• Clinical Research •

Central alterations of brain networks in patients with optic neuritis: a resting state fMRI study

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Abstract

● **AIM:** To assess the alterations in the resting-state function connections between the two cerebral hemispheres in patients with optic neuritis (ON) and healthy controls (HCs).

● **METHODS:** A total of 12 ON patients (six males and six females) and 12 HCs (six males and six females) who were highly matched for sex, age, and educational level were recruited. They underwent functional magnetic resonance imaging (fMRI), testing and brain activities were assessed using the degree centrality (DC) method. Correlation analysis between the mean DC values in specific brain areas and behavior performances was analyzed as well. Linear correlations between A anxiety scale (AS) and depression scale (DS) values and DC values in brain regions of patients with ON were also analyzed.

● **RESULTS:** The areas that showed a higher DC value in ON patients were the right angular gyrus and bilateral precuneus, while the left insula and left superior temporal gyrus (LSTG) were regions that presented a lower DC value in ON patients. A receiver operating characteristic (ROC) curve analysis confirmed the accuracy of the area under the curve (AUC) assessment. Linear analysis showed anxiety scale (AS) and depression scale (DS) values in the left insula were both negatively correlated with DC values, while best corrected visual acuity logMAR-R (BCVA logMAR-R) showed a negative correlation with DC in the LSTG.

● **CONCLUSION:** The study explores altered brain activities of specific regions in patients with ON. The results provide clues for revealing the underlying mechanism of ON development.

● **KEYWORDS:** optic neuritis; functional magnetic resonance imaging; resting state
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INTRODUCTION

Optic neuritis (ON) characteristically presents as acute, unilateral, painful vision loss. ON is a demyelinating disease of the optic nerve that can initiate inflammation and cause dramatic loss of vision in the unilateral eye. The incidence of ON is (0.94-2.18)/100 000 worldwide[1] and the most vulnerable population affected by ON are people who are 20-years-old to 49-years-old. ON is a neural disease that can easily lead to blindness[2]. ON can be the manifestation of a demyelinating disease of the central nerve system at an early stage, or a consequence of infection or systemic autoimmune dysfunction. ON can be present in isolation as well as the

primary symptom of optic neuromyelitis. According to the consensus of Chinese experts on the diagnosis and treatment of ON, the disease is classified into idiopathic ON, which includes idiopathic demyelinating ON or multiple sclerosis related optic neuritis (MS-ON), optic neuromyelitis related ON, and other demyelinating diseases of the central nervous system; infection-related ON; autoimmune ON; and unclassified ON. Among these classifications, the majority have idiopathic or multifocal demyelinating disease, such as multiple sclerosis (MS), optical neuromyelitis (NMO), or acute disseminated encephalomyelitis (ADEM)[3]. For patients with ON, 80% have a dramatic decrease in vision, while 60% progress to blindness unilaterally or bilaterally within 7.7d after the first episode[4]. With high morbidity, young age of onset, and high risk of blindness, ON can affect the normal life of patients to a great extent, which burdens the patient's family and society as well. Different types of ON treated with different methods can result in varied prognoses for vision. Therefore, careful clinical examination and appropriate antibody testing are required to avoid permanent vision loss and associated sequelae[5].

Twenty percent of MS patients present with ON as a main characteristic of the disease, while the majority experience ON during the progression of the disease. Although brain magnetic resonance imaging (MRI) testing is not necessary for diagnosing ON, it is still considered to be an imperative method for assessing the progression of MS and the risk of developing ON in the future. Therefore, diagnosis of ON will become increasingly dependent on MRI scans showing brain alterations, such as enlargement of a T1-weighted gadolinium, an increase in T2 signals, or enlargement of involved optic nerves in ON patients[6]. Resting state functional magnetic resonance imaging (rs-fMRI) can be applied to detect brain activities that occur when subjects do not perform certain specified tasks, and it is currently widely used in the study of brain functional connectivity. Analysis using rs-fMRI is a dependable way to assess activities of local brain areas in resting state, is repeatable, and can minimize the interference caused by behavioral variability as well. With additional advantages, such as accurate positioning and the ability to combine functions with structures[7], rs-fMRI has vital significance for understanding the pathophysiology of diseases. In the diagnostic and pathological studies of the optic nerve, we used to be limited mainly to the study of optic nerve demyelination and rarely studied the functional changes in the brain of optic nerve patients. We studied ON patients using rs-fMRI, which helped us to further understand the neuropathological mechanisms of ON and to treat patients with early intervention in brain function.

Degree centrality (DC) is used to evaluate connections in the brain at the voxel level. The evaluation is based on direct connections between every single node and voxel in cerebral networks and can be used to define regions of interest. In studies on obesity, Parkinson's disease, trigeminal neuralgia, and unilaterally acute open injury, DC measurements have provided significant results[8-9]. However, the method has not been applied in research on ON yet. To further understand the neurophysiological mechanism of ON, our study analyzed alterations of the brain functional connection center in ON patients using DC.

PARTICIPANTS AND METHODS

Ethical Approval 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.

Participants In total, 12 patients with ON (six males and six females) were recruited from the Department of Ophthalmology at the First Affiliated Hospital of Nanchang University in Jiangxi Province, China. The criteria for selecting patients were[10]: 1) patients had acute vision loss; 2) patients had an abnormal visual evoked potentials (VEP) or relative pupillary block; 3) patients had an abnormal visual field that was related to neural fiber injury; 4) patients had no intracranial anatomical abnormalities shown by conventional MRI; 5) patients did not have congenital or acquired diseases such as neurological or psychiatric disorders; 6) patients had not received prior treatment for ON disease; 7) right eyes were available for evaluation; 8) patients were capable of undergoing MRI examination. The exclusion criteria were: 1) the patient had acute vision loss that was caused by other retinal diseases or neurological diseases; 2) the patient had a family background indicating high risk of neurological or psychiatric disorders; 3) complications were present that could affect the prognosis; 4) the presence of MRI contraindications; 5) the patient had a history of addiction, including drugs, smoking, or alcohol consumption.

In addition, we also recruited 12 subjects as healthy controls (HCs) who were highly matched with the ON patients regarding age, gender, and education level. The criteria for selecting optimal subjects were: 1) healthy ocular states with corrected visual acuity (VA) in the naked eye of 1.0; 2) healthy organic status, including the heart, blood pressure, and other cardiac functions; 3) a family background with low risk of neurological or psychiatric disorders; 4) subjects did not have headaches or eye pain; 5) right eyes were available for study; 6) there were no visual pathway or brain parenchymal abnormalities shown by head MRI (Figure 1).

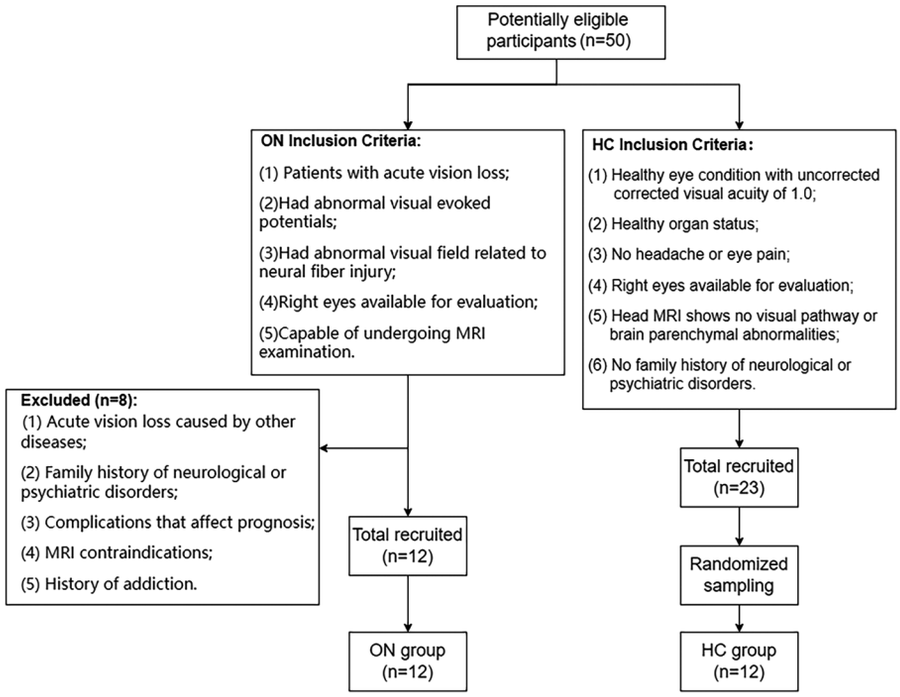

Figure 1 Inclusion procedure ON: Optic neuritis; HC: Healthy control.

Magnetic Resonance Imaging All participants were examined with a 3-Tesla MRI scanner (Trio, Siemens, Germany) with their eyes closed. Whole-brain scanning was performed under the parameters of: repetition time at 2000ms; echo time at 40ms; flip angle=90°; thickness/gap=4.0/0.5 mm; field size 240×240 mm; acquisition matrix=64×64; axial sections=30; and volume=240[11].

Functional Magnetic Resonance Imaging Data Processing All acquired data were analyzed with MRIcro (www.MRIcro.com), SPM8 (http://www.fil.ion.ucl.ac.uk/spm), DPARSFA (http://rfmri.org/DPARSF), and the resting state data analysis toolkit (REST, http://www.restfmri.net) in sequence. The top 10 images were collected, followed by the remaining 230. The volumes that were greater than two in X, Y, or Z directions were excluded. The impacts on the resting Bold signal with the global signal regression were reduced[12].

Degree Centrality Due to the voxel function network, DC was evaluated by calculating the significant super-threshold correlation numbers of the tested subjects. The voxel orientation DC of each participant was converted into a Z-score plot using the equation:

$$Zi=DCi-mean_{all}/std_{all}$$

where Zi is the Z value of the subject that was numbered i; DCi is the DC value of the voxel that was numbered i; $mean_{all}$ is the mean DC value of all detected voxels; and std_{all} is the standard deviation of the detected DC values[13].

Receiver Operating Characteristic Curve We hypothesized that differences in DC values can be considered as another index for diagnosis as well as prediction of treatment outcomes, which could be tested by the receiver operating characteristic (ROC) curve. The area under the curve (AUC) ranged between 0.5−0.7 or 0.7−0.9, respectively, and the accuracy could be considered low or high.

Correlation Analysis Between Brain Function and Clinical Behavior Clinical data such as the course of disease and pain level of ON patients were gathered to assess the associated relationship between mean DC values of abnormal brain regions in the ON group and patient clinical performances. The evaluation was performed by correlation analysis, with $P<0.05$ as the statistical threshold.

Statistical Analysis We applied SPSS (version 20.0) to compare the differences in the clinical data for both ON and HC groups, which were assessed using two independent sample *t*-tests. For DC value analysis, both groups underwent *t*-tests to locate the center of the neural networks in the brain. To reduce the interfering impacts of age and gender, we repeated the *t*-test twice to assess voxel differences between the two groups (double-tail, GRF correction, $P<0.001$ at the voxel level, $P<0.05$ at the clustering level)[14].

Clinical Data Analysis A two-sample *t*-test was performed to compare the behavior data (IBM SPSS for Windows systems, version 20.0) with $P<0.05$ being considered as the statistical threshold.

Correlation Analysis All patients were asked to complete the self-rating depression scale[15] and Hamilton anxiety scale[16], and the Aanxiety scale (AS) and depression scale (DS) values analyzed for correlation with DC values using GraphPad Prism 8, and correlation graphs generated based on the results.

RESULTS

Demographic and Visual Measurements Among the 12 ON

Table 1 Demographics and clinical measurements between ON and HC groups

Characteristics	ON	HCs	*t*	*P*
Male/female	6/6	6/6	NA	NA
Age (y)	44.83±10.65	45.83±11.02	-0.267	0.842
Weight (kg)	56.12±7.63	58.17±5.65	-0.476	0.617
Height (cm)	165.32±9.51	161.22±6.76	-0.476	0.643
BMI (kg/m^2)	20.32±1.54	21.17±1.56	-0.076	0.916
Duration of ON (d)	4.22±3.65	NA	NA	NA
Duration from onset of ON to rs-fMRI scan (d)	5.48±3.54	NA	NA	NA
Best-correted VA, right	0.25±0.25	1.05±0.25	-4.765	0.002
Best-correted VA, left	0.45±0.25	1.05±0.15	-4.637	0.006

ON: Optic neuritis; HC: Healthy control; NA: Not applicable; BMI: Body mass index; VA: Visual acuity; rs-fMRI: Resting state-functional magnetic resonance imaging.

patients (typical fundus photographs; Figure 2) and the 12 HC subjects, one patient was eliminated due to the large cranial swing during the examination, and the maximum head motion parameter was 1.5 mm. In addition, one case was eliminated due to cerebral infarction. The ON and HC groups were well-matched with age, gender, and education level. The statistical correction was an Alphasim correction, with a threshold of 0.001 and a voxel cluster value of 13.

Differences in age (P=0.842) and weight (P=0.617) were insignificant between the ON and HC groups. However, the BCVA-right (P<0.01) and the BCVA-left (P<0.01) were significantly different between the ON and HC groups. In addition, the average duration of ON was 4.22±3.65d and the average duration of ON from the onset time to rs-fMRI scan was 5.48±3.54d (Table 1).

Degree Centrality Differences Voxel morphometry was applied to explore the DC differences between ON patients and HC subjects. Compared to the HC group, the DC values were increased in the right angular gyrus (RAG) and bilateral precuneus (BP) in the ON group, while they were decreased in the left superior temporal gyrus (LSTG) and left insula (LI) in the ON group (Table 2; Figures 3-4). In the comparison between the ON group and the HCs group, significant differences were observed in certain brain regions. For ON >HCs: The RAG showed montreal neurological institute (MNI) coordinates X=39, Y=-60, Z=36, brodmann area (BA) 40, peak voxels 25, T-value 5.326, region of interest (ROI) 4. BP showed MNI coordinates X=-3, Y=-57, Z=21, BA unspecified, peak voxels 29, T-value 4.6888, ROI 3. For ON<HCs: The LSTG showed MNI coordinates X=-66, Y=-21, Z=9, BA 42, peak voxel 25, T-value -5.9006, ROI 1. The LI showed MNI coordinates X=-36, Y=3, Z=9, BA unspecified, peak voxel 23, T-value -6.7714, ROI 2. Average DC values in four specific brain regions for the ON group and HCs group are as follows: Left LSTG: Average DC value for ON group is -0.032525051, and for HC group is 1.263601872. LI: Average DC value for ON group is -0.520136078, and for HC group is 0.537546445. BP: Average DC value for ON group is 1.228188477, and for HC group is 0.226660529. RAG: Average DC value for ON group is 0.980508962, and for HC group is 0.007618709.

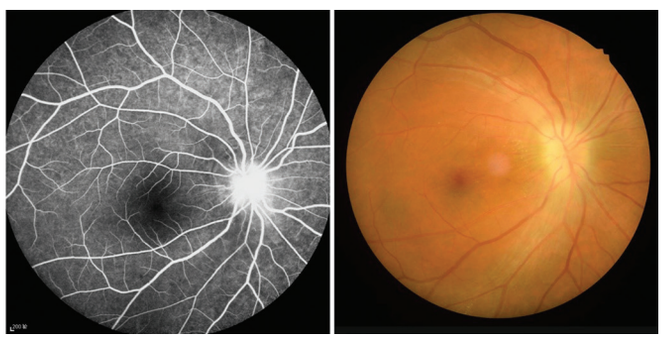

Figure 2 Typical fundus photographs of optic neuritis patients.

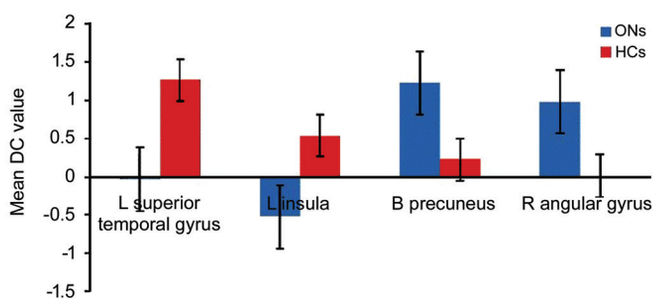

Figure 3 The average DC values of the 4 specific brain regions in ON and HC groups ON: Optic neuritis; HC: Healthy control; DC: Degree centrality; L: Left; R: Right; B: Bilateral.

Receiver Operating Characteristic Curve AUC values of the ROC curve in specific regions of the brain were as follows: the AUC was 0.924 for RAG (P<0.001; 95%CI: 0.820–1.000) and 0.924 for BP (P<0.001; 95%CI: 0.808–1.000); the AUC was 1 for LSTG (P<0.001; 95%CI: 1.000–1.000) and 0.979 for LI (P<0.001; 95%CI: 0.931–1.000; Figure 5).

Correlation Analysis Linear analysis results showed that AS (r=0.8276, P<0.0001) and DS (r=0.6824, P=0.0009) in the LI both indicated negative correlations with DC values (Figure 6). The best-corrected visual acuity (BCVA) logMAR-R (r=0.5250, P=0.0077) was negatively correlated with DC in the LSTG as well (Figure 6).

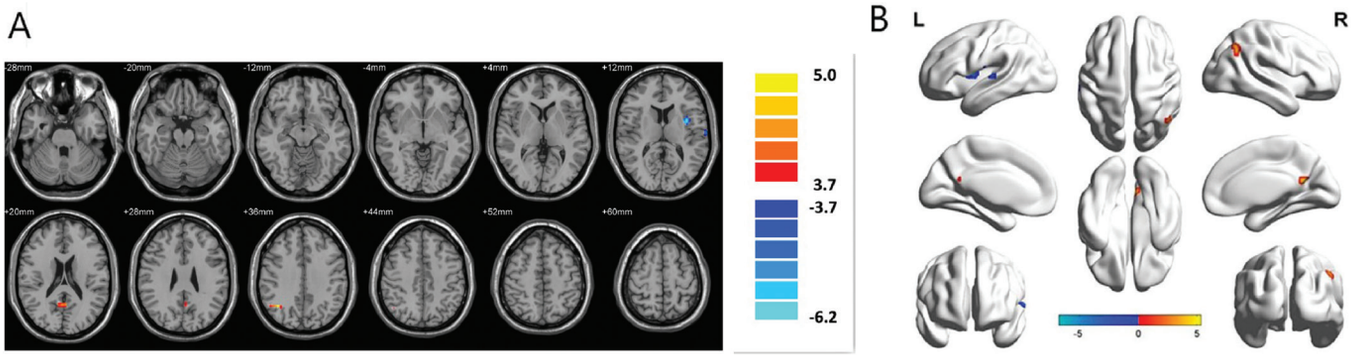

Figure 4 Comparison of voxels between ON and HC groups A: Changes of the mean value of horizontal DC in ON patients. In ON group, the DC values of the RAG and BP were significantly increased compared to HC group, while which of the LSTG and LI were decreased. Yellow areas indicated higher DC values (double tailed, voxel level: *P*<0.001, GRF correction, clustering level: *P*<0.05), and blue areas represented lower DC values. B: Three-dimensional shape of the brain. ON: Optic neuritis; HC: Healthy control; LSTG: Left superior temporal gyrus; LI: Left insula; BP: Bilateral precuneus; RAG: Right angular gyrus; DC: Degree centrality; GRF: Gaussian random field.

Table 2 DC differences of 4 specific brain areas between ON and HC groups during fMRI examination

Group	LSTG	LI	BP	RAG
1	0.388680072	0.340593865	1.562884045	1.198138387
1	-0.774986542	0.502878875	0.549153744	0.042581202
1	0.415390044	0.53911177	1.387468942	1.307934185
1	0.786544798	0.865664643	0.742422882	0.567682854
1	-0.84671765	0.010866616	0.839148528	0.75931375
1	-0.33232679	0.771715046	1.745362699	0.657217101
1	-0.400415737	0.588777302	1.040435925	0.802215558
1	0.909185119	0.903420269	1.602039039	1.411850681
1	0.31548471	0.591159196	1.598999971	1.682024565
1	0.588963825	0.690299435	1.344179197	1.554211435
1	-0.873608347	0.602498071	0.936453184	0.657315388
1	0.214107114	-0.165352152	1.389713569	1.125622444
2	-1.071762394	-0.402526874	0.633993397	-0.073153211
2	-1.768270745	-0.187596454	1.449630992	-0.069647988
2	-1.106527386	-1.036777237	-0.270532919	-0.492947236
2	-1.487033962	-0.406634467	0.349134076	0.067389006
2	-1.245232559	-0.80995383	0.397228405	-0.171234765
2	-0.898268577	-0.630441721	0.036574415	0.679665825
2	-1.347482772	-0.834154463	-0.311481881	-0.146503712
2	-1.355379455	-0.30789653	0.809784368	-0.009131705
2	-1.051839602	-0.831259797	-0.947453304	-0.441737799
2	-1.663858974	0.40582172	0.512945218	0.268771154
2	-1.233663158	-0.916192565	-0.138047342	-0.284951707
2	-0.933902881	-0.492945124	0.198150918	0.764906641

1: ON groups; 2: HC groups; ON: Optic neuritis; HC: Healthy control; LSTG: Left superior temporal gyrus; LI: Left insula; BP: Bilateral precuneus; RAG: Right angular gyrus; DC: Degree centrality; fMRI: Functional magnetic resonance imaging.

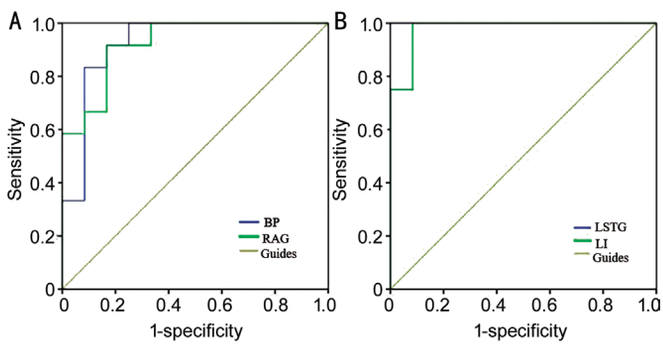

Figure 5 ROC curve analysis of the mean DC values for altered brain regions A: AUC was 0.924 for RAG (*P*<0.001; 95%CI: 0.820-1.000), and 0.924 for BP (*P*<0.001; 95%CI: 0.808-1.000). B: AUC was 1 for LSTG (*P*<0.001; 95%CI: 1.000-1.000), and 0.979 for LI (*P*<0.001; 95%CI: 0.931-1.000). ROC: Receiver operating characteristic; DC: Degree centrality; CI: Confidence interval; AUC: Area under the curve; LSTG: Left superior temporal gyrus; LI: Left insula; BP: Bilateral precuneus; RAG: Right angular gyrus.

DISCUSSION

This study was the first to assess how ON can affect brain activity measurements under the condition of rs-fMRI with DC technology. We aimed to locate functional connections in the brains of ON patients. Based on fMRI, the brain can be divided into several function networks, which cover various brain regions that are anatomically unrelated. Functional connections reflect correlations between brain activities that are closely related. Compared to the HC group, LSTG and LI had decreased DC values in ON patients, while RAG and BP had increased DC values (Figure 7). These brain areas are associated with several cognitive abilities, such as the subjective experience of memory, long-term memory, visual and spatial information, hearing, and language functions, including pronunciation, language repetition, speech recognition, and organization as well as planning language expression and language creation.

The angular gyrus, which has the shape of an arch, surrounds the end of the superior temporal sulcus of the temporal lobe, which is equivalent to Brodmann's area 39. The angular gyrus is the visual language center (reading center), which if injured,

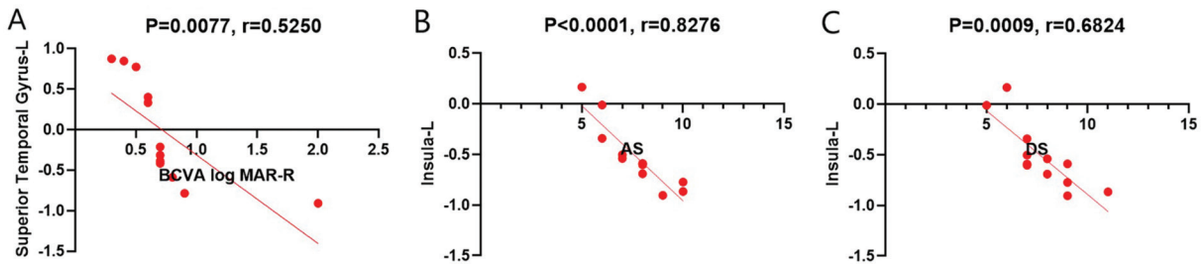

Figure 6 Correlation analysis between AS, DS, BCVA logMAR-R and DC values in specific brain areas A: Negative correlation between BCVA logMAR-R and DC values in superior temporal gyrus-L; B: Negative correlation between AS and DC values in insula-L; C: Negative correlation between DS and DC values in insula-L. AS: Anxiety scale; DS: Depression scale; L: Left; BCVA: Best-corrected visual acuity.

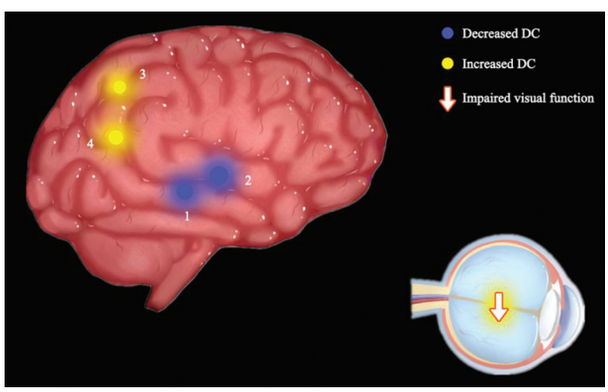

Figure 7 DC results of ON patients' electroencephalogram activity Compared to HCs, DC values of the following regions were significantly changed: 1) LSTG (BA 42, t-5.9006); 2) LI (t-6.7714); 3) BP (t-4.6888); 4) RAG (BA 40, t-5.326). The size of the spot indicated the degree of change in the DC results. ON: Optic neuritis; HC: Healthy control; LSTG: Left superior temporal gyrus; LI: Left insula; BP: Bilateral precuneus; RAG: Right angular gyrus; DC: Degree centrality; BA: Brodmann area.

does not lead to visual impairment, but leads to people who could formerly read losing this ability. The left angular gyrus plays a key role in simulation and memory[17]. A number of studies have pointed out that the gyrus is related to subjective experiences that contribute to memory[18], which also play a vital role in generating subjective experiences of memory[19]. In humans, gyrus dysfunctions do not cause amnesia, but impair some aspects of episodic memory.

The precuneus is part of the superior parietal lobule that is located on the medial side of the cerebral hemisphere. Recent brain functional imaging studies have pointed out that the precuneus was related to various cognitive functions at a high level, including episodic memory, information processing that is self-related, and different aspects of emotions such as panic and depression. In addition, the precuneus gyrus is a vital structure in the formation of complex long-term memories. In the process of gradually establishing a memory, extensive increases in connections between the precuneus and neural networks distributed at the parietal temporal cortex indicated that the precuneus plays a central role in the networks that mediate formation of visual spatial long-term memory, and it may also act as a distributed neocortex network with a core structure supporting the encoding of complex visual spatial information in long-term memory[20]. Recent studies of navigation-based memory information[21], well-integrated spatial information retrieval[22], and the activity of retrieved visuospatial memory traces[23] have consistently indicated that the precuneus plays a crucial role in the memory of complex visuospatial information. Depressive disorders are mainly composed of negative emotional symptoms such as low mood, lack of interest, lack of energy, feelings of worthlessness, and suicidal thoughts. The precuneus was shown to be associated with anxiety[24] and depression[25]. In addition, alterations in the precuneus and other brain regions are associated with the severity of depression[26], where the changes may also be related to disorders in aspects of fear perception[27]. The default mode network (DMN) includes the posterior precuneus, angular gyrus, middle temporal gyrus, superior frontal gyrus, and medial frontal gyrus[28]. An increasing amount of evidence has verified that the DMN can play a vital role in depression and anxiety[29].

Increased DC values observed in the RAG and BP brain regions may indicate impairments such as episodic memory, ability to process information, and problems of consciousness. The 41 and 42 regions of the superior temporal gyrus and the transverse temporal gyrus are highly related to auditory functions, while the anterior temporal lobe is associated with mental activities. The left anterior temporal superior gyrus is mainly involved in various aspects of higher-order auditory processing[30], which also has a role in auditory–verbal semantic processes; that is, verbal information[31], ability to understand speech[32], and processing verbal stimuli[33]. In addition, another study suggested that the left anterior temporal gyrus was also involved in processing the auditory vocabulary and environmental sounds, as well as in ignoring irrelevant changes in auditory objects[34]. Human emotions and mental activities are associated with the orbitofrontal cortex as well as the temporal lobe. The posterior part of the superior temporal gyrus is the center of audition and speech in the dominant

hemisphere, and is known as Wernicke's area. Previous studies pointed out another aspect of superior temporal functions in that disorders of the specific area may lead to eye diseases, and quadrant blindness can even occur with temporal lobe damage. Unusual activation of the lateral temporal region was reported in patients with ON that led to consequences of visual dysfunction[35]. In diabetic retinopathy, it was found that the amplitude low-frequency fluctuation (ALFF) of the superior temporal gyrus was lower than that of the control group, which may affect visual abilities[36]. Due to the above, it can be inferred that abnormal DC values of the superior temporal gyrus may reflect impairment of speech processing and disorders of visual functions in ON patients to some extent.

The brain insula (or insula) is a complex brain region that is not fully understood. Studies have shown that the LI is associated with multiple language functions including phonological planning, language repetition, and speech recognition[37]. Insula activation was confirmed in multiple language tests involving word generation[38], naming[39], and speech discrimination[40]. The insula also has an impact on auditory processing[41]. Based on these studies, the conclusion that the insula is related to language is highly confirmed. Moreover, rather than being involved in a single linguistic process, the insula is involved in multiple linguistic processes simultaneously. The anterior part of the insula is involved in the organization and planning of language expression, as well as language creation; the middle and the back are related to vocabulary knowledge, word retrieval, language understanding, and speech recognition. In addition, the insula may also lead to core symptoms of depressive disorders[42]. Since DC values in the LI of ON patients were significantly lower than DC values in the HC group, we speculated that when ON occurred, the functional activity of brain regions that are closely related to hearing, language information processing, and depressive disorders are reduced.

In conclusion, changes in DC at multiple brain regions in ON patients may indicate a compensation effect of brain function to maintain stability in the internal network, which may have an impact on ON patients' auditory, visual, verbal, and social emotional problems, such as depression and anxiety. The changes and potential impacts of different brain regions are as follows: The experimental result of RAG is ONs>HCs (ON group greater than HCs group); Brain Function: part of the default model network, visual language center, memory; Expected outcome: social and emotional problems, depression, and anxiety. The experimental result of BP is ONs>HCs; Brain Function: part of the default network, Coordination of movement, visual spatial image, and working memory; Expected outcome: Depression and anxiety. The Experimental Result of LSTG is ONs<HCs; Brain Function: associated with auditory and eye diseases; Expected Outcome: Impairment of speech processing and visual functions. The experimental Result of LI is ONs<HCs Brain; Brain Function: auditory and verbal information processing; Expected Outcome: Decrease of auditory and verbal processing ability, depression, and anxiety. The ROC curve provides a standardized and statistically significant analysis method for distinguishing ON patients from HCs. When DC values were <0.2, 0.2−0.4, 0.4−0.6, 0.6−0.8, and >0.8, the accuracy was poor, average, medium, substantial, and nearly perfect, respectively. ROC analysis showed that AUC values of DC in specific brain regions were: RAG (0.924, P<0.001), BP (0.924, P<0.001), LSTG (1, P<0.001), and LI (0.979, P<0.001). As all AUC values were higher than 0.8, ON could be diagnosed by increased DC values of specific brain areas. In conclusion, our results revealed the DC value examination using fMRI for RAG, BP, LSTG, and LI, may be a useful diagnostic index for ON patients.

Our study had some limitations. First, our sample size was relatively small. As our study focused on alterations of functional brain areas in ON patients, we did not look for structural abnormalities in specific brain areas. It was not clear whether structural abnormalities can lead to functional alterations in the same areas, or whether functional changes predispose subjects to ON diseases. Longitudinal studies can be helpful for exploring the pathogenesis of ON.

Taken together, our study identified unusual brain activities in four specific areas, which may also indicate abnormal activity in other sense-related brain regions. Changes in activity recorded in various brain areas can provide valuable information on ON pathology. Unusual DC values in these areas can determine the occurrence of ON, which is helpful for early diagnosis and treatment of ON. In patients with ON, delayed diagnosis often delays the best treatment period, leading to visual dysfunction, anxiety and other uncomfortable symptoms. Visual impairment has also been reported that results in multiple society- and emotion-related problems[43]. Patients with depression were also more likely to overreport visual impairment than those with no depression[44] (Figure 8).

At present, rs-fMRI technology can be applied in the diagnosis of several encephalopathy and visual diseases at an early stage, and fMRI has provided the possibility for ON diagnosis and intervention. More clinical data are needed to show whether screening has the same results in people with poor health and complications. This is a highly multidisciplinary and interdisciplinary task.

There are some limitations to this study. Although the results we obtained are statistically significant, but there is still the defect of small sample size, and the sample size can be increased in the future to further verify our results and conclusions. Finding suitable clinical trials for patients is

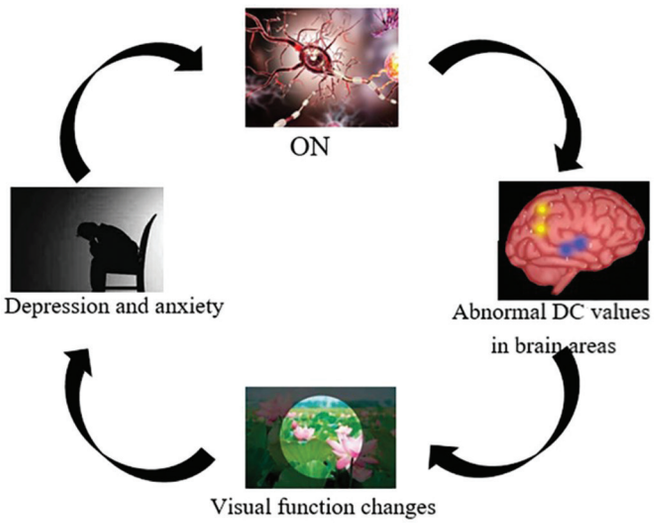

Figure 8 The relationship between optic neuritis and fMRI ON can lead to DC value changes in various brain areas, which can result in visual impairment and symptoms of depression and anxiety. At the same time, visual impairment and emotional disorders can interact with each other. ON: Optic neuritis; DC: Degree centrality; fMRI: Functional magnetic resonance imaging.

crucial for improving treatment methods and enhancing patient care. However, due to the free format of medical documents and the complexity of clinical trial selection criteria, this process is very difficult for doctors, both time-consuming and prone to errors. This leads to a shortage of patients participating in clinical trials and a low proportion of recruited and retained patients. However, recent large-scale language models have shown potential in interpreting electronic health records, helping to accurately match patients and clinical trials on a large scale. In future research, we will use various methods to increase the sample size as much as possible to better confirm our conclusions.

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