted to enhance the depth of insight in this field.

The modular structure serves as one of the structural foundations for brain regions to function during typical resting brain activity.[15] Each module within the brain network carries out distinct and autonomous cognitive functions, establishing connections between different modules when a task necessitates the collective involvement of multiple cognitive functions.[16] Within the modular structure of the network, interconnections between modules are sparse, yet intra-module connections are dense, thereby preserving a balance between functional specialization and module integration, thereby creating a modular isolation model.[17] Modular isolation models are currently applied in a range of biomedically significant studies. For instance, research has revealed a significant age-related increase in intramodular connectivity within the Default Mode Network (DMN), the Frontal-Parietal Network (FPN), and the Sensorimotor Network (SMN).[18] The presence of decreased module separation within the Frontal-Parietal Network (FPN) has been observed in patients with major depressive disorder (MDD).[17] Elevated modular segregation of the Frontal-Parietal Network (FPN), the Cingulo-Opercular Network (CON), and the cerebellum (Cere) has been observed in female patients with bulimia nervosa.[19] At present, the neurophysiological mechanism behind the symptoms of patients with DR remains unclear, and the utilization of fMRI in investigating brain activity and network modifications in DR patients is limited. The modular segregation of whole brain functional networks in DR patients is currently unexplored. Considering these gaps, the potential utilization of modular isolation models for studying brain activity and network changes in DR patients is indicated.

Graph theory offers a distinctive quantitative methodology for delineating the organization of entire brain networks, especially through resting-state data[20] and is currently an effective method for describing the segregation of brain network modules. The PC is a measure that quantifies both inter- and intra-module connections in brain networks, enabling the assessment of modular segregation in brain networks.[21] Thus, with the assistance of a potent graph-theoretic metric like PC, we are able to uncover the anomalous modular segregation of brain networks in patients with DR.

In this study, we initially computed the mean PC value for each module and subsequently examined the number of intra- and inter-module connections to investigate which connections were linked to clinical symptoms of DR. Drawing from prior research, our hypotheses were as follows: (1) alterations in specific brain network module separations would be observed in the DR group compared to theHC group; (2) changes in inter-module connections would be evident in the DR group compared to the HC group.

Materials and Methods

Participants

In the current study, a total of 89 participants were included, comprising 46 DR patients (22 males and 24 females) and 43 HC (22 males and 21 females), matched in terms of gender, age, and handedness. The participants were recruited from the Department of Ophthalmology at Jiangxi Provincial People's Hospital. The number of ethical is 2023A0138.

All patients met the diagnostic criteria for diabetic retinopathy as per the International Clinical Diabetic Retinopathy Disease Severity Scale.[22] The diagnostic criteria for DR patients incorporated fasting plasma glucose levels ≥ 7 mmol/L, random plasma glucose levels ≥ 11.1 mmol/L, or a 2-hour glucose level ≥ 11.1 mmol/L. Moreover, patients with

nonproliferative DR exhibited features such as microaneurysms, hard exudates, and retinal hemorrhages. In our study, All patients with DR underwent fundus photography and fluorescein angiography.

The exclusion criteria for DR patients encompassed the presence of proliferative DR with retinal detachment, vitreous hemorrhage, additional ocular-related complications (such as cataract, glaucoma, high myopia, or optic neuritis), as well as the existence of diabetic nephropathy or diabetic neuropathy.

All HC met the specified criteria, inclusive of normal fasting plasma glucose levels are between 3.9 mmol/L (70 mg/dL) and 5.6 mmol/L (100 mg/dL), random plasma glucose levels < 11.1 mmol/L, HbA1c levels < 6.5%, absence of ocular diseases (myopia, cataracts, glaucoma, optic neuritis, or retinal degeneration), and binocular visual acuity ≥ 1.0.

Statement of Ethics

The study was conducted in compliance with the principles outlined in the Declaration of Helsinki and obtained approval from the ethical committee of Jiangxi Provincial People's Hospital. Prior to participation, all individuals involved in the study provided written informed consent.

Image Acquisition

All participants were instructed to relax, keep their eyes closed, and maintain a motionless state without falling asleep during the resting-state fMRI scanning. Resting-state fMRI data were obtained using a 3T MRI system. Functional images were captured using a gradient-echo-planar imaging sequence with parameters including TR/TE = 2000 ms/25 ms, thickness = 3.0 mm, gap = 1.2 mm, acquisition matrix = 64 × 64, flip angle = 90°, field of view = 240 mm × 240 mm, voxel size = 3.6 mm × 3.6 mm × 3.6 mm, and 35 axial slices.

fMRI Preprocessing

The preprocessing was conducted using the Data Processing and Analysis Toolbox (DPABI) for Brain Imaging in MATLAB. This toolbox is specifically designed to minimize initial signal instability and confirm that participants had acclimated to the scanning environment.[23] 1) The initial 10 volumes for each participant were discarded, resulting in 230 remaining volumes. 2) Slice time correction was applied to the retained images. 3) Head motion correction was implemented to ensure all head movements were limited to translations of less than 2 mm or rotations of less than 2 degrees, with any exceedances leading to exclusion from further analyses. 4) Regressing out nuisance signals involved six motion parameters, the white matter signal, and the cerebrospinal fluid signal. 5) The spatial normalization was carried out into the Montreal Neurological Institute (MNI) template. 6) Detrending was performed to eliminate linear trends. 7) Temporal filtering (0.01–0.1 Hz) was applied to eliminate low-frequency drift and high-frequency noise.

Brain Network Construction and Graph Theory Analysis

All graph theory analyses were conducted using GRETNA, with a functional brain template subdividing the brain into 160 regions encompassing cerebral and cerebellar areas. In this study, the 160 regions of interest (ROIs) were classified into six functional modules identified as the default-mode network (DMN), frontal-parietal network (FPN), cingulo-opercular network (CON), sensorimotor network (SMN), visual network (VN), and the cerebellum (Cere).[24]

First, we calculated the PC to quantify the degree of module segregation. PC is calculated using the formula $PCi = 1 - \sum_{m \in M} \left(\frac{kim}{ki}\right)^2$. In this formula, M is the set of modules, m refers to a module in a set of modules M, kim is the number of connections between node i and other nodes in the module m, and ki is the total number of connections of node i in the whole brain network.[21] The PC quantifies the patterns of inter- and intra-module connectivity of node.

Furthermore, we computed the count of intra-module connections within each module and the count of inter-module connections in each pair of modules. The tally of inter-module connections is obtained by adding up the connections between all nodes in one module and all nodes in another module. Lastly, to investigate abnormal modular segregation at the node level, we determined the PC of each node within the module demonstrating atypical modular segregation. Figure 1 depicts a schematic representation of the processing steps.

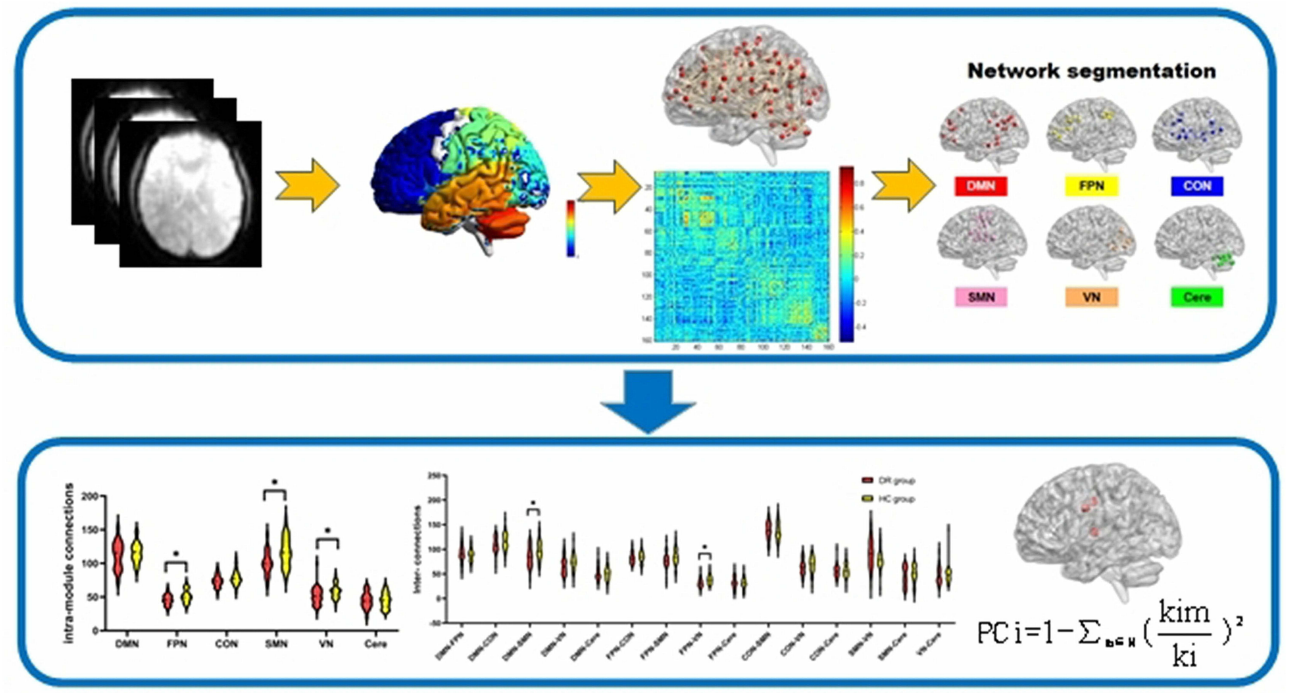

Figure 1 Schematic representation of the processing steps. The entire brain is divided into six functional modules, consisting of the Default Mode Network (DMN), Frontal-Parietal Network (FPN), Cingulo-Opercular Network (CON), Sensorimotor Network (SMN), Visual Network (VN), and Cerebellum (Cere) based on prior studies.

Statistical Analyses

Both the chi-square ($\chi 2$) test and independent-samples *t*-test were utilized to compare clinical variables between the two groups using SPSS version 16.0 (SPSS Inc., Chicago, IL, USA).

A two-sample *t*-test was conducted to compare the between-group variances in the mean PC of each module, the counts of intra-module and inter-module connections, and the PC of each node within the module exhibiting abnormal modular segregation. To address multiple comparisons, a Bonferroni correction was applied with a significance threshold set at $p < 0.05$.

Results

The clinical characteristics of the participants were depicted in Table 1. Age and gender were comparable between the two groups, showing no significant differences ($p > 0.05$).

Table 1 Clinical-Demographic Characteristics of the DR and HC Groups

Condition	DR Group	HC Group	t	p
Gender (male/female)	22/24	22/21	N/A	N/A
Age (years)	55.02 ± 3.41	53.13± 2.92	-0.174	0.862
BCVA-OD	0.33 ± 0.13	1.09± 0.18	–22.629	0.001*
BCVA-OS	0.28± 0.185	1.37 ± 0.12	-32.278	0.001*

Note: $\chi 2$ test for sex (n). Independent *t* test for the other normally distributed continuous data (means ± SD).* indicate $p<0.001$.

Abbreviations: DR, diabetic retinopathy; HC, healthy control; N/A, not applicable; BCVA, best corrected visual acuity; OD, oculus dexter; OS, oculus sinister; DR, diabetic retinopathy; HC, healthy controls.

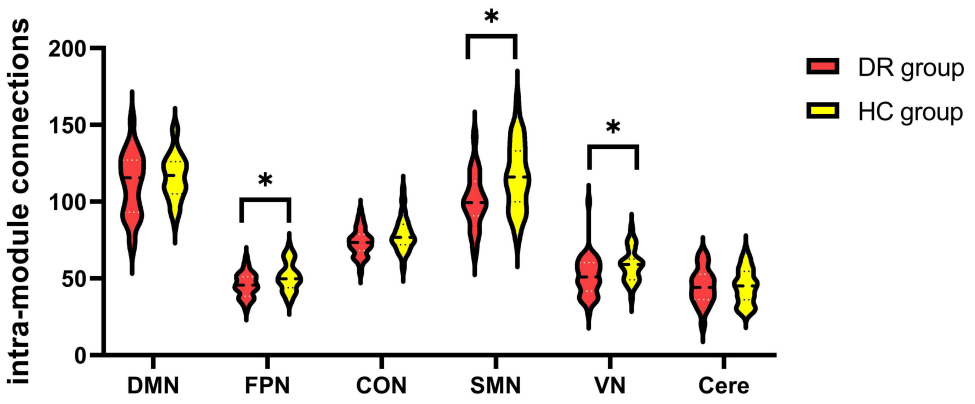

Figure 2 Between-group differences of mean participant coefficient (PC). Diabetic retinopathy (DR) patients showed significantly lower PC on the fronto-parietal network (FPN), the sensorimotor network (SMN) and the visual network (VN) than the healthy controls (HC).
Note: *Indicates $p < 0.05$.

Different Mean PC of the Modules

As shown in Figure 2 and Table 2, the mean PC of DR group showed significantly lower on the FPN ($t = -3.052$, $P_{corrected} = 0.0030$), the SMN ($t = -3.774$, $P_{corrected} = 0.0003$) and the VN ($t = -3.049$, $P_{corrected} = 0.0030$) than the HC group.

Different Inter-Module Connections

Based on the above results, we further measured whether the effects of intra- and inter-module connectivity were anomalous. As shown in Figure 3 and Table 2, DR displayed significantly decreased inter-module connections between the DMN and SMN ($t = 3.238$, p uncorrected = 0.0017), FPN and VN ($t = 3.653$, p uncorrected = 0.0004) relative to the HC group.

Different PC of Nodes

As shown in Figure 4 and Table 3, DR patients exhibited significantly changed PC in the left thalamus ($t = 4.245$, Pcorrected = 0.0001), the right frontal ($t = 4.869$, Pcorrected = 0.0001) and the right precentral gyrus ($t = 4.212$, Pcorrected = 0.0001).

Discussion

This study utilized graph theoretical analysis to investigate potential differences in resting-state network integration/segregation between diabetic retinopathy (DR) patients and healthy participants. Our results indicated that the DR group displayed significantly lower mean PC in the Frontal-Parietal Network (FPN), the Sensorimotor Network (SMN), and the

Table 2 Significant Differences in the Mean PC of Modules and the Inter-Module Connections

	DR (Mean ± SD)	HC (Mean ± SD)	t-value	P-value
Mean PC of the modules				
FPN	45.61±7.788	50.62±9.491	−3.052	0.0030
SMN	100.9±17.50	114.8±22.90	−3.774	0.0003
VN	51.21±12.54	58.10±10.58	−3.049	0.0030
Inter-module connections				
DMN and SMN	98.00±19.17	84.50±20.22	3.238	0.0017
FPN and VN	38.50±8.658	31.70±8.891	3.653	0.0004

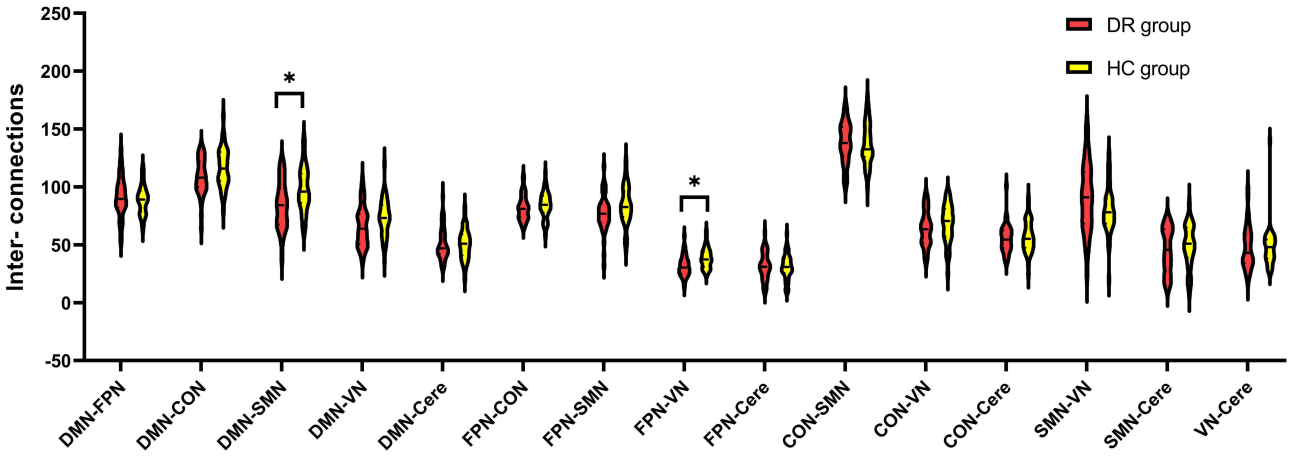

Figure 3 Between-group comparison of inter-module connections and their correlation with HAMD scores. Compared with the healthy controls(HC), the Diabetic retinopathy (DR) patients exhibited significantly decreased inter-module connections between the default-mode network (DMN) and the sensorimotor network (SMN), the frontal-parietal network (FPN) and the visual network (VN).
Note: *indicates p < 0.01.

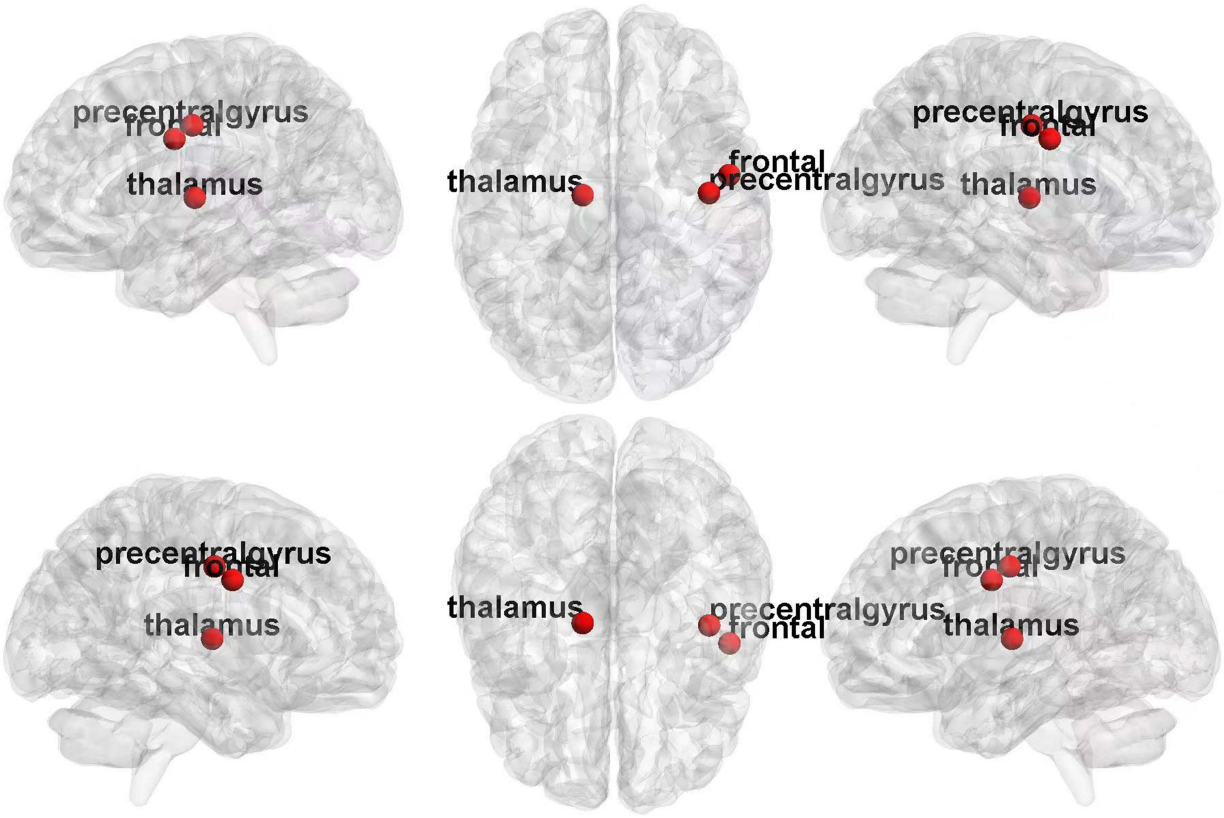

Figure 4 Significant differences in the PC of nodes.DR patients exhibited significantly changed PC in the left thalamus (t = 4.245, Pcorrected = 0.0001), the right frontal (t = 4.869, Pcorrected = 0.0001) and the right precentral gyrus (t = 4.212, Pcorrected = 0.0001).

Visual Network (VN) compared to the control group. Moreover, the DR group demonstrated enhanced inter-module connections between the Default Mode Network (DMN) and the SMN, and between the FPN and the VN. These outcomes suggest that, from a modularity standpoint, the onset of diabetic retinopathy is associated with irregularities in the intra- and inter-module connectivity of brain network modules.

Table 3 Significant Differences in the PC of Nodes

PC of the Nodes		
	t-value	**P-value**
L-thalamus	4.245	0.0001
R-frontal	4.869	0.0001
R-precentral gyrus	4.212	0.0001

We observed that DR patients exhibited a significantly reduced PC in the Frontal-Parietal Network (FPN) compared to the HC group, indicating increased intra-modular connections and decreased inter-modular connections in DR. The key brain regions of the FPN include the lateral prefrontal cortex (lPFC), midcingulate gyrus, and inferior parietal lobule (IPL). In a study conducted by Zhang et al, it was noted that patients with type 2 diabetes mellitus (T2DM) demonstrated notably lower functional connectivity (FC) between the pregenual anterior cingulate cortex (pACC) and the bilateral hippocampus, increased FC between the pACC and the bilateral lateral prefrontal cortex (LPFC) and left precentral gyrus, as well as decreased FC between the retrosplenial cortex (RSC) and right cerebellar Crus I.[13] A prior study also indicated that individuals with poorer glycemic control exhibited reduced responses in the left temporal and prefrontal regions during encoding.[25] Matthew et al discovered that the frontoparietal control network (FPCN) has a pivotal function in executive control, with its subsystem, the FPCN, potentially specializing in the management of visuospatial perceptual attention.[26] The Sensorimotor Network (SMN) is predominantly composed of sensory regions (e.g, posterior central gyrus) and motor areas (eg, anterior central gyrus), with extensions into supplementary motor regions. In a previous study, Frøkjær et al identified decreased cortical thickness in the posterior central gyrus of the brain in individuals with type 1 diabetes mellitus.[27] Several years later, abnormal activity in central cortical areas among patients with diabetes mellitus (DM) during the resting state was once more detected through resting-state EEG frequency analysis and source localization.[28] In conclusion, the findings of this study suggest that patients with DR exhibit various abnormalities in brain networks, specifically within the Frontal-Parietal Network (FPN) and Sensorimotor Network (SMN), which could potentially signify a pathogenic mechanism of DR.

The Visual Network (VN) is situated in the occipital and temporal lobes of the brain, primarily responsible for the processing of visual information.[29] One of the primary clinical symptoms in DR patients is severe vision loss. It has been commonly reported in prior studies that diabetes is linked with both functional and structural alterations in the visual center. In our study, we verified that the mean Participation Coefficient (PC) of the Visual Network (VN) was significantly lower in the DR group compared to the healthy control (HC) group. Previous research has indicated that individuals with Type 2 Diabetes Mellitus (T2DM) often exhibit reduced grey matter volume in the middle occipital gyrus.[30] Another study was shown that individuals with Type 2 Diabetes Mellitus (T2DM) without retinopathy exhibit reduced grey matter volume in the occipital lobe.[31] Qi et al reported that DR patients exhibited FC disruptions between V1 and higher visual regions at rest, which may reflect the aberrant information communication in the V1 area of DR individuals.[32] This indicates that the severe vision loss symptoms observed in patients with DRcould be attributed to diabetes-induced alterations in the brain's visual network.

Moreover, compared to the healthy controls (HC), the patients with diabetic retinopathy (DR) displayed significantly reduced inter-module connections between the Default Mode Network (DMN) and the Sensorimotor Network (SMN), as well as between the Frontal-Parietal Network (FPN) and the Visual Network (VN). In a study by Chen et al, it was reported that individuals with Type 2 Diabetes Mellitus (T2DM) present with increased path lengths, decreased overall efficiency, and disrupted long-distance connections in functional brain networks.[33] The graph-theoretic analysis indicates that the heightened module separation of the Frontal-Parietal Network (FPN), the Sensorimotor Network (SMN), and the Visual Network (VN) might be associated with the reduced inter-module connections between the Default Mode Network (DMN) and the SMN, and between the FPN and the VN. This novel insight offers a new perspective on investigating the neurobiological mechanisms underlying DR. This study partly indicates a decline in the information

transmission efficiency of specific brain functional regions in individuals with diabetic retinopathy. In future treatments and rehabilitation for individuals with diabetic retinopathy, there should be a stronger focus on restoring cognitive function, sensory-motor skills, and visual abilities specific to DR patients.

At the node level, notable alterations were observed in the PC of the thalamus, frontal gyrus, and precentral gyrus within the DR group in comparison to the HC group. The preceding discussion has highlighted the existence of brain network irregularities in the frontal and central gyrus among individuals with DR. Furthermore, in a study by Chen et al, it was documented that the functional connectivity of the thalamus is notably decreased in patients with Type 2 Diabetes Mellitus (T2DM) relative to the HC.[34] In their study, Wang et al identified elevated resting-state functional connectivity (rsFC) in cortical regions across various subdivisions of the thalamus in individuals with Type 2 Diabetes Mellitus (T2DM).[35] Liu et al proposed that there is an elevation in thalamo-cortical functional connectivity in individuals with Type 2 Diabetes Mellitus (T2DM) as revealed by resting-state functional MRI.[36] In summary, there are also aberrant alterations in the thalamus within the brain network of DR. In our current study, several limitations should be acknowledged. Firstly, (1) the PC calculations might be influenced by the number of nodes in the module. Secondly, (2) the study's small sample size and brief resting-state fMRI acquisition time necessitate a larger sample size and longer scan duration to enhance result accuracy. Thirdly, (3) the participants in this study were geographically limited and did not represent other ethnic groups. Lastly, (4) only Dosenbach's template was utilized for network construction, suggesting that a different template should be considered to validate the study results in future investigations.(5) Diabetic retinopathy may be linked to a range of systemic conditions such as circadian rhythm and hypertension. These concurrent conditions may influence brain networks, and upcoming studies aim to mitigate these confounding variables.

Conclusions

This study revealed heightened modular segregation in the FPN, SMN, and VN, along with reduced inter-modular connectivity between the DMNand SMN, as well as between the FPN and VN. Furthermore, significant alterations in the PCwere observed in the thalamus, frontal gyrus, and precentral gyrus. These results indicate a potential association between the pathogenesis of diabetic retinopathy and irregularities in intra- and inter-modular connectivity within brain networks from a modular perspective. In future studies, we will integrate multimodal magnetic resonance imaging for analyzing the structural networks related to diabetic retinopathy. Concurrently, we will investigate pre- and post-treatment alterations in brain networks among DR patients to pinpoint sensitive neurobiological markers that can serve as crucial imaging references for future diabetic retinopathy treatments.

Data Sharing Statement

The raw data supporting the conclusions of this article will be made available. Further inquiries can be directed to the corresponding author.

Acknowledgments

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Disclosure

The authors declare that they have no conflicts of interest with regard to this work.

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