Altered brain network centrality in patients with orbital fracture: A resting-state functional MRI study

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Abstract. The present study aimed to investigate potential functional network brain-activity abnormalities in individuals with orbital fracture (OF) using the voxel-wise degree centrality (DC) technique. The present study included 20 patients with OF (12 males and 8 females) and 20 healthy controls (HC; 12 males and 8 females), who were matched for gender, age and educational attainment. Functional magnetic resonance imaging (fMRI) in the resting state has been widely applied in several fields. Receiver operating characteristic (ROC) curves were calculated to distinguish between patients with OF and HCs. In addition, correlation analyses were performed between behavioral performance and average DC values in various locations. The DC technique was used to assess unprompted brain activity. Right cerebellum 9 region (Cerebelum_9_R) and left cerebellar peduncle 2 area (Cerebelum_Crus2_L) DC values of patients with OF were increased compared with those in HCs. Cerebelum_9_R and Cerebelum_Crus2_L had area under the ROC curve values of 0.983 and 1.000, respectively. Patients with OF appear to have several brain regions that exhibited aberrant brain network characteristics, which raises the possibility of neuropathic causes and offers novel therapeutic options.

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Introduction

In ophthalmology, orbital fracture (OF) is a frequent cause of orbital trauma, frequently leading to the impaction of the extraocular muscles and the contents of the orbit. Diplopia, eye movement abnormalities and enophthalmos are the predominant clinical symptoms. This condition is usually found in young adults, with male patients constituting a proportion of 72%, which is mainly due to physical assault (1,2). Facial trauma after a high-energy collision is a common finding in patients with OF and the most common etiology is interpersonal violence, followed by falls and motor vehicle collisions (3,4). The medial wall of the orbital bone, which is the weakest part of the bone, frequently sustains fractures. Following OF, neurological and ocular sequelae are frequent (5). The most frequent ophthalmologic problems that may affect vision are retrobulbar hematoma and trauma to the optic nerve (6). Consequently, it is crucial to treat OF appropriately and rapidly. Typically, the goal of treating an orbital floor fracture is to eliminate any diplopia and enophthalmos that may be present (7). Operations are prioritized during treatment, with autologous bone implantation being the most frequent procedure (8). The most recent procedures are patient-specific computer-aided design/computer-aided manufacturing ceramic implants (9) and three-dimensional (3D) printed model implants (10). Studies have demonstrated that patients have excellent outcomes, with shorter surgical durations and successful functional and esthetic outcomes (11).

Midway through the 1980s, computed facial tomography (CT) offered the most accurate diagnostic evaluation and made it possible to visualize the contents of the orbit in 3D (12). Aggressive surgical methods were used as a result (13). The ocular injuries caused by OF may be characterized using CT scans, but the underlying neurological changes remain elusive. In this context, functional magnetic resonance imaging (fMRI) is becoming a more valuable clinical tool that accurately maps out functional brain networks in individuals and offers a chance to comprehend the neurobiological underpinnings of unique behavioral distinctions (14). In studies on orbital studies associated with brain function alterations, fMRI has been widely used. For instance, patients with advanced monocular blindness exhibited alterations in reduced gray matter volume in particular regions of the brain (15). In addition, it was demonstrated that neural activity in the inferior frontal cortex and superior parietal lobule enable blind individuals to automatically assign directional meaning to echoes (16). However, the mechanisms driving internal brain activity modifications in patients with acute unilateral vision loss following OF remain unclear despite research showing altered visual and brain function in blind patients.

A technique to show the intrinsic connection patterns of whole-brain functional networks is the voxel-wise degree centrality (DC) method. Brain networks that exhibit intrinsic coordinated activity may be identified by functional connectivity (17). The DC method is distinct from the voxel-based morphometry (18) approach, as the use of regions of interest is not required. The DC approach has been used extensively, since it may give inside looks at the functional connectivity of the entire brain, particularly to research brain pathological disorders such as autism (19) and Parkinson's disease (20), which are both neurological conditions (21). On this basis, the present study investigated the clinical correlations in terms of functional connectivity in patients with OF.

Materials and methods

Study participants. The present study recruited 20 patients with OF (sex, 12 males and 8 females; mean age, 51.21 years; age range, 35-61 years) from the Ophthalmology Department of the First Affiliated Hospital of Nanchang University Hospital (Nanchang, China). The present study was performed from July 2020 to June 2021. All patients were diagnosed with OF using CT.

The inclusion criteria were as follows: i) Patients with OF who did not receive surgical treatment; and ii) patients without other ocular diseases, such as cataracts, corneal ulcers, glaucoma or macular degeneration.

The following exclusion criteria were used: i) Presence of other ophthalmic diseases; ii) presence of central nervous system diseases; iii) previous history of ophthalmic surgery; and iv) patients unable to receive MRI examination.

In addition, an equal number of healthy controls (HCs) who met the following criteria were recruited: i) Individuals without ocular or central nervous system diseases; and ii) individuals who had no contraindications for MRI scanning.

The 20 HCs (12 males and 8 females; mean age, 50.96 years; age range, 50.96±10.82 years) were pair-matched with patients in the OF group according to sex, age, body weight and education level (Table I). The Medical Ethics Committee of the First Affiliated Hospital of Nanchang University (Nanchang, China) authorized and approved the methods used in the present study (approval no. cdyfy2021039), which followed the tenets of The Declaration of Helsinki. All participants were volunteers, to whom the purpose, methods, procedures and underlying risks of the study had been explained. All participants signed informed consent forms.

Resting-state (Rs-)fMRI data acquisition. Rs-fMRI data were acquired with a Siemens Trio 3.0 T scanner associated with an 8-channel phased array probe coil (Siemens AG). The Rs-fMRI scanning was performed using the following parameters: Repetition time, 2,000 msec; echo time, 40 msec; flip angle, 90˚; slice thickness/gap, 4.0/1 mm; field of view, 240x240 mm; in-plane resolution, 64x64,30 axial slices and 240 volumes.

Rs-fMRI data processing. MRIcro (www.MRIcro.com) was used to pre-filter and DPARSFA (http://rfmri.org/DPARSF), SPM8 (http://www.fifil.ion.ucl.ac.uk/spm) and the Resting-state Data Analysis Toolkit (http://www.restfmri.net) to preprocess the data as performed in a previous study (22).

Degree centrality. The DC value was calculated using significant suprathreshold correlations between the subjects, or the degree of the binarized adjacency matrix, in the voxel function network based on the individual voxel-wise functional network. The DC map for each individual was transformed into a z-score map using the following equation: Z_i=DC_i-mean/standard deviation (SD), where Z_i refers to the z score of the i^{th} voxel, DCi refers to DC value of the i^{th} voxel and mean refers to DC of all voxels in the brain mask (22).

Clinical characteristics. Personal clinical data were collected after admission. The OF duration (days) of all individuals was also recorded. After examining the best-corrected visual acuity (VA), the results were converted into the minimum logarithmic. In addition, a visual evoked potential (VEP) examination was performed with the patient's consent.

Statistical analysis. Demographic and clinical data were analyzed using the independent samples t-test in SPSS 20.0 software (IBM Corp.) to identify any significant differences in clinical features between the patients with OF and HCs. $P<0.05$ was considered to indicate a statistically significant difference. Data are presented as the mean ± SD. An independent two-samples t-test in SPSS 20.0 was used to compare the DC data between patients with OF and HCs. Receiver operating characteristic (ROC) curve analyses, which were used to classify the mean DC values in various brain areas of the patients with OF, as well as the calculation of the T-value in Table II, were performed using SPSS 20.0. The correlations between behavioral performance and mean DC values were evaluated with Pearson's correlation analysis using GraphPad Prism (version 7.0; GraphPad Software; Dotmatics).

Results

Demographics and visual measurements. The present study found similar proportions in sex ($P>0.99$), body weight ($P=0.902$) and age ($P=0.871$) among the participants.

Table I. Characteristics of the study participants.

Characteristics	OF	Healthy controls	t	P-value[a]
Sex			N/A	>0.999
Male	12	12		
Female	8	8		
Age, years	51.21±11.42	50.96±10.82	0.242	0.871
Body weight, kg	68.32±9.24	69.93±9.54	0.165	0.902
Handedness, R	20	20	N/A	>0.999
OF duration, days	11.61±4.14	N/A	N/A	N/A
Best-corrected VA				
Left eye	0.40±0.20	1.05±0.20	-3.763	0.017
Right eye	0.45±0.15	1.00±0.15	-3.064	0.011
Latency right of the VEP, msec	118.16±8.29	100.98±6.17	3.554	0.017
Amplitude right of the VEP, μV	6.87±2.42	14.16±1.93	-6.643	0.009
Latency left of the VEP, msec	116.12±7.11	101.21±1.32	4.532	0.022
Amplitude left of the VEP, μV	7.42±2.73	16.74±2.52	-5.732	0.012

[a]Independent Student's t-tests comparing two groups. N/A, not applicable; OF, orbital fracture; VA, visual acuity; VEP, visual evoked potential; R, right.

Table II. Brain areas with significant differences in voxel-wise degree centrality between the OF and HC groups.

	Montreal Neurological Institute coordinates					
Brain areas	X	Y	Z	Brodmann area	Number of voxels	T-value
Right cerebellum 9 region	-3	-24	-21	-	164	4.6322
Left cerebellar peduncles 2 area	-30	-78	-48	93	123	4.2018

The table presents 'OF > HC', i.e. the brain area where the DC value OF of is greater than that of HC. OF, orbital fracture; HC, healthy control.

However, statistically significant differences were found in the best-corrected VA-right (P=0.011), best-corrected VA-left (P=0.017), latency (msec)-right of the VEP (P=0.017), latency (msec)-left of the VEP (P=0.022), amplitudes (μV)-right of the VEP (P=0.009) and amplitudes (μV-left of the VEP (P=0.012) between the two groups (Table I).

Differences in DC. The DC values in patients with OF were significantly higher in the right cerebellum 9 region (Cerebelum_9_R) and left cerebellar peduncle 2 area (Cerebelum_Crus2_L) (Fig. 1A and B; Table II) than in HCs. Fig. 2 presents the mean values of altered DC between patients with OF and HCs.

ROC curve. It was hypothesized that the OF and HC groups have different DC values in distinct brain regions, and the ROC curves were applied to distinguish between OF and HC. In the present study, the areas under the ROC curve were 0.983 (P<0.0001; 95% CI, 0.941-1.000) for the Cerebelum_9_R area and 1.000 (P<0.0001; 95% CI, 1.000-1.000) for the Cerebelum_Crus2_L area (Fig. 3).

Discussion

The orbit is a complex and important anatomical structure. OF is frequently followed by acute injury to the brain, retina, optic nerve, retrobulbar soft tissue and optic nerve, which causes various issues, including eye movement dysfunction and diplopia (23). Rs-fMRI is a type of medical imaging that tracks brain activity using signals that depend on blood oxygen levels. The changes in potential brain functional network activity in patients with OF were examined in the present study using Rs-fMRI and the association between spontaneous brain activity and clinical features in patients with OF was examined using DC technology (18,22). To date, the DC method has been successfully applied to a variety of neurogenic and ophthalmological diseases, with great potential for development. Altered DC values may be a useful biomarker to indicate the abnormal brain activity changes in diabetic retinopathy (24), optic neuritis (25) or Alzheimer's disease (26) (Table III). High-energy trauma is a common cause of OF, which may result in several complications and harm to visual function (3,23). The degree of the retinal, optic nerve and visual impairment may be rapidly and objectively

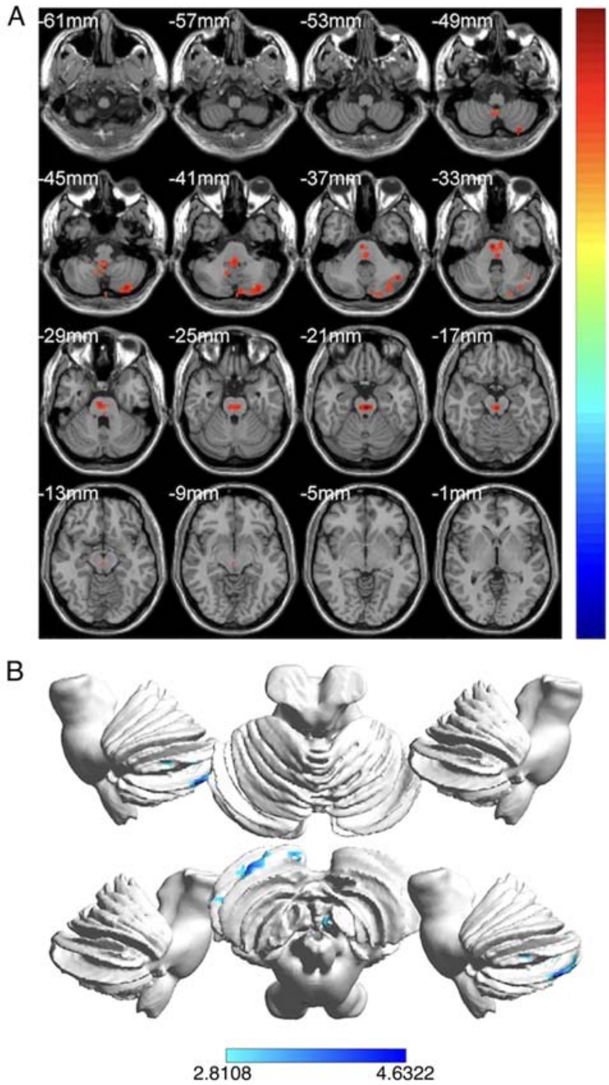

Figure 1. Voxel-wise comparison of DC in the orbital fracture and healthy control groups. (A) Significant differences in DC values were observed in the right cerebellum 9 and left cerebellar peduncles 2 areas. (B) Stereoscopic form. The red areas denote higher DC values and the blue ones denote lower DC values. DC, voxel-wise degree centrality.

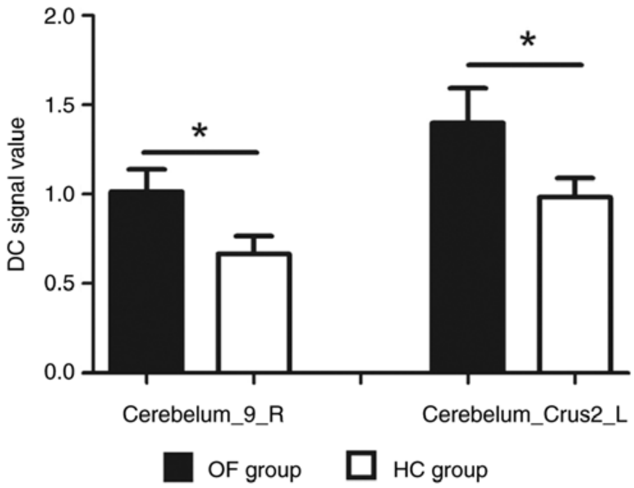

Figure 2. Means of altered DC values in the OF and HC groups. Significant differences exist between two groups in DC values in Cerebelum_9_R and Cerebelum_Crus2_L. *P<0.05 vs. HC. DC, voxel-wise degree centrality; HC, healthy control; OF, orbital fracture; Cerebelum_9_R, right cerebellum 9 region; Cerebelum_Crus2_L, left cerebellar peduncles 2 area.

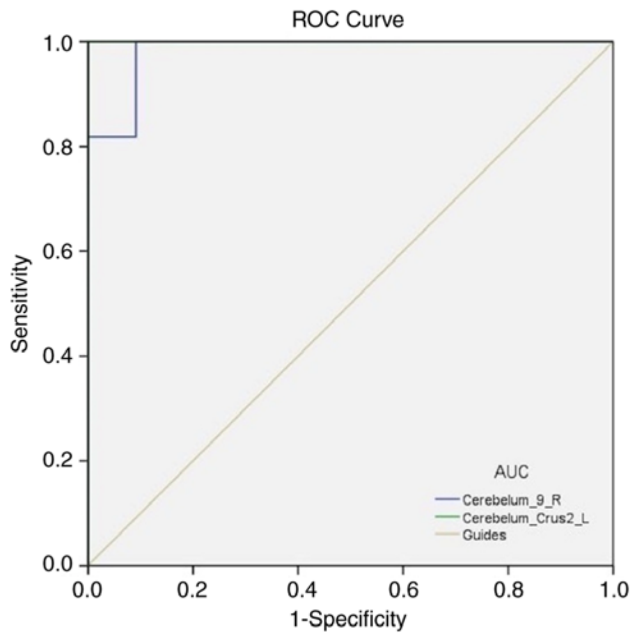

Figure 3. ROC curve analysis of the mean DC values for altered brain areas. The AUC was 0.983 (P<0.0001; 95% CI, 0.941-1.000) for the right cerebellum 9 region and 1.000 for the left cerebellar peduncles 2 area (P<0.0001; 95% CI, 1.000-1.000). ROC, receiver operating characteristic; AUC, area under the ROC curve; Cerebelum_9_R, right cerebellum 9 region; Cerebelum_Crus2_L, left cerebellar peduncles 2 area.

determined by visual electrophysiological testing. The cerebral cortex generates bioelectricity when the retina is activated and this is known as the VEP (27). The VEP has a decreased amplitude and a delayed peak when the optic nerve is damaged by ocular trauma (28). In the present study, patients with OF had significantly worse VA, VEP amplitudes and VEP latency. The present investigation discovered that patients with OF had higher DC values in the Cerebelum_9_R and Cerebelum_Crus2_L compared with those in HCs. Afferent visual pathways may become aberrant as a result of cerebellum diseases (29). It may be hypothesized that the decline in VA is connected to the aberrant cerebellar DC value in patients with OF.

The primary and posterolateral fissures divide the cerebellum, which is found in the posterior cranial fossa and into anterior, posterior and pompous lobes (30,31). The control and coordination of muscle tension, voluntary movement and body balance are all functions of the cerebellum. The cerebellum not only immediately and effectively regulates eye movement but may also contribute to long-term visual calibration. More crucially, the cerebellum also ensures the correctness of eye movements, ensuring visual sharpness and clarity (30,32-35). The vestibular nucleus in the brain stem serves as the primary afferent source for the vestibular cerebellum. The vestibular organ integrates position data from the head and the entire body into the vestibular cerebellum, which in turn controls the vestibular nucleus and the pontine reticular structure. In addition to regulating trunk activity, the vestibular cerebellum can also control the activity of the extraocular muscles (36). A

Table III. Voxel-wise degree centrality method applied in ophthalmologic and neurogenic diseases.

A, Ophthalmologic

First author, year	Disease	(Refs.)
Chen *et al*, 2013	Alternating Horner's syndrome	(55)
Cai *et al*, 2015	Glaucoma	(21)
Hu *et al*, 2018	High myopia	(56)
Huang *et al*, 2019	Visual loss	(57)
Huang *et al*, 2021	Diabetic retinopathy	(24)
Wei *et al*, 2022	Optic neuritis	(25)

B, Neurogenic

First author, year	Disease	(Refs.)
Guo *et al*, 2016	Alzheimer's disease	(26)
Deng *et al*, 2019	Bipolar disorder	(58)
Zhang *et al*, 2022	Postpartum depression	(59)

study has indicated that cerebellar damage can impact spatial and temporal visual attention (37). In addition, it has been indicated that patients with cerebellar damage have less effective eye tracking and fixation than HCs (30,32,34,38). The current study suggested that patients with OF had higher cerebellar DC (see spots 1 and 2 in Fig. 4). This indicates that patients with OF may have aberrant cerebellar functional connections, which may be hypothesized to be connected to issues such as eye movement difficulties or a decline in VA in OF.

A total of three sets of cerebellar feet are present in the cerebellum (superior, middle, inferior). Eye movements are tightly associated with all cerebellar feet (33,35,39). Starting from the bottom of the bridge, the middle cerebellar foot is in the outermost of the three pairs and it is situated between the cerebellum and the pons. The primary afferent fibers of the cerebellum, which comprise white matter fibers of the opposing pontine nucleus, are gathered in the middle peduncle of the cerebellum. This nucleus is a gray matter structure responsible for regulating the start, transmission and execution of movement through a closed-loop connection between the cerebellum and the precentral/prefrontal cortex (39-41). Therefore, ipsilateral limb ataxia, nystagmus and vertigo are frequently seen as clinical symptoms of cerebellar middle foot lesions (39). The foot is a key conduit for conveying information about eye movement; thus, a middle cerebellar peduncle injury may result in aberrant eye movement (33,39). A previous study described three patients with cerebellar middle foot hemangiomas (42). During the vertical line of the sight chase test, aberrant eye movement and significant twisting nystagmus were present in all patients. When tracking with the vertical line of sight, nystagmus was indicated to occur as a result after unilateral cerebellar foot damage (42-44). The cerebellum's middle foot includes the Cerebelum_Crus2_L area. The present study demonstrated that the DC value of the Cerebelum_Crus2_L area is larger in patients with OF compared with that in HCs (Table IV), indicating that OF may

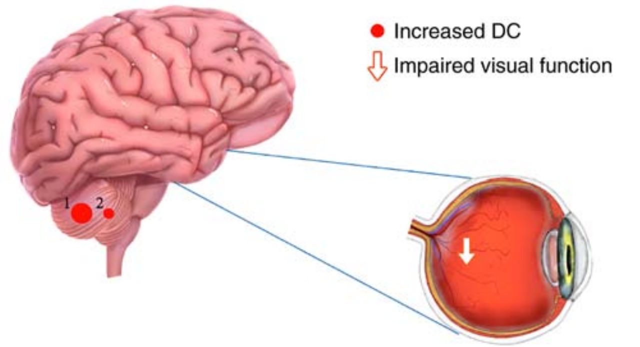

Figure 4. Mean DC values of altered brain areas. The DC values of the following areas were increased to various extents in patients with orbital fractures compared with those in the healthy control group. Spot no. 1 indicates the right cerebellum 9 region (T=4.6322), while spot no. 2 indicates the left cerebellar peduncles 2 area (Brodmann's area 93, T=4.2018). DC, voxel-wise degree centrality.

cause an overactive cerebellar middle peduncle, also known as the pontine arm, and possibly a higher level of functional connectivity.

Ocular motor vermis and caudal fastigial nuclei, ventral uvula and nodulus, and flocculus and para flocculus are the three critical areas of cerebellar control of eye movement (33). The neural network signal encoding vertical line of sight tracking is transmitted to the vestibular cerebellum through the middle foot of the cerebellum (35,36). The posterior lobe of the cerebellum, which contributes to the development of the vestibular cerebellum, contains the right cerebellar region 9 (Cerebelum_9_R). In a previous study, the vestibulo-ocular reflex suggested that eye movement-counteracting head movement was able to maintain a stable line of sight (45). It was discovered that patients with OF had significantly higher DC values in Cerebelum_9_R compared with those in HCs (Table IV), indicating that eye movement impairment in patients

Table IV. Brain areas of altered voxel-wise degree centrality values and potential effects.

Brain areas	Experimental result (DC values)	Brain function	Anticipated results
Right cerebellum 9 region	OF > HCs	Physical balance, muscular tension, motor coordination	Behavioral disorders
Left cerebellar peduncles 2 area	OF > HCs	Connecting structure, associated with eye movement	Visual impairment

DC, voxel-wise degree centrality; OF, orbital fracture; HCs, healthy controls.

with OF may be related to the compensatory mechanism of vestibular cerebellum dysfunction. The paramedian tract cell population and the inferior olivary nucleus are responsible for transmitting retinal slip signals to the para flocculus of the vestibular cerebellum. This is the precise process by which the cerebellum regulates eye movement. In the aforementioned process, the vestibular nucleus participates as the afferent fibers of the flocculus and para flocculus. The vestibular nucleus and vestibular cerebellum are linked via a two-way fiber. To regulate the activity of the muscles in the trunk and extremities, it receives projections from the vestibular nucleus and its efferent fibers change through the vestibular nucleus before reaching the motoneurons in the medial section of the anterior horn of the spinal cord. The middle peduncle of the cerebellum receives nerve fibers from the vestibular nucleus and transmits them to the cerebellum (46-50). Patients with OF had considerably higher DC values in the cerebellar tonsillar and peduncle regions, which are crucial in the development of the vestibular cerebellum. It may be hypothesized that an OF may impair the cerebellum's ability to precisely regulate eye movement, which would reduce VA, and this is consistent with previously published results (51).

In the present study, the mechanism of cerebellar dysfunction caused by OF remains elusive and the associated inflammatory response cannot be ignored. Orbital cellulitis is one of the severe complications of OF (52). Anti-inflammatory therapy is critical in OF. A variety of active substances have been indicated to have neuroprotective and powerful anti-inflammatory effects and are expected to be applied in clinical therapy. Cerebrolysin, a mixture of enzymatic processing peptides from pig brains, protects neurons, primarily by reducing glutamate concentration in the synaptic clefts. In addition, it may reduce oxidative stress and harm to neuronal cells by boosting antioxidant activity and lowering levels of inflammatory cytokines according to the data from Avci *et al* (53). In another study, a bioactive natural product called crocin was able to not only inhibit the production of reactive oxygen species and the secretion of pro-inflammatory cytokines but also reduce the inflammation of various organs/systems (54). However, more relevant studies are needed to further evaluate and improve the therapy for OF.

Although the DC technique is a useful tool for observing whole-brain activity, it has certain drawbacks. First, there are several variables to consider. For instance, differences in disease time courses and physical circumstances among patients may have led to measurement inaccuracies. In addition, the sample size of the current study was small and this may have had an impact on the present DC results. The present findings should be confirmed by further investigations to address these issues and use reliable brain function activity exams.

In conclusion, the present study demonstrated that the cerebellum is involved in the regulation of eye movement and that patients with OF exhibit abnormal spontaneous activity in the middle cerebellar peduncle and posterior cerebellar lobe compared with that in the HC group. In addition, focusing on the damage to the extraocular muscle and oculomotor nerve, the approach to treating eye movement disorders in patients with OF offers a fresh perspective. The present findings may be helpful in the treatment of individuals with OF. Attention should also be paid to the brain tissue connected to eye movement and VA.

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Availability of data and materials

The datasets used and/or analyzed during the current study are available from the corresponding author on reasonable request.

Authors' contributions

YL and YG conceived, designed and supervised the study. HS collected data and prepared the images. QL and QG collected and interpreted the data and wrote the manuscript. XL, YP, TS, JW, LZ and RL performed data analysis and critically reviewed the manuscript. YS conceived and designed the present study and critically revised the manuscript. All authors have read and approved the final manuscript. HS and YS confirm the authenticity of all the raw data.

Ethics approval and consent to participate

The Medical Ethics Committee of the First Affiliated Hospital of Nanchang University (Nanchang, China) authorized and approved the methods used in the present study (approval no. cdyfy2021039), which followed the tenets of The Declaration of Helsinki. All participants were volunteers, to whom the purpose, methods, procedures and underlying risks of the study had been explained. All participants provided written informed consent.

Patient consent for publication

Not applicable.

Competing interests

The authors declare that they have no competing interests.

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