

Amplitude of Low-Frequency Fluctuation to Determine Disturbed Spontaneous Brain-Activity Pattern in Patients with Diabetic Optic Neuropathy

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Purpose: This study aimed to explore the spontaneous brain activity in patients with diabetic optic neuropathy (DON) by using the amplitude of low-frequency fluctuation (ALFF) technique.

Methods: Sixteen DON patients and 16 age- and sex-matched healthy controls (HCs) were recruited. ALFF along with functional MRI method was used to detect the intrinsic brain activity alterations. The mean values of ALFF in DON patients and HCs were analyzed by receiver operating characteristic (ROC) curves. Pearson's correlation analysis was used to determine the correlation between Hospital Anxiety and Depression Scale (HADS) and ALFF values of DONs.

Results: The DON group showed significantly increased ALFF values in the fusiform gyrus, and decreased ALFF values in the medial frontal gyrus/left frontal superior orbit/right frontal medial orbit, and left frontal inferior triangle. ROC curve analysis indicated that the accuracy of AUC was good. The anxiety scale and depression scale of the DON group were negatively correlated with the ALFF values of the medial frontal gyrus.

Conclusion: DON is a neurodegenerative disease involving multiple brain regions. The abnormal activity of neurons in these brain regions helps to reveal the underlying neural mechanisms of brain activity related to DON.

Keywords: ALFF, fMRI, diabetic optic neuropathy, spontaneous brain activity

Introduction

In recent years, the prevalence of diabetes has increased with changing lifestyles of people.¹⁻³ Diabetic patients are known to develop a variety of systemic and ocular complications, and the most common ophthalmological complications are diabetic retinopathy (DR) and diabetic macular edema.⁴ Nevertheless, diabetic optic neuropathy (DON) can also progress with different forms and potentially threaten patients' vision.⁵ DON refers to the occurrence of monocular or binocular optic disc edema in diabetic patients. It is one of the fundus complications of diabetes and is more common in insulin-dependent diabetes.⁶ Although DON is not rare in clinical practice, it can be easily neglected without representative specificity, and the prevalence of DON is usually underrated in clinical practice. The major clinical characteristics include optic disc neovascularization, fundus alterations and ischemic optic neuropathy.⁷ Therefore, it is important to investigate the latent pathogenesis of DON to aid early diagnosis and ensure better treatment and prevention.

Resting-state fMRI (rs-fMRI) is a brain functional imaging method. It is adopted to observe cerebral activities when an object is at rest and not performing tasks,⁸ and can be employed to study the cerebral functional organization as well as examine alterations during diseases. Amplitude of low-frequency fluctuation (ALFF) is one of the most important rs-fMRI analysis techniques that can reveal the alterations of regional spontaneous brain activity at rest by detecting spontaneous fluctuation in blood oxygen level-dependent signal. The advantage of the ALFF method is that the analysis is simple and there are no basic assumptions. It shows extremely high time stability and long-term retest reliability. This method ensures reliability between subjects and has sufficient specificity to examine individual differences.⁹ ALFF has been employed in many ophthalmological diseases such as glaucoma,^{10–12} high myopia,¹³ strabismus,^{14,15} optic neuritis,¹⁶ ocular trauma,¹⁷ blindness,¹⁸ acute eye pain,¹⁹ retinal detachment²⁰ and diabetic retinal diseases.^{21,22}

Optic neuropathy may prevent the transmission of optical information and subsequently lead to abnormal cerebral activities; however, few studies have looked into the changes of spontaneous brain activities in DON patients. Therefore, in this study, we utilized ALFF to detect the spontaneous brain activity in DON patients to understand whether DON is associated with aberrant functional cerebral activity.

Materials and Methods

Subjects

Sixteen DON patients were recruited from the Department of Ophthalmology, First Affiliated Hospital of Nanchang University between February 2021 to March 2022. The fundus was examined using fundus fluorescein angiography (FFA) and ophthalmic fundus photography (Figure 1). The inclusion criteria for DON were: (1) diagnosed with diabetes; (2) diagnosed with optic disc edema (non-specific congestive edema); (3) early lesions on the optic nerve (painless, persistent loss of vision) with obscure, leaky and low fluorescence as seen on FFA; and (4) absence of any other optic disc edema disease. Exclusion criteria: (1) a history of serious craniocerebral injury; (2) severe mental dysfunctions; (3) excessive drinking history; (4) a history of drug abuse; (5) pregnancy; and (6) subjects with excessive motion.

Additionally, 16 healthy controls (HCs) were recruited. The inclusion criteria for HCs were: (1) no ophthalmological disease history; (2) no neurological or mental diseases; and (3) no other diseases that cause brain lesions. Exclusion criteria: subjects with excessive motion. Subjects were asked to carefully finish the Hospital Anxiety and Depression Scale. The study was ratified by the Human Research Ethics Committee of First Affiliated Hospital of Nanchang University (approval number 2021 (039), February 23, 2021). All participants signed informed consent after understanding the details of the study. All investigations comply with the principles set out in the Declaration of Helsinki.

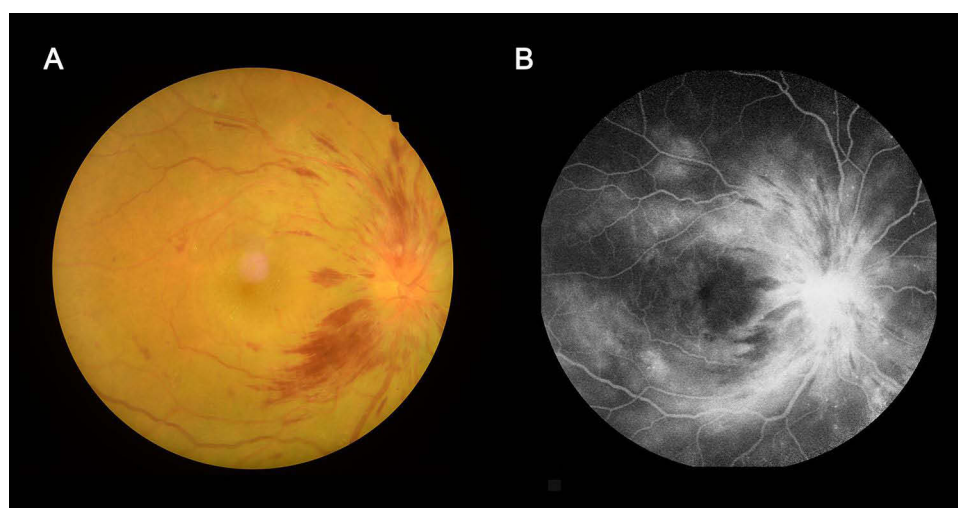


Figure 1 Eye examination data of DON patients.

Notes: Fundus photography (A); Fundus fluorescein angiography (B). Microaneurysms and dilation of the prediscal capillary network were observed. No venous dilatation or capillary closure area were observed.

Abbreviation: DON, diabetic optic neuropathy.

Study Design

DON was diagnosed according to clinical manifestations, visual field defect, VEP, and FFA. All the enrolled patients were admitted to our hospital. HCs were enrolled according to the inclusion criteria above.

All subjects received MRI scanning. We extracted the measurement data and uploaded them to a computer using the Statistical parameter mapping software and the MRIcro software for data analysis. The procedure of scanning are as follows.

MRI Parameters

The MRI scan was performed using Siemens Trio 3.0 T MRI scanner with 8-channel phased array head coil. During the scanning, the participants were asked to keep their eyes closed and focused on the center, and avoid thinking or falling asleep. A 3D metamorphic gradient echo pulse sequence was used to collect the functional data. The scanning parameters were as follows: the repeat time was 2000 ms; the flip angle was 90°; the echo time was 40 ms; the slice thickness/gap was 4.0/1 mm; the field of view was 240 mm×240 mm; and the plane resolution was 64×64. The scanning lasted for 8 min, and there were 30 axial slices in total that spanned the entire brain. A total of 240 functional images were collected eventually.²³

fMRI Data Processing

The preprocessing of the fMRI images were made by Statistical parameter mapping software, and the MRIcro software was used to analyze data. For each object, the first 10 volumes were eliminated for magnetization balance. The residual 230 volumes were managed by slicing time-related procedures and then realigned to the first volume to correct the head movement. All rearranged data were homogenized into standard Montreal Institute of Neurology EPI templates and resampled into 2×2×2 mm³cubes.²⁴

Best-Corrected Visual Acuity

Best-corrected visual acuity was assessed using the Early Treatment Diabetic Retinopathy Study(ETDRS) chart following a standardized refraction protocol. Each row of the ETDRS chart consists of five Sloan letters of the same size and reading difficulty, a total of 14 rows; the size of each line of letters is 0.7943 times the size of the uplink letters; the size of each three-line letter is reduced by half ($0.79433 = 0.5$); the interval between the peer letters is the size of the peer letters, and the interval between the adjacent two rows of visual objects is the size of the lower row letters. The measurement results were expressed as the logarithm of the minimum angle of resolution (LogMAR) or ETDRS score. Subjects were asked to read from the first word in the order of from left to right, from top to bottom until at least 3 letters could not be read in a certain line. Take the previous correctly read letter as the visual acuity record value.²⁵

Visual Evoked Potential

Visual evoked potential (VEP) is the electrical response of the occipital lobe of the cerebral cortex to visual stimulation. It is a potential change caused by the retina receiving stimulation and transmitting to the occipital cortex through the visual pathway. VEP can diagnose the lesions in the visual pathway and evaluate the type and degree of visual dysfunction objectively, quantitatively and locally. VEP is the most sensitive objective examination method for optic neuropathy, which can further confirm the clinical diagnosis.²⁶

Statistical Analysis

Collected functional MRI data were analyzed by the REST software and a two-sided *t*-test. According to the Gaussian random field theory, the voxel level statistical threshold of multiple comprehensive comparisons was set to $p < 0.005$. Alpha sim was corrected at a cluster size >60 voxels and set to $p < 0.005$.

SPSS 20.0 was used to perform an independent sample *t*-test on demographic and behavioral data. $P < 0.05$ was considered to be statistically significant. Receiver operating characteristic (ROC) curve was used to assess whether ALFF value was a diagnostic marker for corresponding brain regions. The diagnostic accuracy was expressed as the area under

the curve (AUC), and the values of 0.5–0.7, 0.7–0.9, and > 0.9 were low, medium, and high, respectively.²⁷ Pearson correlation analysis was used to analyze the correlation between clinical features and ALFF values in specific regions.

Results

Demographics and Behavioral results

The difference of best corrected visual acuity, the bilateral visual evoked potential latency and amplitude between the DON and the HC groups was statistically significant (all $P < 0.05$). The average duration of DON was 54.64 ± 5.23 days. The detailed data of clinical features are shown in Table 1.

ALFF Differences

The DON group showed statistically higher ALFF value in the fusiform gyrus than the HC group; whereas, the ALFF values in the medial frontal gyrus/left frontal superior orbit/right frontal medial orbit, and left frontal inferior triangle decreased significantly in DON patients (Figure 2 and Table 2).

ROC Curve Analysis

The mean ALFF values of DON group and HC group were assessed by ROC curve. The AUCs were as follows: fusiform gyrus, 0.978, ($p < 0.001$) (Figure 3A, DONs>HCs); medial frontal gyrus/left frontal superior orbit/right frontal medial orbit, 1 ($p < 0.001$), left frontal inferior triangle, 0.951 ($p < 0.001$; 95% CI: 0.876–1.000) (Figure 3B, DONs<HCs).

Correlation Analysis

The ALFF value of the DON group in the medial frontal gyrus was negatively correlated with the depression scale ($r = -0.951$, $P < 0.001$, Figure 4A) and the anxiety scale ($r = -0.924$, $P < 0.001$, Figure 4B).

Discussion

Diabetes can affect various organs in the human body and induce several macrovascular and microvascular complications including DR and neuropathy.²⁸ Besides, huge variation in glucose levels and long-term duration may also lead to notable degradation in brain structure and function, ultimately resulting in dysfunction related to changes in neural connectivity,²⁹ such as axonal demyelination and degeneration. Optic nerve ischemia can lead to retinopathy, thereby impairing the integrity.³⁰ Studies have shown that the main reasons of optic neuropathology in diabetic rats were the decrease of the blood flow in optic nerve and the increase of optic nerve vascular permeability.³¹

Table 1 Basic Information of Participants in the Study

Conditions	DON	HC	t	P-value
Male/female	8/8	8/8	N/A	>0.99
Age (years)	54.85±5.67	53.12±5.86	0.261	0.902
Weight (kg)	63.08±7.36	60.98±8.17	0.183	0.853
Handedness	16R	16R	N/A	>0.99
Duration of DON (days)	54.64±5.23	N/A	N/A	N/A
Best-corrected VA-left eye	0.30±0.25	1.05±0.20	-3.642	0.012
Best-corrected VA-right eye	0.25±0.15	1.00±0.15	-3.153	0.009
Latency (ms)-right of the VEP	120.08±10.22	100.65±5.82	3.291	0.006
Amplitudes(uv)-right of the VEP	6.76±2.09	14.27±1.82	-6.076	0.007
Latency (ms)-left of the VEP	114.46±7.35	100.78±3.92	5.597	0.012
Amplitudes (uv)-left of the VEP	8.76±3.16	16.74±2.52	-3.022	0.007

Notes: Independent t-tests comparing two groups ($P < 0.05$).

Abbreviations: DON, diabetic optic neuropathy; HC, healthy control; N/A, not applicable; VA, visual acuity; VEP, visual evoked potential.

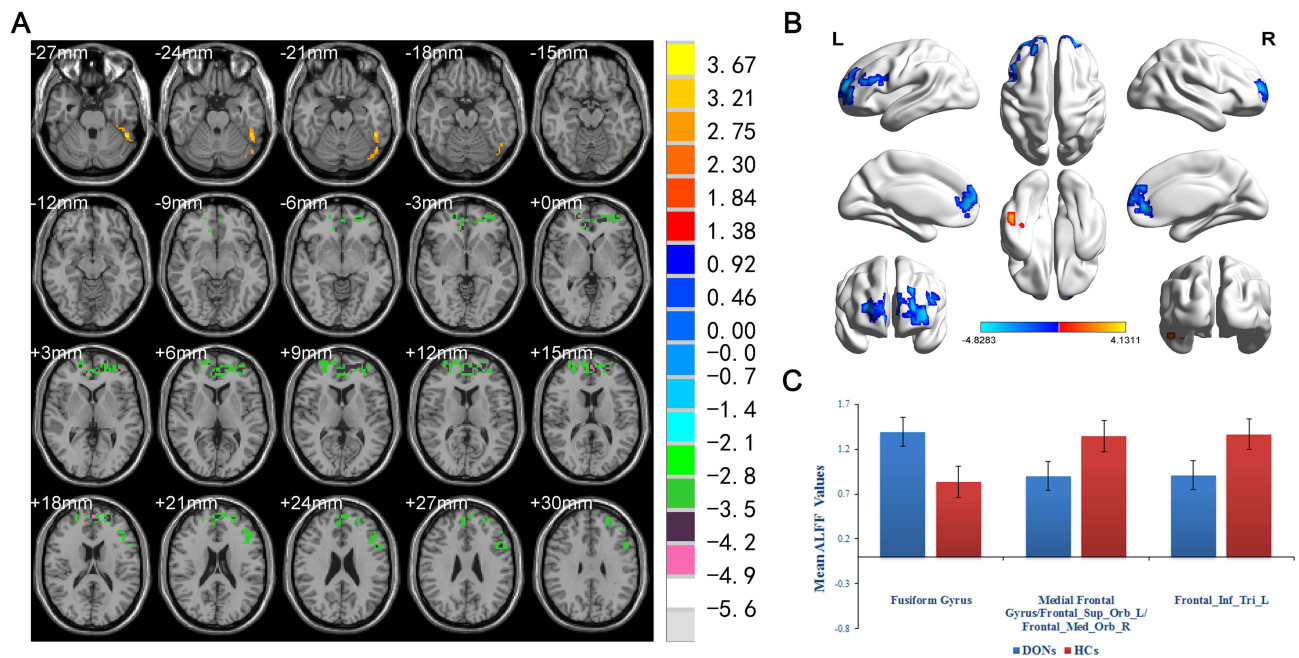


Figure 2 Significant differences of ALFF values between DON and HC groups. **Notes:** (A) Differences in ALFF were found in fusiform gyrus, medial frontal gyrus/left frontal superior orbit/right frontal medial orbit, and left frontal inferior triangle. (B) The stereoscopic form of the cerebrum. The red area indicates an increase in ALFF value; the blue indicates a decrease in ALFF value. (C) The Mean ALFF value between DONs and control group. **Abbreviations:** DON, diabetic optic neuropathy; HCs, healthy controls; ALFF, amplitude of low-frequency fluctuation; Frontal_Sup_Orb_L, left frontal superior orbit; Frontal_Med_Orb_R, right frontal medial orbit; Frontal_Inf_Tri_L, left frontal inferior triangle.

Resting-state functional ALFF is a vital and helpful approach to investigate functional alterations in brain areas and unveil concealed pathological mechanism. This technique has been utilized in several research studies regarding ocular diseases, and represents an important aspect of rs-fMRI. It provides a further approach to understand the functional links between ophthalmic diseases and local spontaneous brain activity and can help us uncover the latent relationship between functional cerebral alteration and DON. In our study, ALFF values increased in the fusiform gyrus, which means the brain region is more active than the normal, indicating that there might be a compensatory process for some impaired function in other brain regions. ALFF values decreased in the medial frontal gyrus and left frontal inferior triangle when compared with the HC group (Figure 5), indicating that these regions might be dysfunctional in subjects with DON.

The individual functions of each cerebral ROI are shown in Table 3, which is strongly associated with emotional processing and visual formation centers. The fusiform gyrus spans part of the temporal lobe and occipital lobe, it is also known as the lateral occipital temporal gyrus.³² This region of the brain has been implicated in high-level visual information processing, including

Table 2 Brain Areas with Significantly Different ALFF Values Between Groups

Conditions	Brain Areas	MNI Coordinates			BA	Peak Voxels	t-value
		x	y	z			
DONs>HCs 1	Fusiform gyrus	-45	-36	-30	20	82	4.1311
DONs<HCs 2	Medial frontal gyrus/ left frontal superior orbit/right frontal medial orbit	0	57	18	10	666	-4.8283
DONs<HCs 3	Left frontal inferior triangle	-51	12	27	44	103	-3.8316

Notes: The statistical threshold was set at voxel level $P < 0.005$ with GRF correction for multiple comparisons. **Abbreviations:** ALFF, amplitude of low-frequency fluctuation; BA, Brodmann area; HCs, healthy controls; DON, diabetic optic neuropathy; MNI, Montreal Neurological Institute.

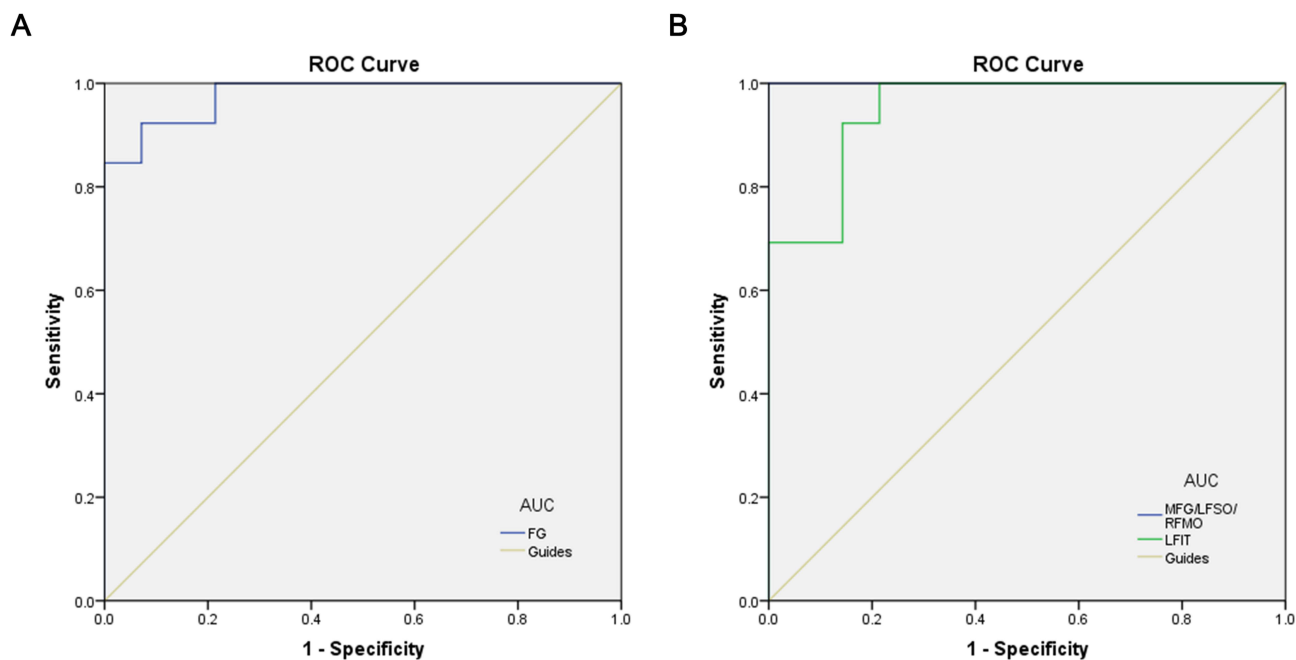


Figure 3 ROC curve analysis of the mean ALFF values for altered brain regions.

Notes: (A) The area under the ROC curve were 0.978, ($p < 0.001$; 95% CI: 0.934–1.000) for FG. (B) The area under the ROC curve were 1 ($p < 0.001$; 95% CI: 1.000–1.000) for MFG/LFSO/RFMO; LFIT 0.951 ($p < 0.001$; 95% CI: 0.876–1.000).

Abbreviations: ALFF, amplitude of low-frequency fluctuation; ROC, receiver operating characteristic; FG, fusiform gyrus; MFG, medial frontal gyrus; LFSO, left frontal superior orbit; RFMO, right frontal medial orbit; LFIT, left frontal inferior triangle.

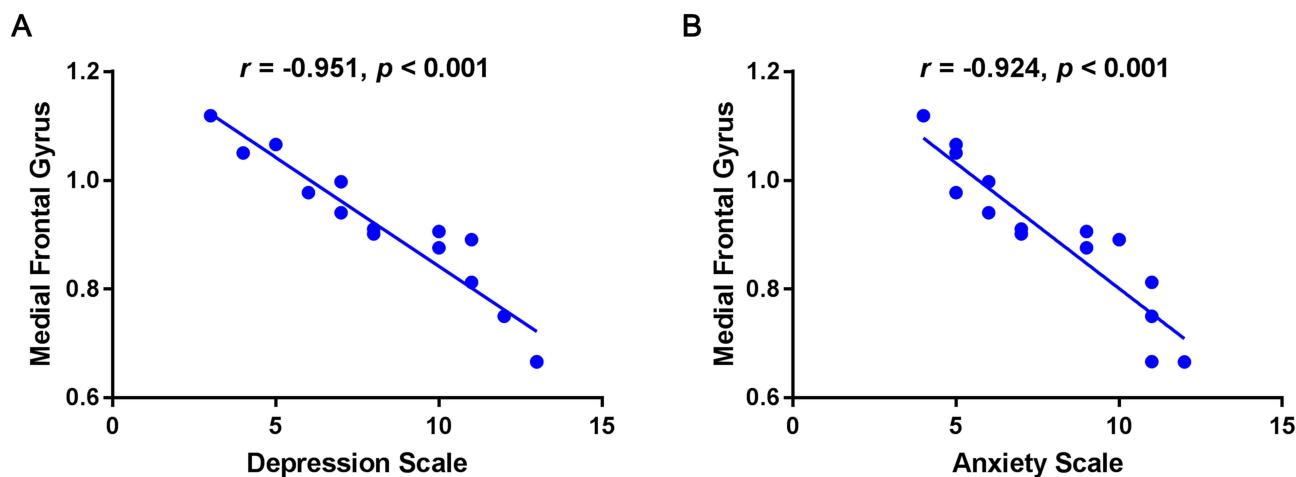


Figure 4 The correlation between the mean ALFF value of medial frontal gyrus and the Hads in DON group.

Notes: (A) The depression scale showed a negative correlation with the ALFF value in the medial frontal gyrus ($r = -0.951$, $P < 0.001$). (B) The anxiety scale showed a negative correlation with the ALFF value in the medial frontal gyrus ($r = -0.924$, $P < 0.001$).

Abbreviations: ALFF, amplitude of low-frequency fluctuation; HADS, Hospital Anxiety and Depression Scale; DON, diabetic optic neuropathy.

recognition of face, object, color and words.³³ Gao et al have proved that ALFF values of the fusiform gyrus significantly increased in retinal vein occlusion patients,³⁴ while Huang et al discovered similar higher fusiform gyrus ALFF values in patients with optic neuritis.¹⁶ In addition, other fMRI researches of ophthalmological patients using other analysis methods also detected functional cerebral activation in the fusiform gyrus.^{35–37} In this study, DON patients showed significantly higher ALFF in the fusiform gyrus, which is consistent with previous results. The frontal inferior triangle is a triangular region of the inferior frontal gyrus and contributes to language comprehension. Lesions in this region may lead to characteristic findings of Broca's aphasia.^{38,39} It has been proven that optic neuritis would show decreased ALFF values in the frontal inferior gyrus,¹⁶ as well as

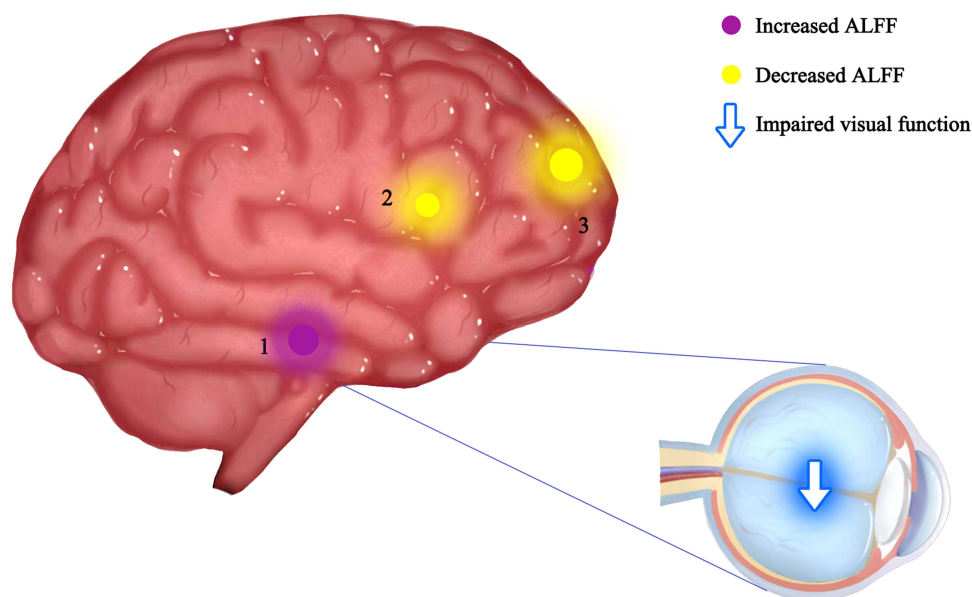


Figure 5 The ALFF results of brain activity in the DON group.

Notes: Compared with the HCs, the ALFF of the following regions were increased to various extents: 1-fusiform gyrus ($t = 4.1311$), and decreased ALFF values in the 2-left frontal inferior triangle ($t = -3.8316$), 3-medial frontal gyrus ($t = -4.8283$). The sizes of the spots denote the degree of quantitative changes.

Abbreviations: ALFF, amplitude of low-frequency fluctuation; DON, diabetic optic neuropathy; HCs, healthy controls.

diabetic patients with vitreous hemorrhage.²² Moreover, lower activation in inferior frontal gyrus were also observed in patients after Lasik surgery⁴⁰ and neuromyelitis optica.⁴¹ Our findings are in accordance with all the above ophthalmology-related diseases. However, our results are partially disparate from several articles on the same topic,^{24,42} mainly because the sample sizes in these three articles were both relatively small, and the technologies used were different, which may cause the difference. The medial frontal gyrus and orbital gyri both belong to the prefrontal cortex, which covers the anterior part of the frontal lobe and participates in various critical cognitive and emotional processing tasks.^{43–46} Previous reports have shown that ALFF values significantly decreased in the medial frontal gyrus in several retinal diseases such as retinal detachment,¹⁹ retinal vein occlusion patients,²³ and optic neuritis.¹⁶ Our results of decreased medial frontal gyrus further confirmed these findings. Besides, we also detected that the ALFF value in the medial frontal gyrus was negatively related to the depression scale and anxiety scale in the DON group. We presumed that visual impairment of DON would impact the normal daily life and then easily lead to emotional alterations such as anxiety and depression. Previous studies have shown that eye symptoms are related to depression and anxiety.^{47,48} Thus, aberrant neural activities might appear in cerebral areas related to emotional processing (Figure 6).

However, our study has some deficiencies. Firstly, the sample size is relatively small, which may lead to low repeatability of the results and excessive effect size. Secondly, the control of blood glucose was inevitably variable among individuals. Thirdly, these findings cannot interpret the specific pathogenesis of DON. Finally, whether the relation between ALFF and DON could be direct or mediated by anxiety and depression has not been fully addressed, we will compare DON patients and depression-matched controls in the future. Despite the above-mentioned limitations, this

Table 3 Brain Regions Alternation and Its Potential Impact

Brain Regions	Experimental Result	Brain Function	Anticipated Results
Fusiform gyrus	DONs>HCs	Higher processing of visual information and perception, face recognition	Mental visual impairment characterized by visual distortion or agnosia and unable to identify faces
Medial frontal gyrus	DONs<HCs	Emotional processing and cognitive control	Mental disorders, including depression and anxiety
Frontal inferior triangle	DONs<HCs	Processing language and speech	Broca's aphasia

Abbreviations: DON, diabetic optic neuropathy; HCs, healthy controls.

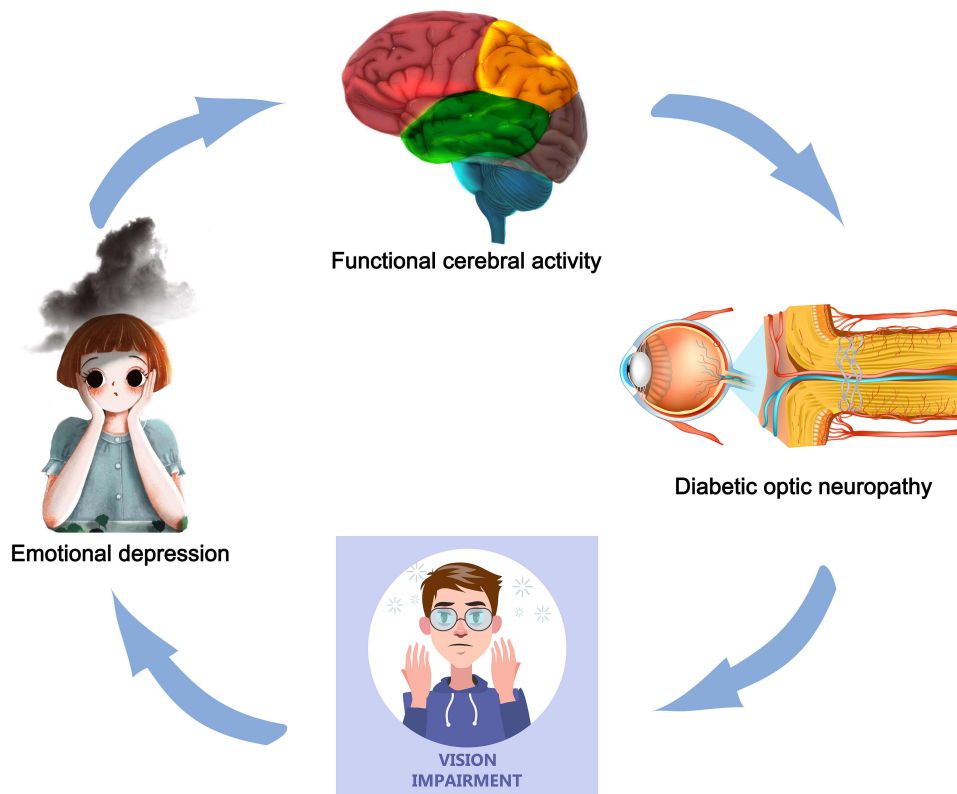


Figure 6 The relationship between ALFF values of the medial frontal gyrus and emotional status.

Notes: Compared with HCs, the ALFF values of the medial frontal gyrus were decreased and DON patients are more likely to have anxiety and depression. (Anxiety and depression are not critical symptoms of DON.).

Abbreviations: ALFF, amplitude of low-frequency fluctuation; DON, diabetic optic neuropathy; HCs, healthy controls.

study showed that DON was relevant to the impairment observed in specific brain regions. Further research about the mechanism of nerve injury following alterations in brain activities should be conducted. We will conduct research including patients from different stages of DON and test the correlation between ALFF value in different brain regions and best-corrected vision in the future.

Conclusion

DON is a neurodegenerative disease involving multiple brain regions. In this study, we discovered abnormal activities of neurons in several specific brain regions, which would help to reveal the underlying neural mechanisms of brain activity related to DON and be valuable to early prediction, prevention and early diagnosis of DON.

Abbreviations

DON, diabetic optic neuropathy; HC, healthy control; N/A, not applicable; VA, visual acuity; VEP, visual evoked potential; DR, diabetic retinopathy; FFA, fundus fluorescein angiography; AUC, area under the curve; ALFF, amplitude of low-frequency fluctuation; BA, Brodmann area; MNI, Montreal Neurological Institute; Frontal_Sup_Orb_L, left frontal superior orbit; Frontal_Med_Orb_R, right frontal medial orbit; Frontal_Inf_Tri_L, left frontal inferior triangle; ROC, receiver operating characteristic; FG, fusiform gyrus; MFG, medial frontal gyrus; LFSO, left frontal superior orbit; RFMO, right frontal medial orbit; LFIT, left frontal inferior triangle; HADS, Hospital Anxiety and Depression Scale.

Ethical Approval and Consent to Participate

The study methods and protocols were approved by the Medical Ethics Committee of the First Affiliated Hospital of Nanchang University (Nanchang, China) and followed the principles of the Declaration of Helsinki. All subjects were

notified of the objectives and content of the study and latent risks, and then provided written informed consent to participate.

Author Contributions

All authors made a significant contribution to the work reported, whether that is in the conception, study design, execution, acquisition of data, analysis and interpretation, or in all these areas; took part in drafting, revising or critically reviewing the article; gave final approval of the version to be published; have agreed on the journal to which the article has been submitted; and agree to be accountable for all aspects of the work.

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Disclosure

The authors have no competing interests to declare regarding this study.

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