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Brain Functional Connectivity Changes in Patients with Acute Eye Pain: A Resting-State Functional Magnetic Resonance Imaging (fMRI) Study

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Data Collection B
Statistical Analysis C
Data Interpretation D
Manuscript Preparation E
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Background: By using functional magnetic resonance imaging (fMRI), we aimed to study the changes in potential brain function network activity in patients with acute eye pain. Also, by using the voxel-wise degree centrality (DC) method, we aimed to explore the relationship between spontaneous brain activity and the clinical features of patients with acute eye pain.

Material/Methods: A total of 15 patients with acute eye pain (5 women and 10 men; EP group) and 15 healthy controls (5 women and 10 men; HC group), were scanned by fMRI. The DC method was used to evaluate changes in spontaneous brain activity. Receiver operating characteristic (ROC) curves were analyzed, and Pearson correlation analysis was used to study the relationship between DC values and clinical manifestations in different regions of brain.

Results: The area of the left limbic lobe showed a reduction in DC value in patients in the EP group. DC values were elevated in the left cerebellum posterior lobe, left inferior parietal lobule, left inferior temporal gyrus, left precuneus, and right cerebellum posterior lobe in the EP group. The visual analog scale value of the eyes in the EP group was negatively correlated with the left limbic lobe signal value and positively correlated with the left inferior parietal lobule signal value. Further, the scores of the hospital anxiety and depression scale and DC value of the left limbic lobe were negatively correlated.

Conclusions: Compared with the HC group, patients with acute eye pain had abnormal patterns of intrinsic brain activity in different brain regions, which may help reveal the potential neural mechanisms involved in eye pain.

Keywords: Eye Pain • Functional Neuroimaging • Magnetic Resonance Imaging

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Background

Eye pain is the most common eye symptom in patients with ocular diseases, and many lesions of the eyeball and its adnexa can cause significant eye pain. Eye pain is not only related to symptoms of the eye, but can also be accompanied by headache [1]. Keratitis or corneal ulcers can cause severe eye pain. Studies have shown that the probability of human infection with infectious keratitis is 0.148% [2]. In addition, studies have shown that patients who experience keratectomy often have corneal pain symptoms [3]. The cornea is a structure with rich innervation in the human body, and its main sensory and nutrient nerves are the trigeminal ocular branches. Currently, the main method of treating keratitis or corneal ulcers is the use of antibiotics; however, there is no effective way to alleviate the eye pain associated with these conditions [4].

The direct cause of corneal pain is damage to the corneal nerves that triggers neural sensory networks, which are associated with cluster headaches [1]. Experimental studies in mice have shown that the pain caused by damaged corneal nerve fibers can activate neurons in the anterior cingulate cortex, rostroventral medulla, and insular cortex [5]. Research has also found that corneal pain can be related to local activation of the primary somatosensory cortex [6]. In addition, studies have confirmed that patients with chronic eye pain may have psychological or mental disorders [7,8], such as anxiety and depression [9].

Resting-state functional magnetic resonance imaging (rs-fMRI) was first developed in the 1990s and is becoming an increasingly important imaging technique because it can perform functional imaging of brain tissue [10]. FMRI has a wide range of applications. Blood oxygen level-dependent imaging (BOLD), diffusion tensor imaging, and magnetic resonance spectrum analysis can be used in fMRI studies. At present, rs-fMRI is widely used in a variety of diseases, such as epilepsy [11], Alzheimer's disease [12], schizophrenia [13], and attention-deficit hyperactivity disorder [14]. However, the rs-fMRI method is a type of acquisition technology and cannot provide data related to the connectivity of the whole brain network. The pathophysiological basis underlying whole brain information processing remains unclear.

Voxel-wise degree centrality (DC) is a voxel-level graph-based network measurement tool. This technique takes each element as a node and then calculates the number of nodes connected to the rest of the nodes, indirectly reflecting the location and importance of the nodes or brain regions in the brain network. DC represents the direct connection sum of a given voxel to the rest of the entire brain voxel without the need for a priori nodes or regions of interest [15]. Therefore, the node with a high DC value can be regarded as the hub of information integration; that is to say, the node with high DC value is a node with substantial direct connection with other nodes. This technique is often used as a network measurement to explore the pathophysiological mechanisms of ocular diseases such as strabismus [16] and glaucoma [17]. The aim of this study was to explore the relationship between spontaneous brain activity and clinical characteristics in patients with acute eye pain and the differences in functional connection between healthy subjects and patients with eye pain.

Material and Methods

Participants

In this study, we recruited 15 patients with acute eye pain (EP group) and 15 healthy controls (HC group) from The First Affiliated Hospital of Nanchang University. There were 10 men and 5 women in both groups. The groups were matched for age, sex, and education level.

The including criteria of all participants were as follows: (1) able to undergo MRI scanning; (2) no other systemic diseases; (3) no mental illness (anxiety, depression, bipolar disorder, or other mental disorders), and (4) no cerebral infarction.

Inclusion criteria for patients in the EP group were as follows: (1) acute condition with corneal ulcer or keratitis and (2) without other types of eye diseases. Exclusion criteria for the EP group were as follows: (1) long-term, chronic eye pain (>3 months); (2) eye pain caused by glaucoma or trauma; (3) with severe, related complications; (4) history of use of painkillers; (5) with pain. Inclusion criteria for the HC group were as follows: (1) no ocular diseases and (2) corrected visual acuity (>1.0).

The study was approved by the medical ethics committee of the First Affiliated Hospital of Nanchang University, and strictly followed the principles of the Declaration of Helsinki.

Parameters for fMRI

Participants in the study were scanned with a Trio 3-Tesla MRI scanner. To obtain the structure image, we used parameters to modulate the gradient echo sequence, as shown in **Table 1**.

fMRI Data Analysis

We used DPARSFA 3.0 and SPM8 to process the data. The procedure for pre-processing included the following steps: (1) the first 10 volumes for each participant was discarded because of the participant's adaptability to the scanning noise and the signal instability; (2) the translation (mm) and rotation (degree) of each participant were estimated to obtain the exercise time after head movement correction; (3) covariate effects of

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Table 1. Information on resting-state functional magnetic resonance imaging parameters.

Data acquisition	Metamorphic gradient echo sequence	3D metamorphic gradient echo pulse sequence
Patient		
Sex		
Male	10	10
Female	5	5
Age, range (years)	51.62±5.20	51.26±5.27
Scan parameters		
Repetition time/ echo time	1900/2.26 ms	2000/30 ms
Thickness/gap	1.0/0.5 mm	4.0/1.2 mm
Acquisition matrix	256×256	64×64
Field of view	250×250 mm	220×220 mm
Flip angle	90°	90°

non-neuronal BOLD fluctuations (including cerebrospinal fluid and white matter signals) were rejected by using a linear regression process; (4) the 3×3×3 mm^3 full-width images were smoothed to 6 mm, and we used the echo plane image template to standardize the fMRI images to satisfy the Montreal Neurological Institute (MNI) space criteria.

Degree Centrality

Each voxel was utilized as a node, and the related voxels were utilized as edges to generate a voxel functional network for each participant. Preprocessed functional images were used for voxel correlation analysis in the condition of DPARSFA's default brain barrier (with a voxel size of 3×3×3 mm^3 and a resolution of 61×73×61 in the MIN-152 standard space). In addition, the Pearson correlation between the time courses of any pair of voxels was calculated, resulting in a 70831×70831 correlation matrix. Based on the individual voxel functional network, we calculated the significant super-threshold correlation number for each participant as a DC value. The relevant calculation equation was $Z_i=DC_i\text{-}mean_{all}/std_{all}$, where Z_i referred to the z-score of the i-th voxel, DC_i referred to the DC value of the i-th voxel, and std_{all} referred to the standard deviation of DC values of all voxels in brain hood [18].

Data Analysis

SPSS version 24.0 was used to perform independent sample *t* tests to show differences in clinical performance between the EP and HC groups. We used the SPM8 toolkit in GLM analysis to investigate the difference in DC values between the EP group and the HC group. Pearson correlation analysis was also used to explore the relationship between mean DC value and clinical manifestations. In addition, we used the hospital anxiety and depression scale (HADS), a self-assessment scale used to analyze the severity of anxiety and depression, and correlation analysis to explore the relationship between DC in different brain regions and anxiety and depression. $P<0.05$ was considered statistically significant and modified by the Gaussian random field theory. Our general statistical approach was as follows:

1. Patient data was collected, including eye pain duration and best corrected visual acuity. Correlation analysis was used to analyze the relationship between the signal value of the brain regions and clinical manifestations.
2. Independent 2-sample *t* tests were then used to analyze clinical performances.
3. The receiver operating characteristic (ROC) curve was used to classify the DC values of different brain regions in patients in the EP group. In addition, we used Pearson correlation analysis to explore the relationship between DC values and the clinical characteristics of patients in the EP group.

Results

Demographics and Visual Measurements

Comparison of clinical data between the EP group and the HC group revealed no significant differences in terms of age ($P=0.796$) or weight ($P=0.845$) (**Table 2**).

DC Values of Different Brain Regions

The DC value of the left limbic lobe in the EP group was significantly lower than that of the HC group. The DC values of the left cerebellum posterior lobe, right cerebellum posterior lobe, left inferior temporal gyrus, left inferior parietal lobule, left precuneus were significantly elevated in the EP group (**Figure 1A, Table 3**). The mean change in DC of patients in the EP group and HC group are shown in **Figure 1B**.

ROC Curve Analysis

The DC values in different regions of the brain were significantly different in the EP and HC groups, showing that DC values could be useful as markers for distinguishing between patients with eye pain and healthy controls. Results of the area under the curve (AUC) analyses were as follows: the left cerebellum posterior lobe (AUC 0.767); right cerebellum posterior lobe (AUC 0.770); left precuneus (AUC 0.749); left inferior temporal gyrus (AUC 0.796) (EP>HC) (**Figure 2A**), and left limbic lobe (AUC 0.749) (EP <HC) (**Figure 2B**).

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Table 2. Demographics and clinical measurements.

Condition	EP	HC	t	P value*
Male/Female	10/5	10/5	N/A	>0.99
Age (years)	51.62±5.20	51.26±5.27	0.260	0.796
Weight (kg)	63.56±7.12	63.18±6.68	0.197	0.845
Handedness	15R	15R	N/A	>0.99
EP duration (years)	27.00±6.21	N/A	N/A	N/A
Visual analog pain scale	4.05±0.94	N/A	N/A	N/A

* There is statistical significance when $P<0.05$. EP – eye pain group; HC – healthy control group; N/A – not applicable; R – right.

Correlation Analysis

The visual analog scale (VAS) value of the eyes in the EP group was negatively correlated with the left limbic lobe signal value (r=-0.789; $P=0.001$) and positively correlated with the left inferior parietal lobule signal value (r=0.561; $P=0.046$). All participants completed the hads. We used SPSS version 24.0 to analyze the correlation between the values of HADS scores and DC. The results showed that the HADS scores and the DC value of left limbic lobe were negatively correlated (r=-0.837; $P=0.001$), as shown in **Figure 3**.

Discussion

Eye pain is an unpleasant sensory and emotional experience that results from physiological pain caused by harmful stimuli to the sensory synapses of the trigeminal ganglion neurons [19]. Neurological and ophthalmic diseases can cause eye pain, including eye and orbital diseases as well as primary and secondary headaches [20]. The cornea has the most abundant nerve tissue and is the most powerful pain generator in the human body. There are many receptors in the nerve endings of the cornea that can sense different stimuli [21]. These stimuli can activate corresponding sensory fibers, causing all types of unpleasant feelings.

The rs-fMRI is a new imaging technique for measuring brain activity by using signals that are dependent upon blood oxygen levels. DC is a voxel-level graph-based network measurement tool that can indirectly reflect the location and importance of nodes or brain regions in the brain network. The DC method has been successfully applied to some ophthalmic diseases and has great developmental prospects.

This study used rs-fMRI to study changes in potential brain function network activity in patients with acute eye pain and used DC technology to explore the relationship between spontaneous brain activity changes and the clinical features of patients with acute eye pain. Our results showed that compared with that of the HC group, the DC value of the left limbic lobe of patients in the acute EP group was significantly lower; while the DC values of the left cerebellum posterior lobe, left inferior parietal lobule, left inferior temporal gyrus, right cerebellum posterior lobe, and left precuneus were significantly higher (**Figure 4**).

Analysis of the Reduction in DC Value in Patients with EP

The limbic lobe refers to the inner side of the cerebral hemisphere and the periorbital structure of the brainstem junction and the corpus callosum, consisting of the subcallosal area, endplate gyrus, cingulate gyrus, hippocampal convolution, hippocampus, and the dentate gyrus [22]. In a previous study, Broca studied the brains of primates and found that the limbic lobe was associated with olfaction; however, more recent studies have found that this lobe carries out many more functions than first thought and represents an important center for regulating visceral activity [23]. Because the limbic lobe is closely related to the insular lobe, temporal pole, orbital gyrus of the cerebral cortex, and the amygdala under the cortex in terms of structure and function, some authors have referred to these structures as the limbic system [24]. The limbic system is related to memory and emotional output. Its main functions are that the hippocampus, as part of the Papez circuit, participates in memory [25] and the amygdala plays roles in emotional response, memory, and drive. The main clinical manifestations of lesions in the limbic system are epilepsy, confusion, and cognitive impairment [26]. In our present study, we found that the DC value of the left limbic lobe (LLL) of patients in the EP group was significantly lower than that of the HC group (see spot no. 6 in **Figure 4**). We suggest that EP may cause dysfunction of the LLL, which may explain the emotional irritability, instability, and headache of patients with eye pain. In addition, according to the correlation analysis shown in **Figure 3C**, we can hypothesize that LLL is related to anxiety and depression.

We also found that the VAS value of the eyes of the EP group showed a negative correlation with the signal value of the LLL

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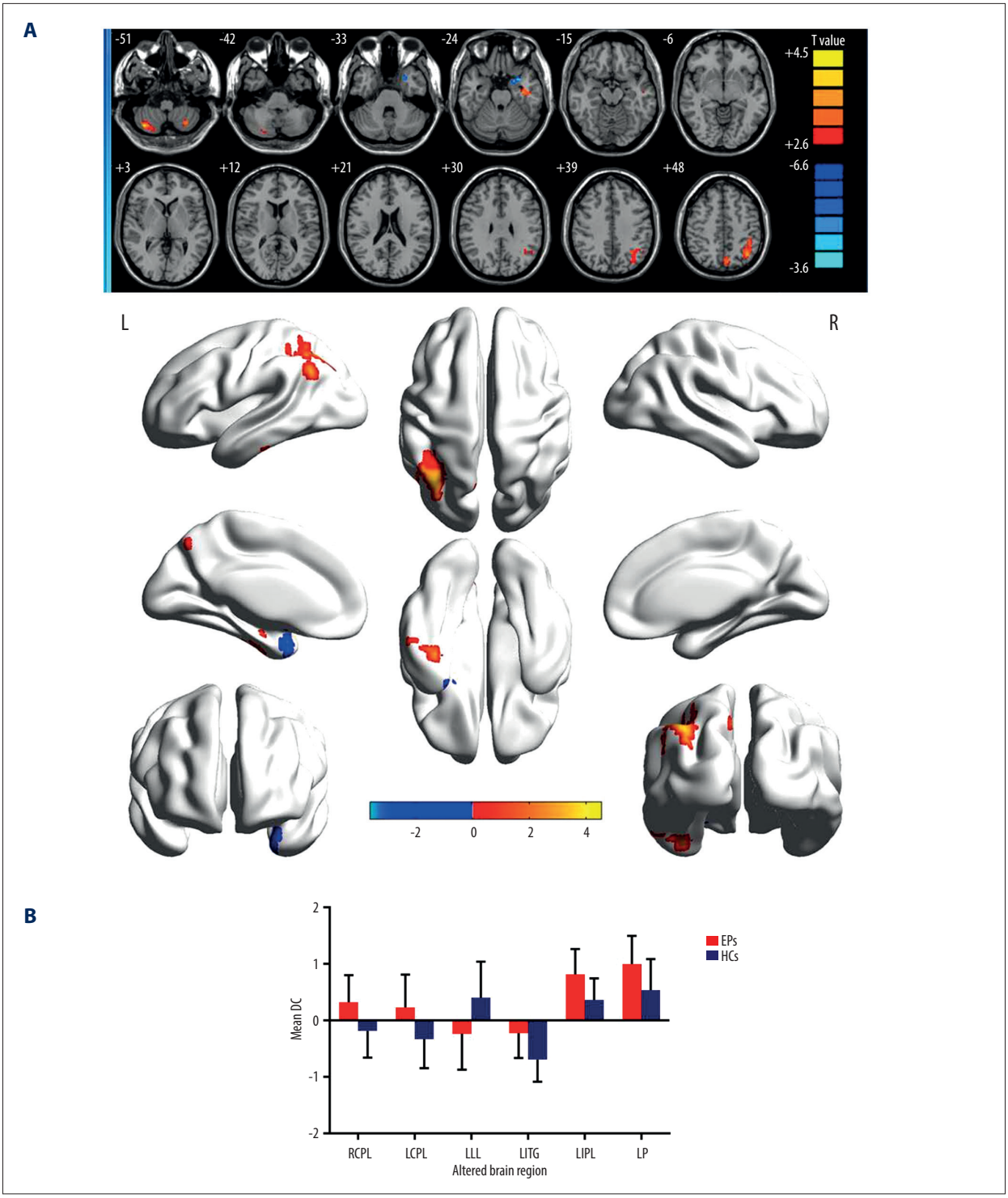

Figure 1. (**A**) Voxel comparison of degree centrality (DC) in the eye pain (EP) and healthy control (HC) groups: significant differences in DC were observed in the left limbic lobe, right cerebellum posterior lobe, left cerebellum posterior lobe, left inferior temporal gyrus, left inferior parietal lobule, and left precuneus. The red area indicates a higher DC value and the blue color indicates a lower DC value. Multiple comparisons were performed using Gaussian random field theory (z>2.3, column by column correction, *P*<0.05), *P*<0.05. (**B**) Average DC values between EP and HC groups. DC – degree centrality; EP – eye pain; HC – healthy control; L – left; R – right; RCPL – right cerebellum posterior lobe; LCPL – left cerebellum posterior lobe; LLL – left limbic lobe; LITG – left inferior temporal gyrus; LIPL – left inferior parietal lobe; LP – left precuneus.

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Table 3. Significant differences in degree centrality between different brain regions of eye pain and healthy control groups.

Brain areas	MNI coordinates			EP and HC			ROI
	X	Y	Z	BA	Peak voxels	T value	
EP>HC							
Right cerebellum posterior lobe	30	-69	-54		94	4.4116	1
Left cerebellum posterior lobe	-33	-66	-54		48	4.5262	2
Left inferior temporal gyrus	-36	-15	-24	20	45	3.7357	4
Left inferior parietal lobule	-36	-63	45	40	158	3.8899	5
Left precuneus	-6	-75	48	7	40	3.6715	6
EP<HC							
Left limbic lobe	-24	9	-30	29	41	-3.5969	3

The statistical threshold was set at the voxel level, and multiple comparisons were made using the Gaussian random field (GRF) theory (z>2.3, *P*<0. 05), *P*<0.05. DC – degree centrality; BA – Brodmann area; HC – healthy control; EP – eye pain; MNI – Montreal Neurological Institute; ROI – region of interest.

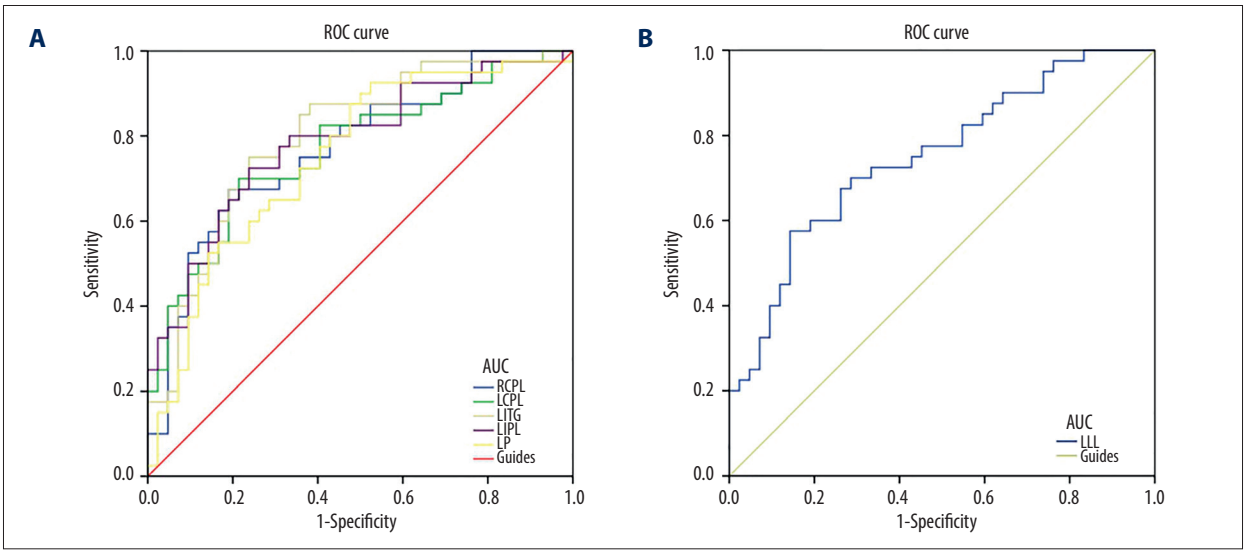

Figure 2. Receiver operating characteristic curve analysis of the mean DC values for altered brain regions. (**A**) The area under the receiver operating characteristic (ROC) curve were 0.770 for right cerebellum posterior lobe (RCPL) (*P*<0.001; 95% confidence interval [CI]: 0.668-0.873); left cerebellum posterior lobe (LCPL) 0.767 (*P*<0.001; 95%CI: 0.663-0.870); left inferior temporal gyrus (LITG) 0.796 (*P*<0.001; 95%CI: 0.699-0.893); left inferior parietal lobe (LIPL) 0.783 (*P*<0.001; 95%CI: 0.683-0.883); and left precuneus (LP) 0.749 (*p*<0.001; 95%CI: 0.642-0.855). (**B**) The area under the ROC curve (AUC) was 0.749 (*P*<0.001; 95%CI: 0.644-0.854) for the left limbic lobe (LLL).

(r=-0.789; *P*=0.001) and that the VAS value reflected the degree of pain in patients with eye pain. We further speculated that the reduced signal value of the LLL may reflect that the eyes of the patients in the EP group were damaged.

Analysis of the Increased DC in Patients with Eye Pain

The posterior part of the cerebellum can receive signals from the cerebral cortex to participate in motor coordination [27], manifesting in the formation and proficiency of delicate movements. Injury to the posterior cerebellum causes a reduction in muscle tension and coordination of voluntary movements [28], which manifests mainly in the accuracy and coordination of movement. Studies have shown that the cerebellum is responsible for performing accurate eye movements [29] and dealing with visual movements. Purkinje cells transmit the only output of the cerebellar cortex to the deep cerebellar nucleus [30], which can cause ataxia when the Purkinje cells are injured. We found that the DC in the cerebellar posterior lobe was increased in patients in the EP group (see spots no. 4 and 5 in **Figure 4**).

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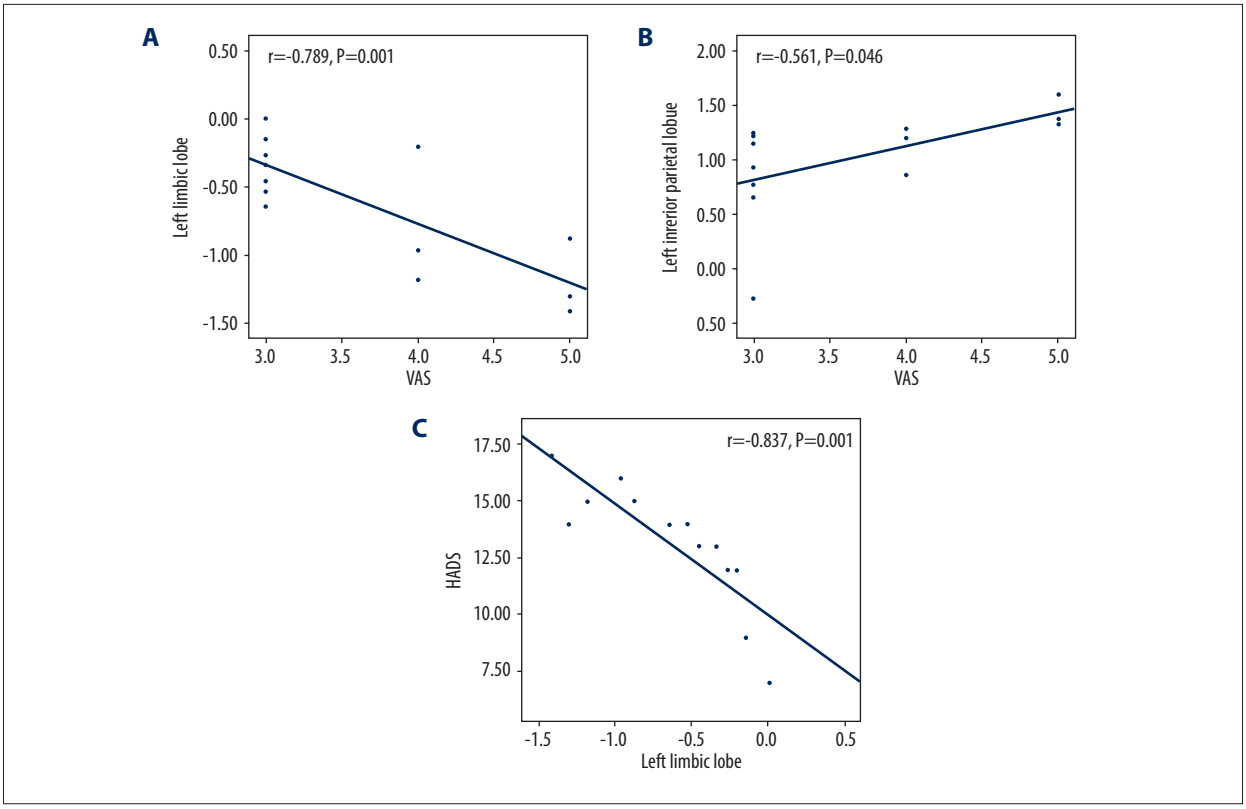

Figure 3. The correlation of visual analog scale, hospital anxiety and depression scale, and signal value in different brain regions. (**A**) The visual analog scale (VAS) value of the eyes of the eye pain (EP) group showed a negative correlation with the signal value of the left limbic lobe (r=-0.789, *P*=0.001). (**B**) The VAS value of the eyes of the EP group showed a positive correlation with the signal value of the left inferior parietal lobule (r=0.561, *P*=0.046). (**C**) The HADS value of the eyes of the EP group showed a negative correlation with the signal value of the left limbic lobe (r=-0.837; *P*=0.001).

This suggests that there may be dysfunction of the posterior cerebellar lobe in patients with eye pain. We suggest that the enhancement of cerebellar functional connections may be related to eye pain-related sensory inputs. Recurrent headache, dizziness, and nausea may therefore be related to an abnormal posterior cerebellar lobe.

The inferior temporal gyrus is located below the temporal transverse gyrus. This area participates in visual processing and may also be related to facial perception and data identification. The occipitotemporal gyrus is related to the recognition of visual objects [31]. The inferior temporal cortex includes the middle and inferior temporal gyrus and can process visual stimuli and participate in memory and recognition of objects [32]. That is to say, this region recognizes the color and shape of an object and stores the information and memory related to the object, so as to be able to identify the object. Prosopagnosia is a disease in which patients cannot recognize and distinguish faces. A previous study reported the case of a patient who was able to identify objects normally but could not recognize faces; this patient was subsequently found to have a lesion on the right fusiform gyrus [33]. In other words, part of the inferior temporal gyrus had lesions, a main causes of the symptoms of such patients [34]. We think the reason eye pain can increase the activity of the left inferior temporal gyrus may the compensatory mechanism of brain visual abnormality in patients with eye pain (spot no. 3 in **Figure 4**).

The inferior parietal lobe (IPL) is located below the interparietal fissure of the parietal lobe and includes the angular gyrus and supramarginal gyrus. The IPL is involved in the interpretation of sensory information and the perception of facial stimuli [35]. It is also related to semantic processing [36] and mathematical operations [37]. Gerstmann syndrome can be caused by IPL lesions, particularly in the dominant hemisphere; the symptoms of this condition are left and right confusion, finger agnosia, dyslexia, dyscalculia, and contralateral hemianopia [38]. It has been reported that most patients with schizophrenia exhibit an abnormal structure of the IPL [39], such as reduced gray matter volume and thinned cortex [40], and that these patients have most of the above symptoms. In addition, apraxia can be caused by lesions of the supramarginal gyrus and angular gyrus [41], which manifests in the absence of paralysis and deep sensory disturbances, whereby the

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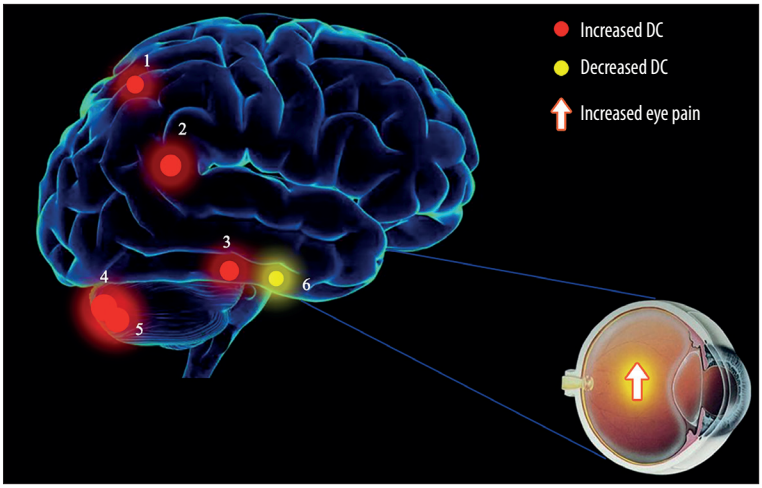

Figure 4. The degree centrality results of brain activity in the eye pain (EP) group. Compared with the healthy control (HC) group, the DC of patients in the EP group in the following regions were elevated: **1**, left precuneus (t=3.6715); **2**, left inferior parietal lobule (t=3.8899); **3**, left inferior temporal gyrus (t=3.7357); **4**, left cerebellum posterior lobe (t=4.5262); and **5**, right cerebellum posterior lobe (t=4.4116). Region **6**, the left limbic lobe (t=-3.5969), was decreased. The sizes of the spots denote the degree of quantitative changes.

Table 4. Brain regions alternations and potential impact.

Brain regions	Experimental result	Brain function	Anticipated results
Left limbic lobe	EP<HC	Regulate visceral activity	Emotional irritability, instability, and headache
Left/Right cerebellum posterior lobe	EP>HC	Participate in the coordination of sports, the formation and proficiency of delicate movements	Recurrent headache, vertigo, and nausea
Left inferior temporal gyrus	EP>HC	Participate in visual processing, related to memory	Blurred vision
Left inferior parietal lobule	EP>HC	Participate in the perception of facial stimuli, interpret sensory information, and also relate to semantic processing and mathematical operations	Blurred vision, dizziness, and grumpy temper
Left precuneus	EP>HC	Participate in visual spatial integration, scene memory recovery and self-awareness	Vertigo, nausea, impatience, and obsessive-compulsive disorder

EP – eye pain group; HC – healthy control group.

limbs have an operational barrier [42]. In addition, the left inferior parietal lobe (LIPL) contributes to the recognition of visual words [43]. In our present study, we found that the DC value of the LIPL in patients in the EP group was significantly elevated, suggesting that eye pain may cause LIPL dysfunction (spot no. 2 in **Figure 4**).

We also observed that the VAS value of the eyes in the EP group showed a positive correlation with the signal value of the left inferior parietal lobule (r=0.561; *P*=0.046). We suspect that when the degree of pain was higher, the signal value of the brain region was also, but this hypothesis needs to be tested further in future studies. We also speculate that an increased signal value of the LIPL may reflect damage to the eyes of patients.

The precuneus is in the medial part of the parietal lobe. This is an important area for visual spatial integration, episodic memory recovery, and self-awareness [44]. The impact of alterations of different brain regions is shown in **Table 4**. Neuroimaging studies have shown that the structure and function of the precuneus are abnormal in patients with obsessive-compulsive disorder [45], while other studies have reported a positive correlation between the gray matter of the left precuneus and harmful symptoms [46]. Studies have also shown that auditory verbal hallucinations in patients with schizophrenia can be associated with changes in the structure and function of the left precuneus [47]. Other studies have shown that the posterior cingulate and precuneus are the initial locations for the development of Alzheimer's disease [48]. In addition, the precuneus is the judgment center of verbal politeness [49] and can assess inconsistencies between tactile and visual texture information

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Table 5. DC method applied in ophthalmological diseases.

Author	Year	Disease	Increased DC	Decreased DC
Wang et al [51]	2017	Acute unilateral open globe injury	Bilateral primary visual cortex and left PCUN	Right insula, left insula, RIPL/SMG, IPL/SMG, right supplementary motor area and right postcentral gyrus
Tan et al [52]	2017	Adult comitant exotropia strabismus	Right superior temporal gyrus, bilateral anterior cingulate, right superior temporal gyrus, and left inferior parietal lobule	Right cerebellum posterior lobe, right inferior frontal gyrus, right middle frontal gyrus and right superior parietal lobule/primary somatosensory cortex
Hu et al [53]	2018	High myopia	Right cerebellum posterior lobe, left precentral gyrus/postcentral gyrus, and right middle cingulate gyrus	Right inferior frontal gyrus/insula, right middle frontal gyrus, and right supramarginal/inferior parietal lobule
Zhu et al [54]	2019	Trigeminal neuralgia	Right lingual gyrus, right postcentral gyrus, left paracentral lobule, and bilateral inferior cerebellum	/
Wang et al [55]	2019	Diabetic nephropathy and retinopathy	BP	RITG, LSG
Liu et al [56]	2020	Exophthalmos of primary hyperthyroidism	/	Cerebellum posterior lobe
Zhang et al [57]	2020	Ophthalmectomy	Left cerebellum posterior lobe, left middle frontal gyrus1, right supramarginal gyrus, left middle frontal gyrus, right middle frontal gyrus	Left lingual gyrus, bilateral lingual lobe, left cingulate gyrus

DC – degree centrality; PCUN – precuneus; RIPL – right inferior parietal lobule; SMG – supramarginal gyrus; IPL – inferior parietal lobule; BP – bilateral precuneus; RITG – right inferior temporal gyrus; LSG – left subcallosal gyrus regions.

[50]. A summary of previous studies is presented in **Table 5**. In the present study, we found a significant elevation in DC value of the left precuneus of patients in the EP group, suggesting that eye pain may lead to over activation of left precuneus activity (spot no. 1 in **Figure 4**). Therefore, we speculate that patients with eye pain will have hyperfunction of visual spatial integration, and dizziness, vomiting, and obsessive-compulsive personality, among other symptoms. Our team has made significant progress in this area in previous research [51-57].

Limitations

It should be noted that there are still many limitations in this study. The sample size of this study is small, and there may be deviation; therefore, we need to use a larger sample size to explore these concepts in future studies. Also, because the subjects were all from the same hospital, there may be collection bias.

Conclusions

In conclusion, this study showed that patients with eye pain had abnormal spontaneous activity in many brain regions compared with healthy control participants, which provided insight into the neurological variation in patients with eye pain and facilitated the interpretation of the potential mechanisms underlying eye pain. Patients with eye pain should not only pay attention to physical therapy; psychological therapy should also be involved as early as possible. We hope that our results can be beneficial to the treatment of patients with eye pain.

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Statement

This was not an industry supported study.

Conflicts of Interest

None.

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