Altered Brain Network Centrality in Patients With Orbital Fracture: A Resting-State fMRI Study. Running Head: DC Alterations in OF Patients

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Abstract

Objective: We aimed to identify potential functional network brain-activity abnormalities in patients with orbital fractures (OFs) by using the voxel-wise degree centrality (DC) method.

Methods: We selected 20 patients with OFs (12 men and 8 women) and 20 healthy controls (HCs; 12 men and 8 women) matched by gender, age, and education level for this study. Resting-state functional magnetic resonance imaging (fMRI) has been widely used in various disciplines. We calculated receiver operating characteristic (ROC) curves to differentiate characteristics between patients with orbital fractures and HCs; in addition, we applied correlation analyses between behavioral performance and average DC values in different areas. The DC method served to evaluate spontaneous brain activity.

Results: The DC values of patients with OFs were higher in the right cerebellum 9 area (Cerebelum_9_R) and left cerebellar peduncle 2 area (Cerebelum_Crus2_L) than those in HCs. The area under the curve (AUC) values for Cerebelum_9_R and Cerebelum_Crus2_L were 0.983 and 1, respectively. The accuracy of our ROC curve analysis result was reliable.

Conclusion: Many brain regions seem to show abnormal brain network characteristics in patients with orbital fractures, suggesting potential neuropathic mechanisms.

Introduction

Orbital fractures (OFs) are a common orbital trauma in ophthalmology, usually resulting in orbital wall injury and impaction of extraocular muscles and orbital contents. The main clinical manifestations are enophthalmos, eye movement disorders, and diplopia.

This condition is usually found in young adults, and men make up a large proportion of them. Facial trauma after a high-energy collision is a common finding in these patients (the most common etiology is interpersonal violence, followed by falls and road traffic accidents)[1]. Orbital fractures occur often in the medial wall, the weakest portion of the orbital bone. Orbital fractures are associated with high rates of ocular and neurological complications. Traumatic optic neuropathy and retrobulbar hematoma are the most common ophthalmologic complications, and they may lead to ocular visual impairments[2]. Therefore, the correct and timely treatment of orbital fractures is important. The orbital floor fracture treatment usually focuses on relieving any diplopia and enophthalmos present[3].

During treatment, operations are prioritized, with implantation being the most common procedure. Patient specific CAD/CAM ceramic implants[4] and 3D printed model implants[5] are the newest techniques available. Studies have shown excellent outcomes for patients, with decreasing surgical times and good functional and aesthetic results.

In the mid-1980s, computed facial tomography (CT) provided the best possible diagnostic assessment and enabled three-dimensional (3D) visualization of the orbital contents. This led to aggressive surgical approaches[6]. CT scans can help manage the ocular trauma after OFs, but the underlying neural alterations remain largely unclear. In this context, fMRI is becoming a more useful clinical tool that reliably delineates functional brain networks in individuals, and it provides an opportunity for understanding the neurobiological basis of individual behavioral differences[7]. fMRI has been extensively used in orbital studies associated with brain function alterations. For example, reduced gray matter volume (GMV) changes have been documented in specific parts of the brain of patients with advanced monocular blindness (MB)[8]. In addition, superior parietal lobule (SPL) and inferior frontal cortex (IFC) activations have been shown to allow blind participants to automatically assign directional meaning to echoes[9]. Although studies depict visual and brain function alterations in blind patients, we still need to understand the mechanisms underlying internal brain activity alterations in patients with acute unilateral vision loss after orbital fractures.

Voxel-wise degree centrality (DC) is a method to reveal the intrinsic connectivity patterns of whole-brain functional networks. Functional connectivity can define brain networks that show intrinsic coordinated activity[10].The DC method does not need the definition of regions of interest (ROIs) and differs from the Voxel-Based Morphometry (VBM)[11] technique. Since DC can provide inside views into the functional connectivity of the whole brain, it is always preferred to other network metrics. The DC method has been applied in many areas (especially to study neural pathological diseases, including autism[12] and Parkinson's disease[13]). In this study, we examined functional connectivities in patients with orbital fracture and their association with clinical characteristics.

Subjects And Methods

Subjects. We recruited 20 patients with OF from the Ophthalmology Department of the First Affiliated Hospital of Nanchang University Hospital in Jiang Xi Province of China. The relevant inclusion criteria were: 1) patients with orbital fracture, who had not undergone surgical treatment; and, 2) patients without other ocular diseases (such as cataract, corneal ulcer, glaucoma, or macular degeneration).

The relevant exclusion criteria were: 1) presence of other ophthalmic diseases; 2) presence of central nervous system diseases; 3) having had ophthalmic surgery before; and, 4) patients unable to undergo an MRI examination.

In addition, we recruited 11 HCs matched by sex, age, and education level, who met the following criteria: 1) They lacked ocular or central nervous system diseases; and, 2) they lacked MRI scanning contraindications.

The 20 HCs were pair-matched with patients in the OF group according to gender, age, weight, and education level. The Medical Ethics Committee of the First Affiliated Hospital of Nanchang University authorized and approved the methods used in the present study, which followed the tenets of the Declaration of Helsinki. All participants were voluntaries, who had been explained the purpose, methods, procedures and underlying risks of the study. All participants signed informed consent forms.

MRI data acquisition. We acquired all MRI data with a Siemens Trio 3.0 T scanner associated with an 8-channel phased array probe coil (Trio; Siemens, Munich, Berlin, Germany). The MRI scanning parameters were based on those of a previous study(14).

fMRI data processing. We used MRIcro (www.MRIcro.com) 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 (REST, http://www.restfmri.net) to preprocess the data. More details have been published(14).

Degree centrality. We calculated the DC value by 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 voxel-wise DC map for each individual was transformed into a z-score map, using the following equation:

Zi= DCi – mean /std. Where Zi refers to the z score of the ith voxel, DCi refers to DC value of the ith voxel, mean refers to DC of all voxels in brain mask and std refers to the standard deviation[14].

Statistical analysis. For demographic and clinical data, we used independent two-sample *t*-tests in SPSS 20.0 software (IBM Corporation, Armonk, NY, USA) to calculate differences in clinical features between patients and HCs; and, we considered P<0.05 as indicative of statistical significance. We used independent two-sample t-tests in the SPM8 toolkit to compare DC data between OF patients and HCs.

The association between behavioral performance and mean DC values was evaluated with correlation analyses.

Results

Demographics and visual measurements. We found similar proportions in gender (P>0.99), weight (P=0, 902), and age (P=0.871) among the participants. However, we found statistically significant differences in the best-corrected visual acuity (VA)-right (P=0.011), best-corrected VA-left (P=0.017), latency (ms)-right of the VEP (P=0.017), latency (ms)-left of the VEP (P=0.022), amplitudes (uv)-right of the VEP (P=0.009), and amplitudes (uv)-left of the VEP (P=0.012) between the two groups (Table 1).

Table 1
Basic information of participants in the study

Condition	DON	HCs	t	P-value*
Male/female	12/8	12/8	N/A	>0.99
Age (years)	51.21±11.42	50.96±10.82	0.242	0.871
Weight (kg)	68.32±9.24	69.93±9.54	0.165	0.902
Handedness	20 R	20 R	N/A	>0.99
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
Best-corrected VA-right eye	0.45±0.15	1.00±0.15	-3.064	0.011
Latency (ms)-right of the VEP	118.16±8.29	100.98±6.17	3.554	0.017
Amplitudes (uv)-right of the VEP	6.87±2.42	14.16±1.93	-6.643	0.009
Latency (ms)-left of the VEP	116.12±7.11	101.21±1.32	4.532	0.022
Amplitudes (uv)-left of the VEP	7.42±2.73	16.74±2.52	-5.732	0.012

Abbreviations: Independent t-tests comparing two groups (P < 0.05); HCs, healthy controls; N/A, not applicable; OF, orbital fractures; VA–visual acuity; VEP–visual evoked potential.

DC differences. The DC values in patients with OF were significantly higher in the Cerebelum_9_R and left Cerebelum_Crus2_L areas (Figure 1a, b and Table 2) than in HCs. Figure 2 presents the mean altered DC values between patients with OF and HCs.

Table 2
Brain areas with significant differences in DC between the OF and HC groups

Brain areas	MNI coordinates			BA	Number of voxels	T value
	X	Y	Z			
Patient > HC						
Cerebelum_9 R	-3	-24	-21	-	164	4.6322
Cerebelum_Crus2 L	-30	-78	-48	93	123	4.2018

Abbreviations: BA, Brodmann area; MB, monocular blindness; HC, healthy control; MNI, Montreal Neurological Institute; Cerebelum_9_R, right cerebellum 9 area; Cerebelum_Crus2_L, left cerebellar peduncles 2 area.

Receiver operating characteristic(ROC) curve. We hypothesized that OF and HC groups would have different DC values in distinct brain regions. In this 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. See Figure 3 for details.

Discussion

Orbit has a very complex and important anatomical structure, in addition, orbital fracture is often accompanied by traumatic injury of retina, optic nerve, Retrobulbar soft tissue and brain, which leads to eye movement disorder, diplopia and other complications. (28) Rs-fMRI is a new medical imaging technique that uses signals dependent on blood oxygen levels to monitor brain activity. In this study, Rs-fMRI was used to study the changes of potential brain functional network activity in patients with orbital fractures, and DC technology was applied to discuss the relationship between spontaneous brain activity and clinical characteristics in patients with orbital fractures(Table 3). (11,14,26) Orbital fractures are often caused by high-energy violence, which may lead to retinal and optic nerve damage, leading to visual function damage. (29,30)Visual electrophysiological examination can timely and objectively reflect the degree of retinal and optic nerve and visual impairment. Visual evoked potential (VEP) is the bioelectricity produced by the cerebral cortex when the retina is stimulated. When the optic nerve is injured by ocular trauma, the visual evoked potential shows a decrease in amplitude and a delayed peak. (31)In this study, the visual acuity of patients with orbital fracture decreased significantly, Amplitudes (uv) of the VEP decreased significantly, and Latency (ms) of the VEP increased significantly. In our study, we found that compared with the HCs, patients with OFs presented increased DC values in the Cerebellum_9_R and Cerebellum_Crus2_L. Cerebellum disorders may lead to abnormalities in afferent visual pathways(Table 4). (32)We speculate that the abnormal cerebellar DC value in patients with orbital fracture is related to the decrease of visual acuity. The cerebellum is located in the posterior cranial fossa, The cerebellum is divided into anterior, posterior, and pompous lobes via the primary and posterolateral fissure; (15,33) The cerebellum is involved in the regulation and coordination of body balance, voluntary movement, and muscle tension. More importantly, the cerebellum is also responsible for the accuracy of eye movements, ensuring visual acuity and clarity, the cerebellum can not only instantly and accurately regulate eye movement, but also play a role in long-term visual calibration. (15,16,18,34,35) The afferent pathway of the vestibular cerebellum comes mainly from the vestibular nucleus in the brain stem. The vestibular organ receives position information from the head and the whole body and integrates it in the vestibular cerebellum, controlling the vestibular nucleus and the pontine reticular structure, in addition to controlling trunk activity, vestibular cerebellum can also regulate the activity of extraocular muscles, Studies have shown that cerebellar injury can affect spatial and temporal visual attention. Studies have shown that the smooth eye tracking and fixation ability of patients with cerebellar injury are lower than those of normal controls.(15,16,34,36,37)and we found that cerebellar DC increased in patients with OFs (see spots 1 and 2 in figure 4). This suggests that there may be cerebellar functional abnormalities in patients with orbital fractures, and we think that abnormal cerebellar functional connections may be related to complications such as eye movement disorders or the decrease of visual acuity in orbital fractures. Analysis of the increased DC values in Cerebelum_Crus2_L The cerebellum has three pairs of cerebellar feet (upper, middle and lower). All cerebellar feet are closely related to eye movements. The middle cerebellar foot, starting from the bottom of the bridge, is in the outermost of the three pairs, and the middle cerebellar foot is located between the cerebellum and the pons. The stem is a bridging bundle composed of transverse fibers, and there are a small number of transverse fibers between the structure of the pontine network and the cerebellar cortex. The middle peduncle of the cerebellum collects the main afferent fibers of the cerebellum, which is composed of the white matter fibers of the contralateral pontine nucleus. This nucleus is a gray matter structure responsible for the closed-loop pathway between the cerebellum and the precentral / prefrontal cortex and controls the initiation, transmission and execution of movement. [18,19,38] Therefore, the clinical manifestations of cerebellar middle foot lesions usually include ipsilateral limb ataxia, nystagmus and vertigo. A foot injury in the middle of the cerebellum may lead to abnormal eye movement because the foot is an important channel for transmitting eye movement information. Injury to the middle part of the cerebellum may lead to abnormal eye movement, because the middle part of the cerebellum is an important channel for transmitting eye movement information. [18,19,39]Cerebelum_Crus2_ L region is part of the middle foot of the cerebellum. A previous study reported three patients with cerebellar middle foot hemangioma. All patients had abnormal eye movement and strong twisting nystagmus during vertical line of sight pursuit test. Unilateral cerebellar foot injury can lead to nystagmus during vertical line of sight tracking. [40,41,42]Our study shows that the DC value of cerebellar _ Crus2_L region in OFs patients is higher than that in HCS patients, indicating that the level of functional connectivity of cerebellar middle peduncle (also known as pontine arm) is higher, suggesting that the DC value of Cerebelum_Crus2_L area of OFs patients is higher than that of HCS patients, suggesting that the level of functional connectivity of cerebellar middle peduncle (also known as pontoon arm) is higher. Analysis of the increased DC values in Cerebelum_9_R The three important areas of cerebellar control of eye movement are ocular motor vermis (OMV) and caudal fastigial nuclei; ventral uvula and nodulus; flocculus and para flocculus, the neural network signal that encodes vertical line of sight tracking is transmitted to the Vestibular cerebellum through the middle foot of the cerebellum. [18,19,38] The right cerebellar area 9 (cerebelum_9_r) is a part of the posterior lobe of the cerebellum, which participates in the formation of the Vestibular cerebellum. Vestibulo-Ocular Reflex(OVR) can ensure a stable line of sight through eye movement opposite to the head movement, in our current study. [43] We found that the DC value of right cerebellar area 9 (cerebelum_9_r) was significantly increased in patients with OFs, suggesting that eye movement disorder in patients with OFs may be related to the compensatory mechanism of vestibular cerebellum disfunction. The precise mechanism of cerebellar regulation of eye movement is that the signals of eye motoneurons are transmitted to the flocculus of vestibular cerebellum through the cell population of paramedian tract (PMT), and retinal slip signals is transmitted to para flocculus through inferior olivary nucleus (ION). Vestibular nucleus participates in the above process as the afferent fibers of flocculus and para flocculus. There is a two-way fiber connection between the vestibular cerebellum and the vestibular nucleus. It receives projections from the vestibular nucleus, and its efferent fibers change through the vestibular nucleus, and then reach the motoneurons in the medial part of the anterior horn of the spinal cord through the vestibular spinal tract to control the activity of the muscles of the trunk and extremities. The vestibular nucleus sends nerve fibers to the cerebellum through the middle peduncle of the cerebellum. [44—48] The DC values of cerebellar peduncle region and cerebellar tonsillar region involved in the formation of vestibular cerebellum are significantly increased in patients with OFs. We think that orbital fracture may affect the process of precise regulation of eye movement in cerebellum, and lead to a decrease in visual acuity.

Table 3
DC Method Applied in Ophthalmologic and Neurogenic Diseases

	Author	Year	Disease
Ophthalmologic diseases	Cai F[14]	2015	Closure glaucoma
	Wang et al[20]	2017	Open globe injury
	Tan et al[21]	2017	Exotropia strabismus
	Huang et al[22]	2017	Late monocular blindness
	Liu et al [23]	2019	Exophthalmos of Primary Hyperthyroidism
	Zhang et al[24]	2020	Ophthalmectomy
Neurogenic diseases	Zhu et al[25]	2017	Trigeminal neuralgia
	Wang et al[26]	2019	Diabetic nephropathy and Retinopathy
	Wu et al[27]	2020	Diabetic optic neuropathy

Table 4
Brain areas of altered DC values and its potential effects

Brain areas	Experimental result	Brain function	Anticipated results
Cerebelum_9_R	OF>HCs	Physical balance, muscular tension, motor coordination	Behavioral disorders
Cerebelum_Crus2_L	OF<HCs	Connecting structure, associated with eye movement	Visual impairment
Abbreviations: Cerebelum_9_R area, right cerebellum 9 area; Cerebelum_Crus2_L, left cerebellar peduncles 2 area; OF, orbital fractures; HCs, healthy controls.			

Conclusion

To sum up, this study shows that, compared with the participants in the healthy control group, abnormal spontaneous activity occurs in the middle cerebellar peduncle and posterior cerebellar lobe of patients with orbital fracture, and the cerebellum is an important participant in the regulation of eye movement. the treatment of eye movement disturbance in this orbital fracture patient provides a new angle, in addition to paying attention to the injury of extraocular muscle and oculomotor nerve. Attention should also be paid to the brain tissue related to eye movement and visual acuity, we hoped that our results will be beneficial to the treatment of patients with orbital fractures.

Prospects And Limitations

The DC method is an effective way to monitor whole-brain activity, but it has limitations. First of all, there is no single variable. For example, the time courses of the disease and the physical conditions differed among patients and may have caused measuring errors. In addition, our sample size was relatively small and may have affected our DC results. Another study correcting these drawbacks and with accurate brain function activity examinations should confirm our results.

Declarations

The authors report having no conflicts of interest related to this work.

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Figures

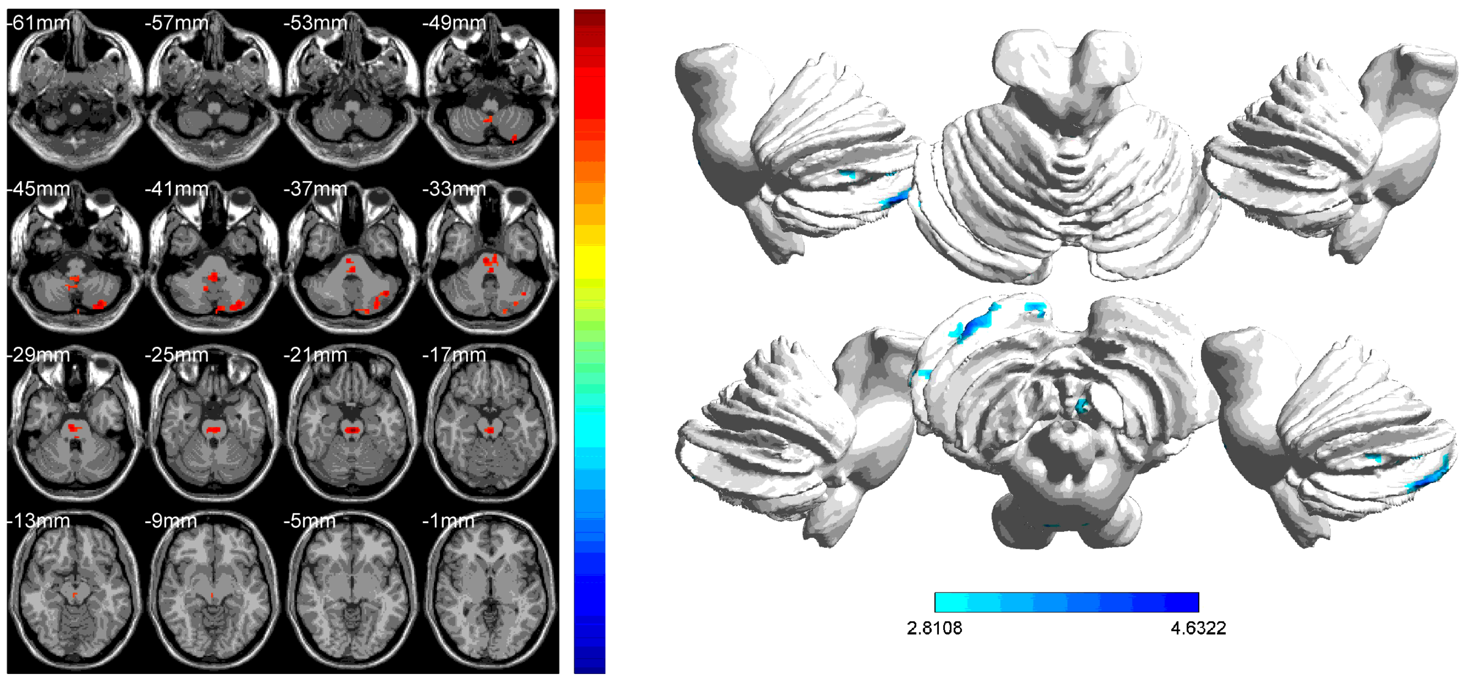

Figure 1

Voxel-wise Comparison of DC in the OF and HC groups a) Significant differences in DC values observed in Cerebelum_9_R and Cerebelum_Crus2_L areas. b) Stereoscopic form. The red areas denote higher DC values, and the blue denotes lower DC values. Abbreviations: DC, degree centrality; OF, orbital fracture; HC, healthy control; Cerebelum_9_R, right cerebellum 9 area; Cerebelum_Crus2_L, left cerebellar peduncles 2 area.

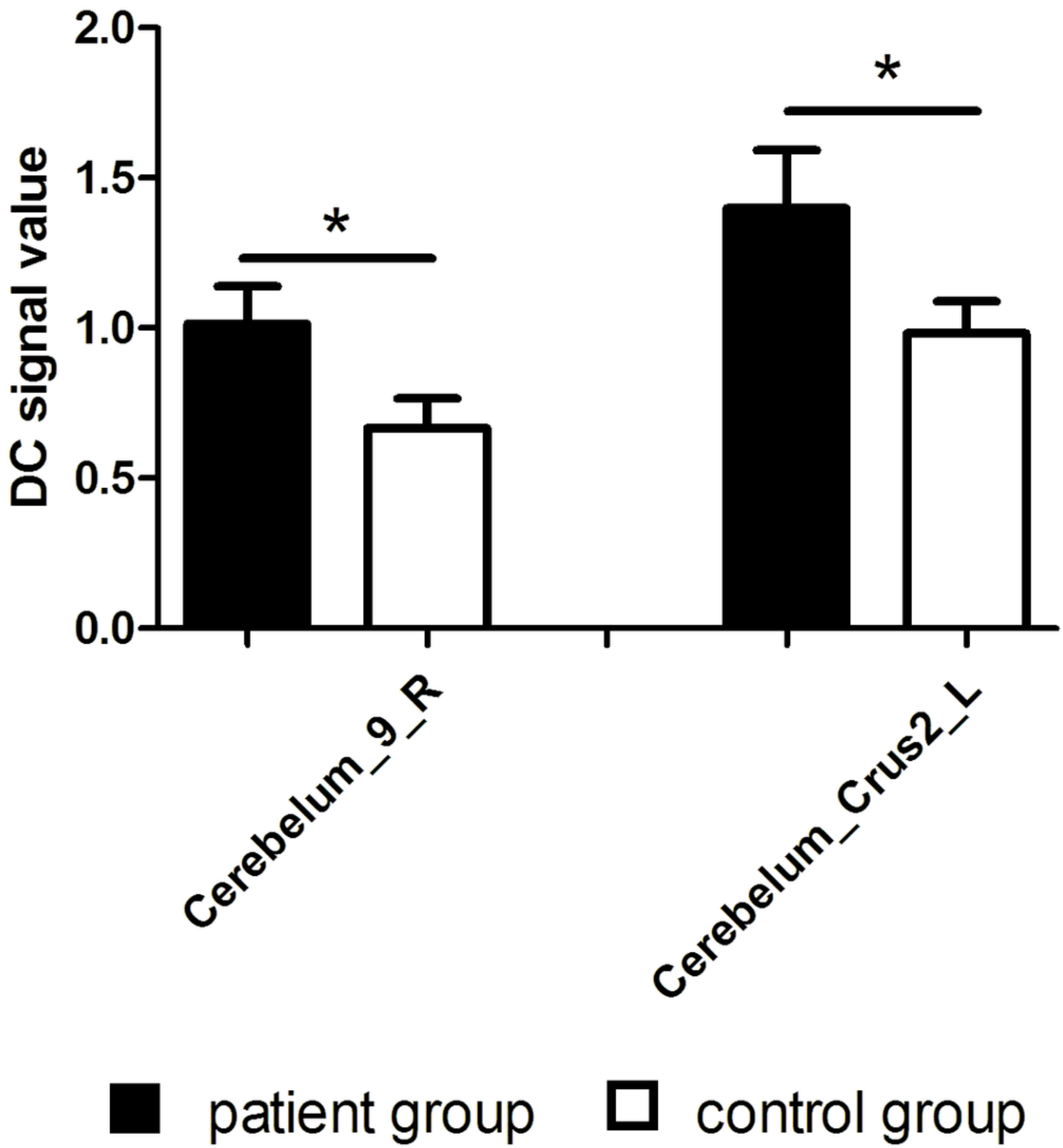

Figure 2

Mean altered DC values in the OF and HC groups “ * ” refers to P < 0.05 Abbreviations: DC, degree centrality; Cerebelum_9_R, right cerebellum 9 area; Cerebelum_Crus2_L, left cerebellar peduncles 2 area.

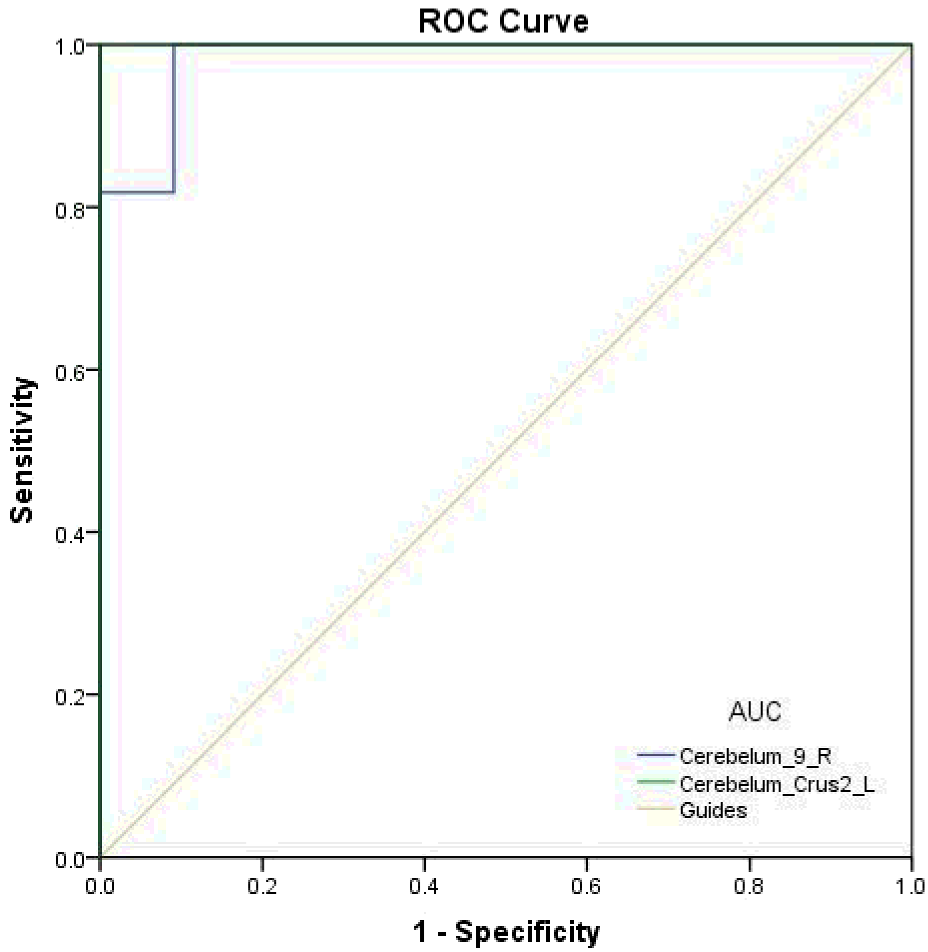

Figure 3

ROC curve analysis of the mean DC values for altered brain areas The area under the ROC curves were 0.983, (p<0.0001; 95% CI, 0.941-1.000) for the Cerebelum_9_R area and 1.000 for the Cerebelum_Crus2_L area (p<0.0001; 95% CI, 1.000-1.000). Abbreviations: AUC, area under the curve; ROC, receiver operating characteristic.

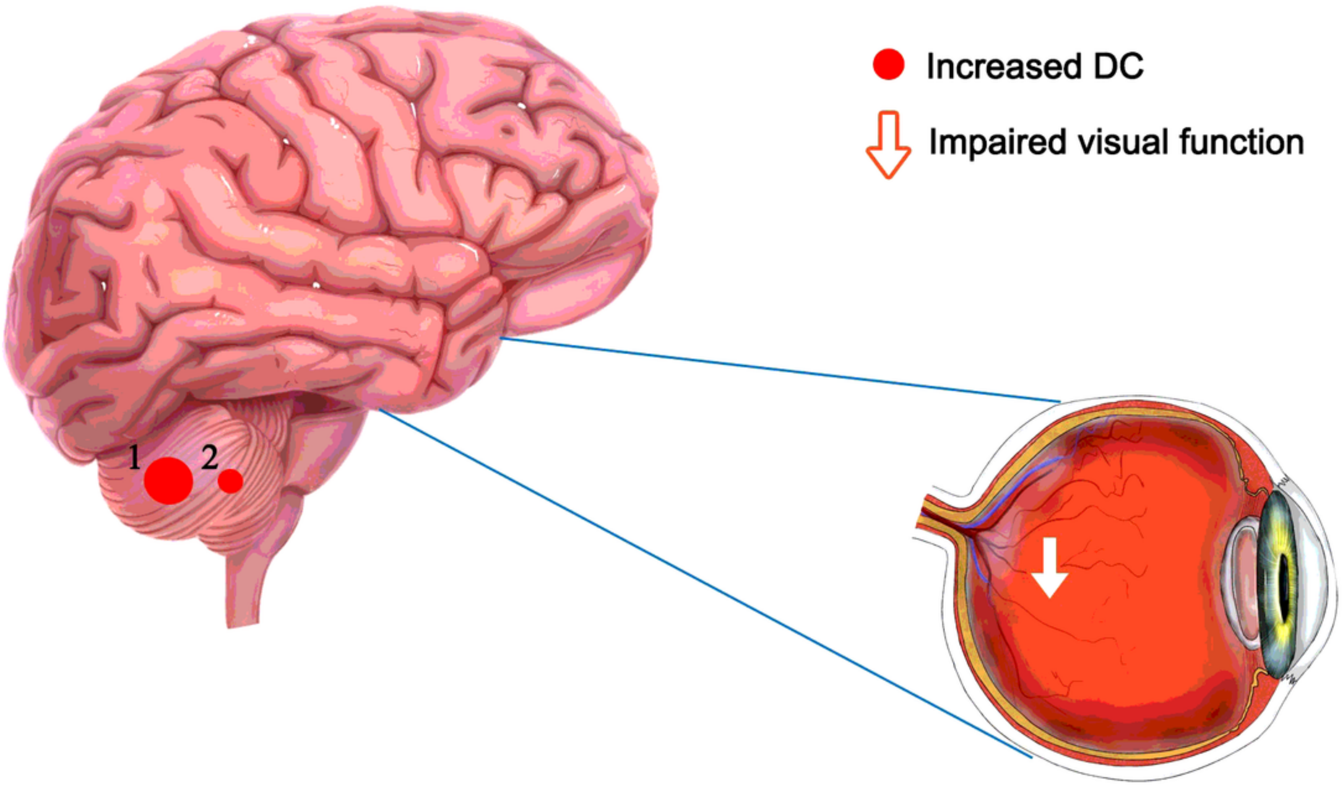

Figure 4

Mean DC values of altered brain areas The DC values of the following areas were increased to various extents in patients with OF compared with those in HCs: 1-Cerebelum_9_R area (t = 4.6322), 2-Cerebelum_Crus2_L area (BA 93, t = 4.2018). Abbreviations: HCs, healthy controls; BA, Brodmann's area