· **Clinical Research** ·

Altered spontaneous brain activity pattern in patients with ophthalmectomy: an resting-state fMRI study

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Abstract

● **AIM:** To use the voxel-wise degree centrality (DC) method to explore the underlying functional network brain-activity in patients with ophthalmectomy.

● **METHODS:** A total of 32 ophthalmic surgery patients (10 women and 22 men), and 32 healthy subjects (10 women and 22 men) highly matched in gender, age, and the same operation method. Everyone experienced a resting-state functional magnetic resonance imaging scan. The spontaneous brain activity could be assessed by DC. Correlation analysis was used to explore the relationships between the average DC signal values and behavior performance in different regions. Receiver operating characteristic (ROC) curve analysis was utilized to differentiate between ophthalmectomy patients and healthy controls (HCs).

● **RESULTS:** Compared with HCs, ophthalmectomy patients had greatly reduced DC values in left lingual gyrus, bilateral lingual lobe, left cingulate gyrus, and increased DC values of left cerebellum posterior lobe, left middle frontal gyrus1, right supramarginal gyrus, left middle frontal gyrus2, right middle frontal gyrus. However, we did not find that there was a correlation between the average DC values from various brain regions and clinical manifestations.

● **CONCLUSION:** Dysfunction may be caused by ophthalmectomy in lots of cerebral areas, which may show the potential pathological mechanism of ophthalmectomy and it is beneficial to clinical diagnosis.

● **KEYWORDS:** degree centrality; ophthalmectomy; resting state; spontaneous brain activity

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INTRODUCTION

When the function of the eye is completely lost or cannot be saved, in order to relieve eye pain and reduce the threat to life, we can perform ophthalmectomy. Although ophthalmectomy relieves the patient's condition, it is a destructive disfigurement procedure that causes facial deformities and physical and mental health problems. Patients are often prone to be different degrees of depression, anxiety, insomnia and negative emotions. Studies have shown that patients with self-reported depression scale (SDS) and self-assessment anxiety scale (SAS) scores after ophthalmectomy were significantly higher than healthy controls (HCs). Therefore, it is especially important to perform the necessary psychological counseling for patients undergoing ophthalmectomy.

There are many causes of ophthalmectomy in patients, such as eyeball atrophy, eye trauma, endophthalmitis, absolute glaucoma, and choroidal melanoma. Among them, ocular trauma is the main cause of monocular blindness, which can lead to serious damage to the structure and function of the eyeball, resulting in loss of vision or ophthalmectomy[1]. Children and adolescents are the main victims of ocular trauma[2-3]. Studies have shown that about 1.6 million people worldwide suffer from blindness in both eyes due to ocular trauma, 2.3 million have low vision due to ocular trauma and 19 million blind or visual impairments[4]. Patients with ocular trauma often show strong psychological anxiety before surgery, and there are different degrees of depression and anxiety after surgery[5]. Therefore, how to prevent ocular trauma is not only a personal problem but also a major social problem.

Resting-state functional magnetic resonance imaging (rs-fMRI) is a kind of functional brain imaging technology, which has been the focus of neuroimaging research in recent years. In the resting state, brain neurons have spontaneous activity and transmit to other neurons, making the brain form complex dynamic functional structure on the network level[6]. At present, we use rs-fMRI regularly in optic neuritis, primary angle-closure glaucoma, Parkinson's disease, epilepsy, and brain injury[7-11], its application prospect is not limited. The human cerebrum is a complex network system in dynamic balance, the analysis of human brain complex network based on graph theory has become a hot spot in current research[12-13]. The degree centrality (DC) is the simplest method to describe the role and status of nodes in brain networks without defining the involved regions [region of interests (ROIs)][14]. It can evaluate the network structure of human cerebrum connectivity at the voxel level. Therefore, we has successfully used DC method to study the neuropathological mechanism of various diseases[15-19]. In this study, we used DC method to investigate the relationship between changes in brain function network structure and clinical features of patients with ophthalmectomy.

SUBJECTS AND METHODS

Ethical Approval All procedures performed in studies involving human participants were in accordance with the ethical standards of the First Affiliated Hospital of Nanchang University Ethical Committee and with the 1964 Helsinki Declaration and its later amendments or comparable ethical standards. Informed consent was obtained from all individual participants included in the study.

A total of 32 ophthalmectomy patients (10 women and 22 men) were collected from the Department of Ophthalmology of the First Affiliated Hospital of Nanchang University. The diagnostic criteria of ophthalmectomy were: 1) history of eye disease, monocular vision loss to light or no light perception not rule out congenital eye; 2) comply with the indications of eyeball enucleation patients; 3) eliminate other anophthalmos.

Totally 32 HCs (10 women and 22 men) highly matched in gender, age, and the same operation methods were also collected. All HCs met the following criteria: 1) normal brain parenchyma with head magnetic resonance imaging (MRI); 2) no eye disease, naked eye or the corrected visual acuity (VA) >1.0; 3) normal mental nervous system; 4) without MRI signal (such as cardiac pacemaker, the body is equipped with metal device, *etc.*).

Magnetic Resonance Imaging Parameters The 3-Tesla MR scanner (Trio, Siemens, Munich, Germany) was for MRI scanning. Use the following parameters to obtain the whole-brain T1-weights with a varying gradient-recalled echo sequence: (thickness=1.0 mm, gap=0.5 mm, flip angle=9°, repetition time=1900ms, echo time=2.26ms, acquisition matrix=256×256, field of view=250×250 mm^2). Functional images were collected with these parameters (repetition time=2000ms, echo time=30ms, thickness=4.0 mm, gap=1.2 mm, acquisition matrix =64×64, flip angle =90°, field of view=220×220 mm^2, 29 axial).

Functional Magnetic Resonance Imaging Data Processing Pre-filter all the data with MRIcro (www.MRIcro.com) and preprocess them by DPARSFA (http://rfmri.org/DPARSF), SPM8 (http://www.fil.ion.ucl.ac.uk/spm) and the Resting-state Data Analysis Toolkit (http://www.restfmri.net). There were 230 volumes to be collected after deleting the first 10 points in time. Volumes excluded from this study because of the x, y, or z directions >2. The previous study[16] prescribed more details.

Degree Centrality Based on the individual voxel functional network, DC was calculated by counting the number of significant over-threshold correlations (or the degree of the binarized adjacency matrix) between the subjects. Use the following equation[16] to convert the voxel-wise DC map of each individual to a z-score map: Z_i=DC_i $mean_{all}$/std_{all}, where Z_i is the z score of its voxel and DC_i is its DC value of the its voxel, $mean_{all}$ is the average DC value of all voxels in brain hood, and std_{all} is the standard deviation of DC values of all voxels in brain hood.

Brain-behavior Correlation Analysis Cerebrum areas with diverse DC values from two groups were categorized as ROI. The linear correlation analysis was used in ophthalmectomy group to search the interrelationship between the DC values of each ROI and clinical manifestations. P<0.05 was deemed to have statistical significance.

Statistical Analysis We used SPSS20.0 software (SPSS, Chicago, IL, USA) with independent sample t test to compare the population and clinical variables from ophthalmectomy and HC groups, and P<0.05 was deemed to have statistical significance. The voxel-wise DC in each group was performed with one sample t-test. Furthermore, independent two-sample t-test was performed using gender and age as nasty covariates in the default gray scale matter to assess intergroup differences in voxel-style DCs using REST V1.8. For multiple comparisons using Gaussian Random Field (GRF) theory, P<0.05, z>2.3, and a corrected cluster P<0.05 was deemed to have statistical significance.

To classify the average DC values in distinct cerebrum areas of ophthalmectomy subjects from HCs, the receiver operating characteristic (ROC) curve method was used. Pearson correlation analysis was used to study correlations between the DC values of diverse cerebrum regions and clinical characteristics of patients undergoing ophthalmic surgery.

Table 1 Demographics and clinical measurements of ophthalmectomy patients and the HCs

Conditions	Ophthalmectomy	HCs	t^a	P^b
Male/female	22/10	22/10	N/A	N/A
Right eye/left eye	16/16	16/16	N/A	>0.99
Age (y)	54.63±11.72	55.69±11.21	0.134	0.739
Weight (kg)	53.43±8.16	54.45±6.24	0.107	0.853
Handedness	32R	32R	N/A	>0.99
Duration of ophthalmectomy (h)	46.39±8.60	N/A	N/A	N/A
HADS-A	5.43±1.52	N/A	N/A	N/A
HADS-D	9.13±1.94	N/A	N/A	N/A

HCs: Healthy controls; N/A: Not applicable; HADS-A: Hospital anxiety and depression scale-anxiety; HADS-D: Hospital anxiety and depression scale-depression. [a]Independent *t*-test; [b]Value between ophthalmectomy and HCs.

Table 2 Brain areas with significantly different DC between patients with ophthalmectomy and HCs

Brain region	BA	MNI coordinates			Voxels	*t*
		X	Y	Z		
Ophthalmectomy >HC						
Left cerebellum posterior lobe	/	-27	-75	-45	42	3.4195
Left middle frontal gyrus1	10	-36	54	-12	40	4.5334
Right supramarginal gryus	40	63	-54	18	55	4.6031
Left middle frontal gyrus2	10	-48	30	39	59	4.9024
Right middle frontal gyrus	10	30	15	60	64	4.1662
Ophthalmectomy <HC						
Left lingual gryus	18	-15	-87	-6	62	-4.306
Bilateral limbic lobe	32	6	36	21	186	-5.0474
Left cingulate gyrus	24	-9	0	33	81	-5.0657

DC: Degree centrality; HCs: Health controls; BA: Brodmann area; MNI: Montreal Neurological Institute; L: Left; R: Right. The statistical threshold was set at voxel with $P<0.05$ for multiple comparisons using GRF theory (z>2.3, cluster-wise $P<0.05$ corrected).

RESULTS

Demographics and Visual Measurements The age of ophthalmectomy patients and HCs was 54.63±11.72y and 55.69±11.21, respectively. Meantime, the average hospital anxiety and depression scale-anxiety (HADS-A) and hospital anxiety and depression scale-depression (HADS-D) of ophthalmectomy patients was 5.43±1.52 and 9.13±1.94. The average duration of ophthalmectomy was 46.39±8.60h. The weight ($P=0.853$), age ($P=0.739$) from ophthalmectomy patients and the HCs were highly matched. More information is in Table 1.

Degree Centrality Differences Compared with HCs, patients with ophthalmectomy had significantly reduced DC values in the left lingual gyrus, bilateral lingual lobe, left cingulate gyrus and increased DC values in the left cerebellum posterior lobe, left middle frontal gyrus1, right supramarginal gyrus, left middle frontal gyrus2, right middle frontal gyrus (Figure 1 and Table 2). Ophthalmectomy patients and HCs groups' average DC values are in Figure 2. In the ophthalmectomy group, the average DC values in the cerebrum area has no great relation with behavioral performance ($P>0.05$).

Receiver Operating Characteristic Curve We hypothesized that the differences of DC between the ophthalmectomy and HCs groups could be useful diagnostic markers. The ROC curves were used to analyze the average value of DC of the various cerebrum areas. The areas under the ROC curves (AUCs) for DC values of different brain region were as follows: left cerebellum posterior lobe (0.773), left middle frontal gyrus1 (0.867), right supramarginal gyrus (0.842), left middle frontal gyrus2 (0.873), right middle frontal gyrus (0.864) (ophthalmectomy >HCs; Figure 3A); left lingual gyrus (0.870), bilateral lingual lobe (0.848), left cingulate gyrus (0.900) (ophthalmectomy <HCs; Figure 3B).

DISCUSSION

As far as we know, the analysis is the first investigation to explore functional network brain-activity changes in ophthalmectomy patients by using the DC method. Compared with the HC group, ophthalmectomy patients showed obviously increased DC value in left cerebellum posterior lobe, left middle frontal gyrus1, right supramarginal gyrus, left middle frontal gyrus2, right middle frontal gyrus, and obviously decreased DC value in left lingual gyrus, bilateral

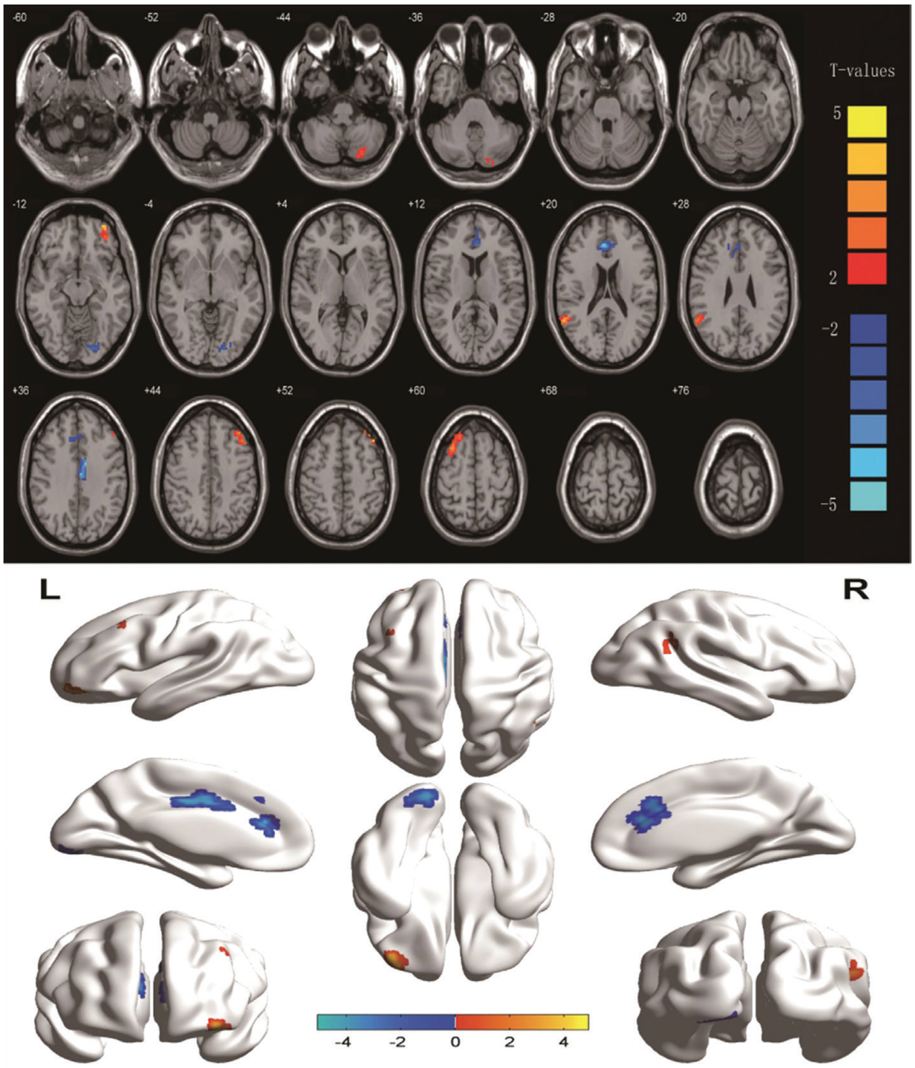

Figure 1 Significant differences of spontaneous brain activity between the ophthalmectomy group and healthy controls The blue areas denote significantly reduced DC brain regions in the left lingual gyrus, bilateral lingual lobe, left cingulate gyrus. The red areas indicate that the left cerebellum posterior lobe, left middle frontal gyrus1, right supramarginal gyrus, left middle frontal gyrus2, and right middle frontal gyrus have higher DC cerebrum areas [P<0.05 for multiple comparisons using GRF theory (z>2.3, cluster-wise P<0.05 corrected)].

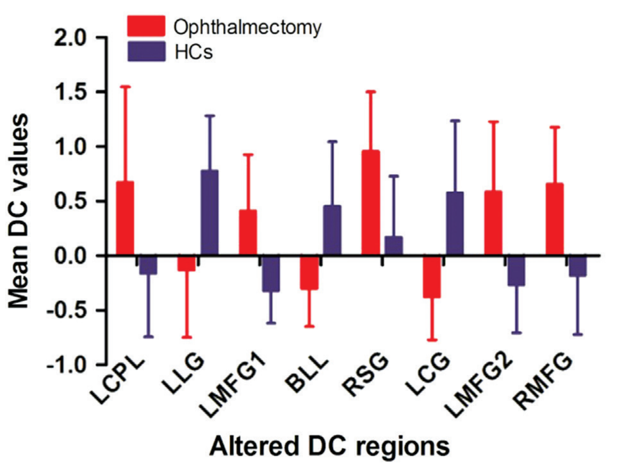

Figure 2 The mean values of altered DC values between the ophthalmectomy and HCs groups Data are expressed as mean± standard deviation.

lingual lobe, left cingulate gyrus (Figure 4). The DC method has been profitably applied in glaucoma[20], strabismus[21], open-globe injury[22] and predicts huge development prospect (Figure 5). Our investigation is the initial study to explore the cerebral functional connectivity involved in ophthalmectomy individuals.

Analysis of the Elevation of Degree Centrality Values in Patients with Ophthalmectomy The middle frontal gyrus is in the frontal lobe, mainly responsible for working memory and attention control[23]. Research indicated that the right MFG could make a significant impact in shifting attention from exogenous to endogenous attentional control[24]. Another study found that the myo-inositol (mI), choline-compounds (Cho), creatine + phosphocreatine (Cr), and N-acetyl-aspartate + N-acetyl-aspartyl-glutamate (tNAA) of ADHD children in middle frontal gyruswere significantly less than normal children[25]. In our previous articles, the values of FLL in middle frontal gyrus of patients with unilateral blindness were greatly increased[26]. In the same way, our present study

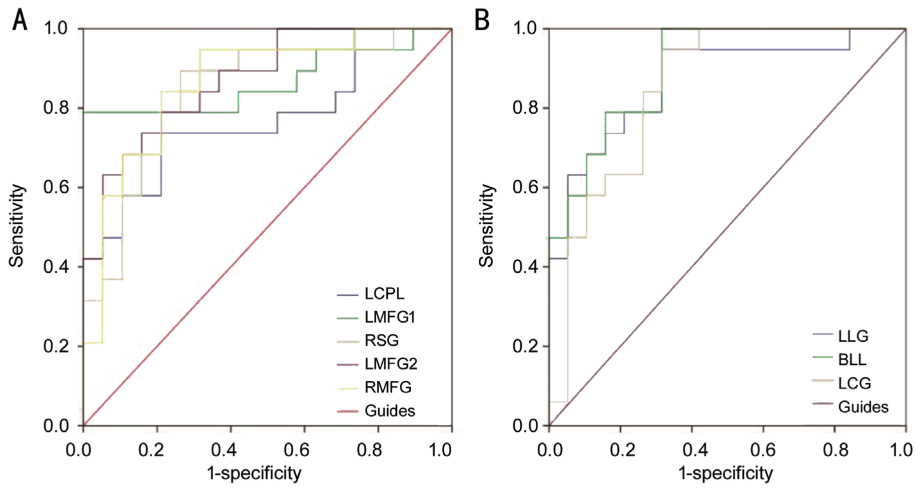

Figure 3 ROC curve analysis of the mean DC values for altered brain regions The AUCs for DC values: LCPL: 0.773, LLG: 0.870, LMFG1: 0.867, BLL: 0.848, RSG: 0.842, LCG: 0.900, LMFG2: 0.873, RMFG: 0.864. LMFG: Left middle frontal gyrus; RMFG: Right middle frontal gyrus; LCPL: Left cerebellum posterior lobe; RSG: Right supramarginal gyrus; LLG: Left lingual gyrus; LCG: Left cingulate gyrus; BLL: Bilateral lingual lobe; AUC: Area under the curve.

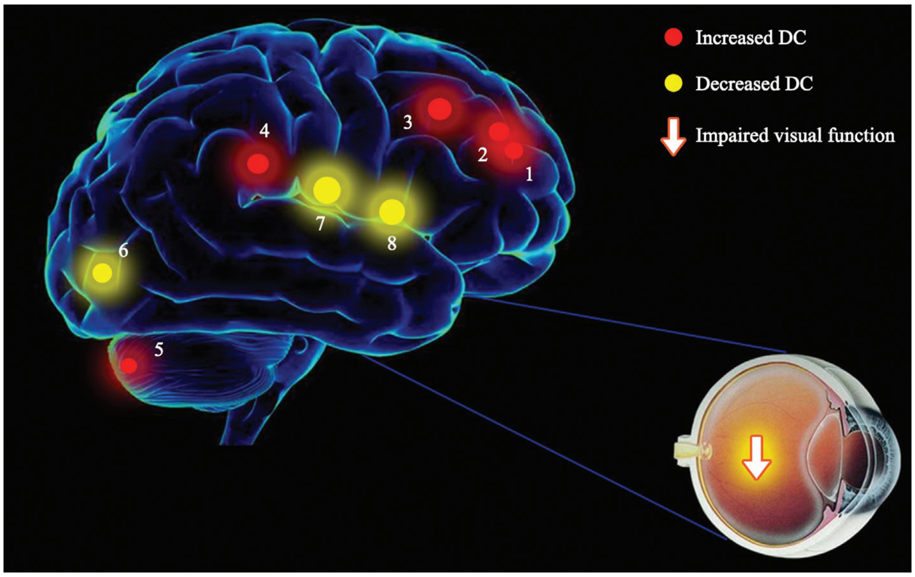

Figure 4 The DC results of brain activity in ophthalmectomy group Compared with the HCs, the DC of the brain areas in ophthalmectomy group were as follows: 1-right middle frontal gyrus (t=4.1662), 2-left middle frontal gyrus1 (t=4.5334), 3-left middle frontal gyrus2 (t=4.9024), 4-right supramarginal gyrus (t=4.6031), 5-left cerebellum posterior lobe (t=3.4195), 6-left lingual gyrus (t=-4.3060), 7- left cingulate gyrus (t=-5.0657) and 8-bilateral limbic lobe (t=-5.0474). The degree of quantitative changes is showed by the sizes of the spots.

observed increased DC values in both the left and right frontal gyrus of patients with ophthalmectomy, indicating that there were abnormalities in the right and left frontal gyrus after ophthalmectomy. We hypothesized that the enhancement of left and right frontal gyrus activity is the brain's compensation mechanism for monocular vision after ophthalmectomy.

The supramarginal gyrus is in the parietal lobe, and participates in brain language coding, visual recognition and oral memory[27-30]. Hartwigsen *et al*[31-32] found that the supramarginal gyrus can coordinate the rapid response with the left dorsal anterior motor cortex, promoting the body to better adapt to the external environment. In our study, we found significantly increased values of DC in the right supramarginal gyrus of the patients with ophthalmectomy, suggesting that ophthalmectomy can lead to excessive activation of the supramarginal gyrus activities. Therefore, we speculated that the visual recognition and language coding ability of the patients were enhanced after ophthalmectomy.

The cerebellum is located in the posterior inferior part of the brain, the posterior fossa, on the back of the medulla oblongata and the pontoon. The cerebellum is mainly responsible for the motor control of the body, and is also related to the cognitive and language implementation[33-34]. One study reported that the posterior vermis was mainly involved in vital-triggered

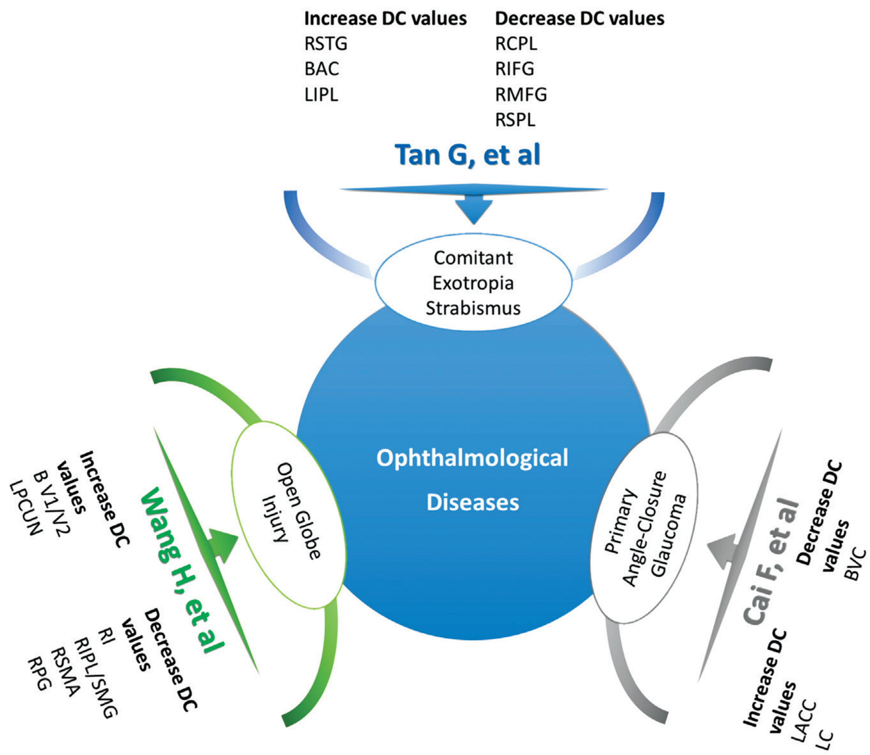

Figure 5 DC method applied in ophthalmological diseases.

saccadic eye movements[35]. Furthermore, numerous researches have confirmed that cerebellum dysfunction can lead to a variety of diseases[36-37]. Zhang *et al*[38] showed that the blood flow in the right cerebellum posterior lobe of patients with depression asthma and non-depression asthma was reduced, and the blood flow in the right cerebellum posterior lobe of patients with depression asthma was higher than the non-depression patients. Uhl *et al*[39] showed that the flow of blood in the cerebellum and inferior occipital cortex of the early blind significantly increased. In our research, we observed that the DC values of left cerebellum posterior lobe was significantly increased in patients with ophthalmectomy. We considered that ophthalmectomy resulted increased activation of the left cerebellum posterior lobe, and the compensation mechanism was activated to compensate for the lack of monocular vision.

Analysis of the Reduction of Degree Centrality Values in Patients with Ophthalmectomy The cingulum, a part of the limbic system, is closely related to the cognitive ability, emotion and memory of the brain[40-42]. Many diseases have been found to have abnormal cingulum, such as schizophrenia, alzheimer's disease, autism, and depression[40,43-46]. From our research, the reduced DC values of the left cingulate gyrus was observed in patients with ophthalmectomy, indicating that there was some dysfunction of the left cingulate gyrus in patients with ophthalmectomy.

The lingual gyrus is mainly responsible for visual process, especially the processing of letters[47]. A previous study reported that there were significantly increased activities in the lingual gyrus during visual development[48]. Jung *et al*[49] found the lingual gyrus might be a potential candidate area for predicting antidepressant reactivity and maintaining cognitive ability in Major Depressive Disorder. Another study disclosed that the Reho values of the lingual gyrus was significantly decreased in patients with panic attacks[50]. And in our study, DC values of the lingual gyrus and bilateral lingual lobe were significantly reduced in the patients with ophthalmectomy, which may be the result of the atrophy of the lingual gyrus and bilateral lingual lobe caused by the absence of visual function in the affected eye after ophthalmectomy.

In conclusion, we found that abnormal spontaneous brain activities of various cerebrum areas in ophthalmectomy patients may suggest the pathophysiological changes after ophthalmectomy. The results may reveal the potential neural mechanism in patients with ophthalmectomy, which maybe were helpful to the clinical differential diagnosis.

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