Detection of Abnormal Spontaneous Brain Activity Patterns in Patients with Orbital Fractures using Fractional Amplitude of Low Frequency Fluctuation

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Abstract

To date, no in-depth study has been conducted on the intrinsic pathological relationship between altered brain activity and related behavioral changes in patients with orbital fracture (OF).The present research aimed to explore the potential functional network cerebrum activities in patients with OF using resting state functional magnetic resonance imaging–fractional amplitude of low-frequency fluctuation (rsfMRI-fALFF). 20 patients with OF and 20 healthy controls (HCs) were included, closely matched in terms of gender, age, weight and education level. To record spontaneous cerebral activity changes, the rsfMRI-fALFF tool was applied. Receiver operating characteristic (ROC) curves and Pearson's correlation analysis were used to analyze mean fALFF values. The Hospital Depression and Anxiety scale was applied to reveal the relationship between emotional states and fALFF values of the right superior temporal gyrus in OF patients.Compared with HCs, significantly lower fALFF values were detected in the left anterior cingulate gyrus (LACG) and right superior temporal gyrus (RSTG) in patients with OF. The mean fALFF values of the RSTG negatively correlated with the depression score as well as anxiety score.The finding of abnormal spontaneous activities in cerebral regions may contribute to more comprehensive understanding of the potential neural network changes in patients with OF.

Introduction

The orbital bones are fragile with no protective surround, making them vulnerable to orbital wall fracture[1], of which trauma is the main cause. Previous research[2] has shown that about half of orbital fractures are isolated and are usually limited to one orbital wall, the orbital floor and medial wall being the most frequently occurring fracture sites[3]. Orbital fractures mostly occur in children and young people, and are more common in males than females[4, 5]. Chi et al. reviewed 733 cases of orbital fractures, among which three quarters were male[6]. Conservative treatment is often used for small orbital fractures without displacement[7], while for large displaced fractures surgical intervention is necessary[8, 9]. Orbital fractures may cause exophthalmos[10], enophthalmos[11], diplopia[12], entropion[13], subconjunctival hemorrhage[14] and even blindness[15]. Therefore, early monitoring and termination of adverse disease progression in patients with OF is very important.The use of modern imaging technology to study the brain activity of patients with OF may be important as a means by which to improve understanding of the mechanism of potential pathological changes in this condition, and may therefore be beneficial to the management of complications. Previous studies have confirmed that the changes of spontaneous brain activity in related brain regions can be used as an indicator of disease progression. Therefore, we try to explore the value of using modern imaging techniques to explore the value of spontaneous brain activity changes as a marker of disease progression in patients with orbital fractures.

Magnetic resonance imaging (MRI), as a widely used auxiliary imaging technology, was developed in the 1980s and provides us a preliminary understanding of the anatomical structure and operating mechanism of the brain [16, 17]. Hemodynamic changes caused by neuronal activity can be qualitatively measured with the help of MRI technology, known as functional magnetic resonance imaging (fMRI). This approach has been used in a variety of studies on the mechanism and effects of spontaneous neuronal activity in the brain, and has been helpful in exploring the pathophysiological changes and pathogenesis of various diseases[18, 19]. The fractional amplitude of low frequency fluctuation (fALFF), a resting state fMRI method,has provided an index for the evaluation of spontaneous neural activity, and its accuracy and sensitivity have been widely confirmed[16]. To our knowledge, the present experiment was the first attempt to explore the connection between spontaneous brain activity and behavioral performance in OF patients using the fALFF method as well as to explore the value of fALFF in evaluating the pathological changes and severity of OF.

Subjects And Methods

Subjects

In total, 20 patients with OF (12 males, 8 females) and 20 matched healthy controls (HCs) participated in this research. The relevant inclusion criteria were: 1) with optic nerve injury; 2) with diplopia; 3) with orbital collapse; 4) with limited eye movement; 5) with surgical treatment; 6) no other ocular diseases (such as macular degeneration); 7) no brain disease (such as cerebral infarction); 8) no history of mental illness; 9 no organic diseases likely to affect MRI examination.

The 20 HCs (12 male, 8 female) were highly similar to the OF group in sex, age, weight and education level. Our study met the ethical standards of the Medical Ethics Committee of the First Affiliated Hospital of Nanchang University as well as the principles of the Declaration of Helsinki. After materials, methods, purpose, and underlying risks of this experiment were explained, each participant signed a declaration of informed consents.

MRI parameters

MRI scanning was conducted using a Trio 3-Tesla MR scanner (Trio; Siemens, Munich, Berlin, Germany) in all participants. During the MRI scanning, other interference factors were excluded, and the subjects remained awake, breathing normally and with good vital signs. The whole-brainT1-weights were obtained with the application of the spoiled gradient-recalled echo sequence. Relevant corresponding parameter settings of structural images were as follows: echo time = 2.25 ms, repetition time = 1800 ms, field of view = 250 × 250 mm^2, layer interval = 0.5 mm, flip angle = 90°, matrix = 256 × 256, thickness = 1.0 mm. Functional images (n = 240) were captured with the following settings: echo time = 30 ms, repetition time = 2000 ms, field of view = 220 × 220 mm^2, flip angle = 90°, matrix = 64×64, thickness = 4.0 mm.

fMRI data processing

All data were pre-filtered using MRIcro (www.MRIcro.com) and then preprocessed the filtered datas using SPM8 (https://www.fil.ion.ucl.ac.uk/spm/). In pre-filtering, the first 10 volumes were regarded as invalid data and excluded to ensure steady signals. Volumes were offset by no more than 2 mm in X, Y, or Z directions. On the basis of the standard echo planar imaging template, images were resampled and normalized (with a standard setting of voxel size 3×3×3 mm, and were smoothed) to enhance signal-to-noise ratio. This method has been described in detail previously[20].

fALFF-analysis

To calculate fALFF, a full-width Gaussian kernel (half maximum = 6 × 6 × 6 mm^3) was used to smooth the remaining 230 images. Band-pass (0.01-0.08Hz) filtering was used to control for movement artefacts and low frequency drift. A fast Fourier transform (FFT) algorithm was used to obtain the signal power spectrum, and fAFLL was calculated as the ratio of the amplitude at each value in the low frequency band (0.01–0.08 Hz) to full-band (0–0.25 Hz) power amplitude.

Brain-behavior correlation analysis

To look for any associations between brain activity and behavioral performance, brain regions of interest were determine based on fALFF values, and Pearson's correlation analysis was used to explore the linear relationship between activities in these regions and clinical manifestations.

Statistical analysis

Using SPSS software version 20.0 (IBM Corp, Armonk, NY, USA), an independent sample t-test was conducted on the common clinical variables and demographic data of OF patients and HCs using a 5% significance level. A two-sample t-test was used to compare the functional data. Based on Gaussian random field theory, the statistical threshold of voxel level in multiple comparison was set at $p < 0.05$. Gaussian random field theory was used to determine the significance of the functional image at the 5% level with a cluster size > 40 voxels. Using the mean fALFF in various cerebral regions of HCs and patients with OF, the areas under the ROC curves (AUC) were obtained. In addition, Pearson correlation analysis was used to look for associations between the mean fALFF values in multiple cerebrum regions and characteristics of clinical behavior in OF patients.

Results

Demographics and Visual Measurements

No significant differences were found between groups in terms of gender ($P > 0.99$), weight ($P = 0.902$), or age (OF, 51.21 ± 11.42; HC, 50.96 ± 10.82; $P = 0.871$). However, best corrected monocular visual parameters were significantly different between groups, as follows: Visual acuities ($P = 0.017$ left and 0.011 right eye), visual evoked potential (VEP) latencies ($P = 0.022$ left and 0.017 right eye) and amplitudes ($P = 0.012$ left and 0.009 right eye). (Table 1)

Table 1
Basic Informations of participants in the study

Condition	OF	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	20R	20R	N/A	> 0.99
Duration of OF (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

Differences in fALFF

In comparison with HCs, patients with OF showed significant lower fALFF values in the left anterior cingulate gyrus (LACG) and right superior temporal gyrus (RSTG). (Fig. 1, Table 2). The mean fAFLL values are shown in Fig. 2.

Table 2
Brain areas with significant differences in fALFF between two groups.

Brain areas	MNI coordinates			BA	Number of voxels	T value
	X	Y	Z			
Patient < HC						
Cingulum_Ant_L	0	18	27	31	172	-4.6941
Temporal_Sup_R	45	-30	15	82	82	-4.399

Receiver operating characteristic (ROC) curves

ROC curves were used to visualize the comparison between average fALFF values of OF patients and HCs, and the areas under the curves (AUCs) were used as indicators of diagnostic accuracy. Using this approach, AUCs of the LATG and RSTG were found to be 0.983 and 1.000, respectively (Fig. 3).

Correlation analysis

In OF patients, significant correlations were found between fALFF values in the RSTG and depression scores (negative correlation: $r = -0.955$, $p < 0.01$) and anxiety scores (negative correlation: $r = -0.899$, $p < 0.01$) (Fig. 4).

Discussion

To our knowledge, the ALFF method has not previously been used to study the potential relationship between brain activity changes and clinical manifestations in patients with OF. This study aimed to explore the cerebral neural changes after orbital fracture uing the fALFF technique (Fig. 5). The study found significantly lower fALFF values in the LACG and the RSTG in OF patients (Fig. 6). In previous studies, the fALFF method has been applied to a series of ophthalmological diseases, including normal-tension glaucoma[20], monocular blindness[21], retinal vein occlusion[22], diabetic retinopathy and nephropathy[23] (Table 3), demonstrating its potential for clinical application.

The anterior cingulate gyrus (ACG) is a functional area associated with many physiological functions, is located in the medial brain and passes longitudinally through the parietal lobe, and its main roles are in memory[24], action– outcome learning[25–27], emotion and reward-related processing[28]. The research of Hornak et al.[29] showed that in some cases, the ACG plays an important part in voice and facial expression recognition, while Lane et al.[30–32] studied anterior cingulate injury in subjective emotional experience, and found that ventral ACG and Brodmann's area 9 may be activated during mood fluctuations. Based on the functions of the anterior cingulate gyrus, some researchers have explored its diagnostic value in Parkinson's disease[33], depression[34] and acute and chronic pain[35]. In addition, a previous study found that the prefrontal cingulate gyrus can respond to visual stimuli[36]. In the present study, given the reduced visual responses in patients with OF, the results may indicate a compensatory mechanism for vision loss in patients with OF.

The superior temporal gyrus (STG) is a functional area of the brain located in the temporal lobe, closely related to emotional and speech processing[37, 38]. The STG is a component of the default mode network, which is inhibited during brain activity and excited during rest. Liu et al.[39] used the rsMRI-fALFF method to study the STG in depression. They found that lower the fALFF values of STG correlatedgreater reductions on the Hamilton rating scale for depression, and inferred that STG neural changes were closely related to the effect of early treatment for depression. In addition, Wang et al.[40] measured functional connectivity density in STG and found that abnormal connectivity is negatively correlated with the treatment effect. In the present experiment, the fALFF value of the right STG in OF patients was significantly lower than that in healthy controls, and we speculate that this decrease may be a compensatory mechanism for the recovery of brain function in patients with OF. The results suggest that the fALFF value may be used as a reliable index to gauge therapeutic effects of clinical treatment. Moreover, it was discovered that in the patients with OF, fALFF values in the RSTG were negatively correlated with anxiety and depression scores, which may indicate a self-regulation mechanism in this brain area, with brain function being temporarily inhibited.(Table 4)

Table 3

ALFF method applied in ophthalmological diseases

Author	Year	Disease	Brain areas	
			Increased fALFF values	Decreased fALFF values
Li HL, et al.(20)	2020	normal-tension glaucoma	_	RAG, RACL
Fang JW, et al. (21)	2020	monocular blindness	LP, RPI, LPI	LCA
Tong Y, et al. (22)	2020	retinal vein occlusion	LC, RC, RB, LI	RC, RT
Wang R, et al. (23)	2021	primary angle-closure glaucoma	BSFG	LC, LMTG RMTG, RPG

Abbreviations: fALFF, fractional amplitude of low-frequency fluctuation; RAG, right angular gyrus; LP, left precuneus; LMTG, left middle temporal gyrus; LCA, left anterior cingulate; RPI, right inferior parietal lobe; LPI, left inferior parietal lobe; RMTG, right middle temporal gyrus; LC, left cerebellum; RC, right cerebellum; RB, right brainstem; RC, right calcarinesulcus; BSFG, bilateral superior frontal gyrus; LIG, left lingual gyrus; RPG, right precentral gyrus; RT, right thalamus; LI, left insula; RACL, right anterior cuneiform lobe.

Table 4

Brain areas of altered fALFF values and its potential effects.

Brain regions	Experimental result	Brain function	Anticipated results
Cingulum_Ant_L	OF＜HCs	Memory, action–outcome learning, emotion and reward-related processing	Behavioral disorders, memory impairment, depression,
Temporal_Sup_R	OF＜HCs	Emotional and speech processing, curative effect index	Mental disorders, speech disorder, reflecting treatment effect

Abbreviations: Cingulum_Ant_L, left anterior cingulate cortex; Temporal_Sup_R, right superior temporal gyrus; OF, orbital fractures; HCs, healthy controls.

This study has some limitations, one of which is the relatively small sample size and the other is that the sample source was limited and not completely matched. Therefore, future research should use larger and more closely matched samples to further clarify the neural changes in patients with orbital fractures, and to provide a more intuitive clinical efficacy index for treatment. In conclusion, this study has demonstrated that patients with OF have reduced fALFF values in specific cerebrum areas, indicating changes in spontaneous brain activity. Further research on the mechanism underpinning brain activity changes in patients with OF may be helpful to advance understanding of this condition.

Declarations

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Author contributions

M.C. was responsible for the formulation and evaluation of the experimental scheme, R.H. was responsible for the writing of the manuscript, Q.G. was responsible for recruiting and screening experimental subjects, L.Z. and H.S. were responsible for preparing experimental materials and executing the experiment, Y.P. , R.L. and Q.L. were responsible for data analysis and collation. S.Y. was responsible for the revision of the paper.

Competing interests

The authors declare no competing interests.

Additional information

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Figures

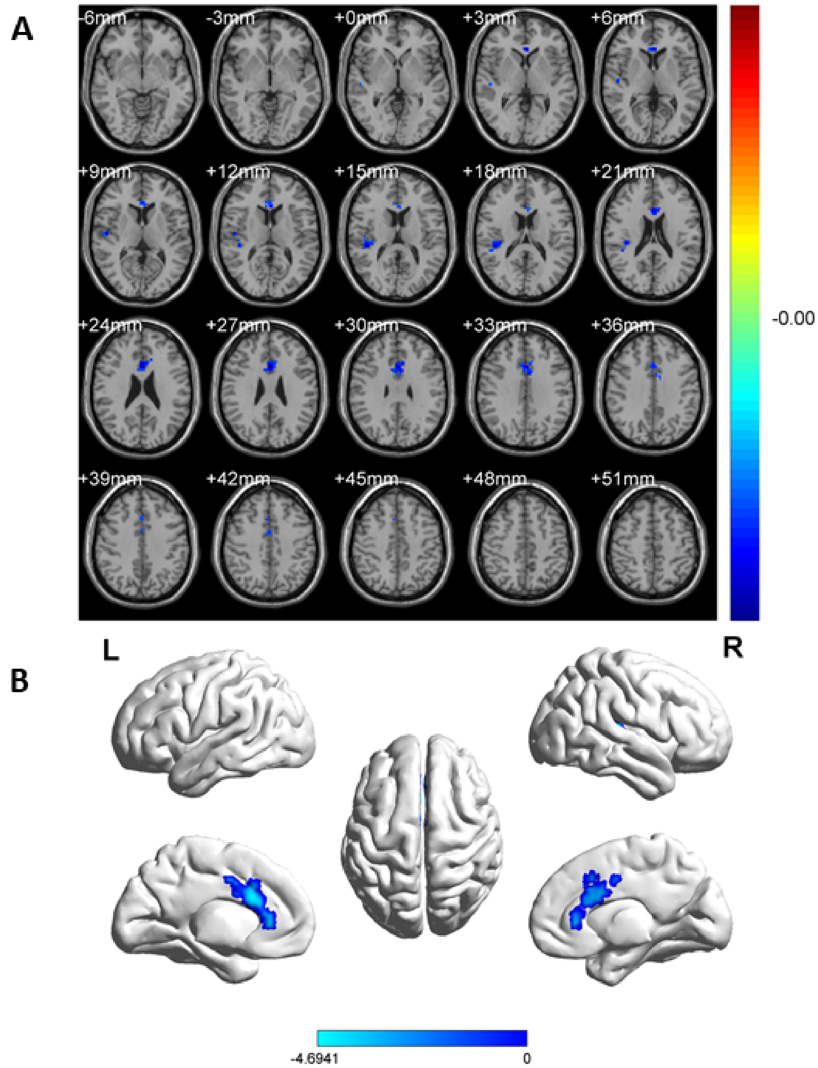

Figure 1

Spontaneous brain activities of OF and healthy controls (A) Different fALFF areas in patients with OF. (B) The blue areas represented lower fALFF values. Abbreviations: L, left; R, right.

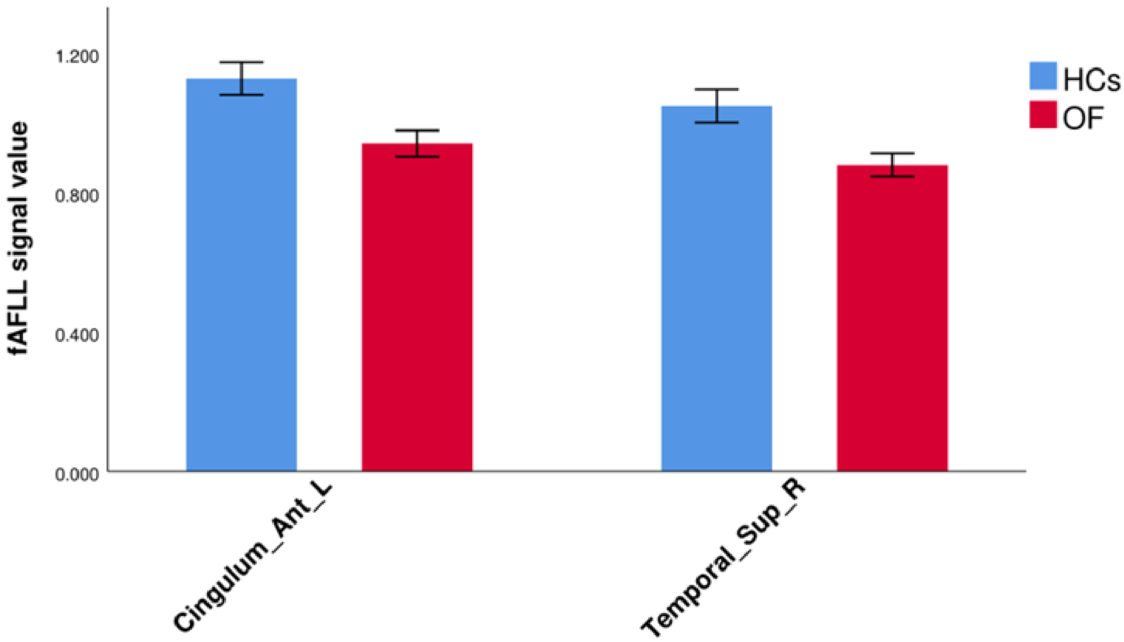

Figure 2

The average fALFF values in OF and HC groups. Abbreviations: Cingulum_Ant_L: left anterior cingulate gyrus; Temporal_Sup_R: right superior temporal gyrus; fALFF:fractional amplitude of low-frequency fluctuation; OF: orbital fractures; HC:healthy control.

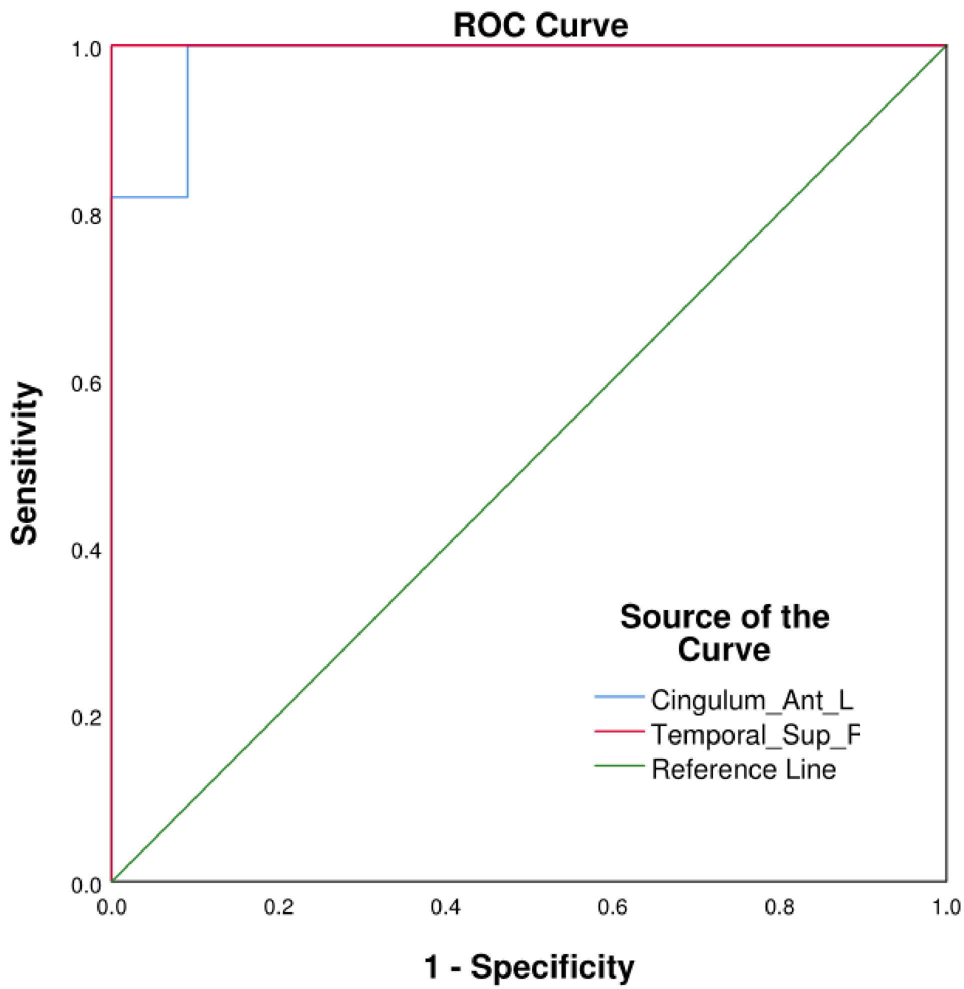

Figure 3

ROC curve analysis of the average fALFF values in different cerebrum areas. AUCs: Cingulum_Ant_L: 0.983, Temporal_Sup_R: 1.000 Abbreviations: Cingulum_Ant_L: left anterior cingulate gyrus; Temporal_Sup_R: right superior temporal gyrus; AUC, area under the curve; ROC, receiver operating characteristic.

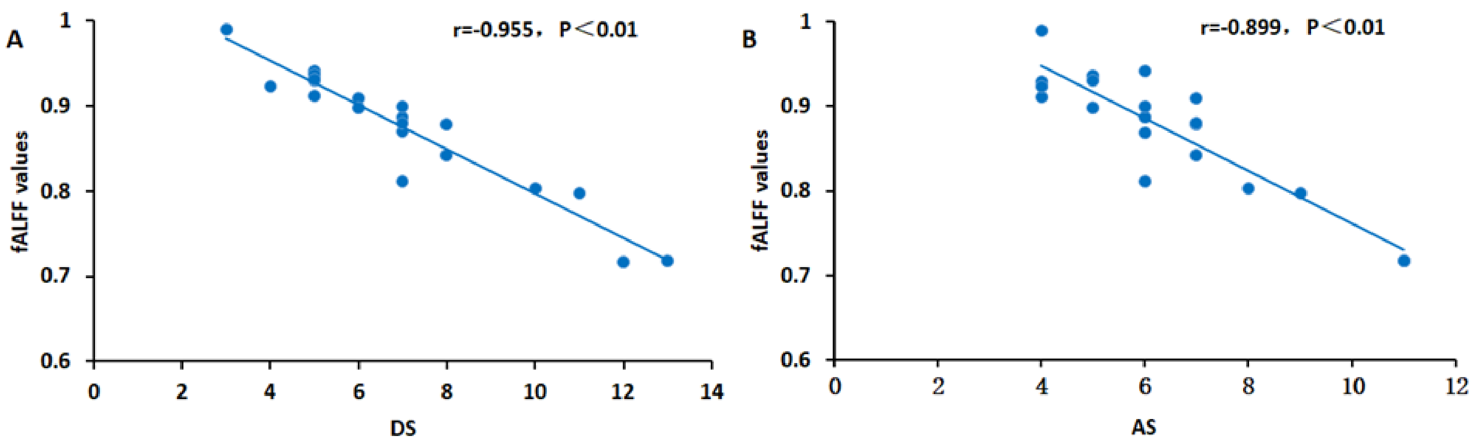

Figure 4

Correlations between the average fALFF values and clinical characteristics in the RSTG. In the RSTG, the DS (r=-0.955,P< 0.01) (A) and AS (r =-0.899, p < 0.01)（B）are both represented a negative relationship with the fALFF values. Abbreviations: fALFF , fractional amplitude of low-frequency fluctuation; DS, depression score; AS, anxiety score; RSTG: right superior temporal gyrus.

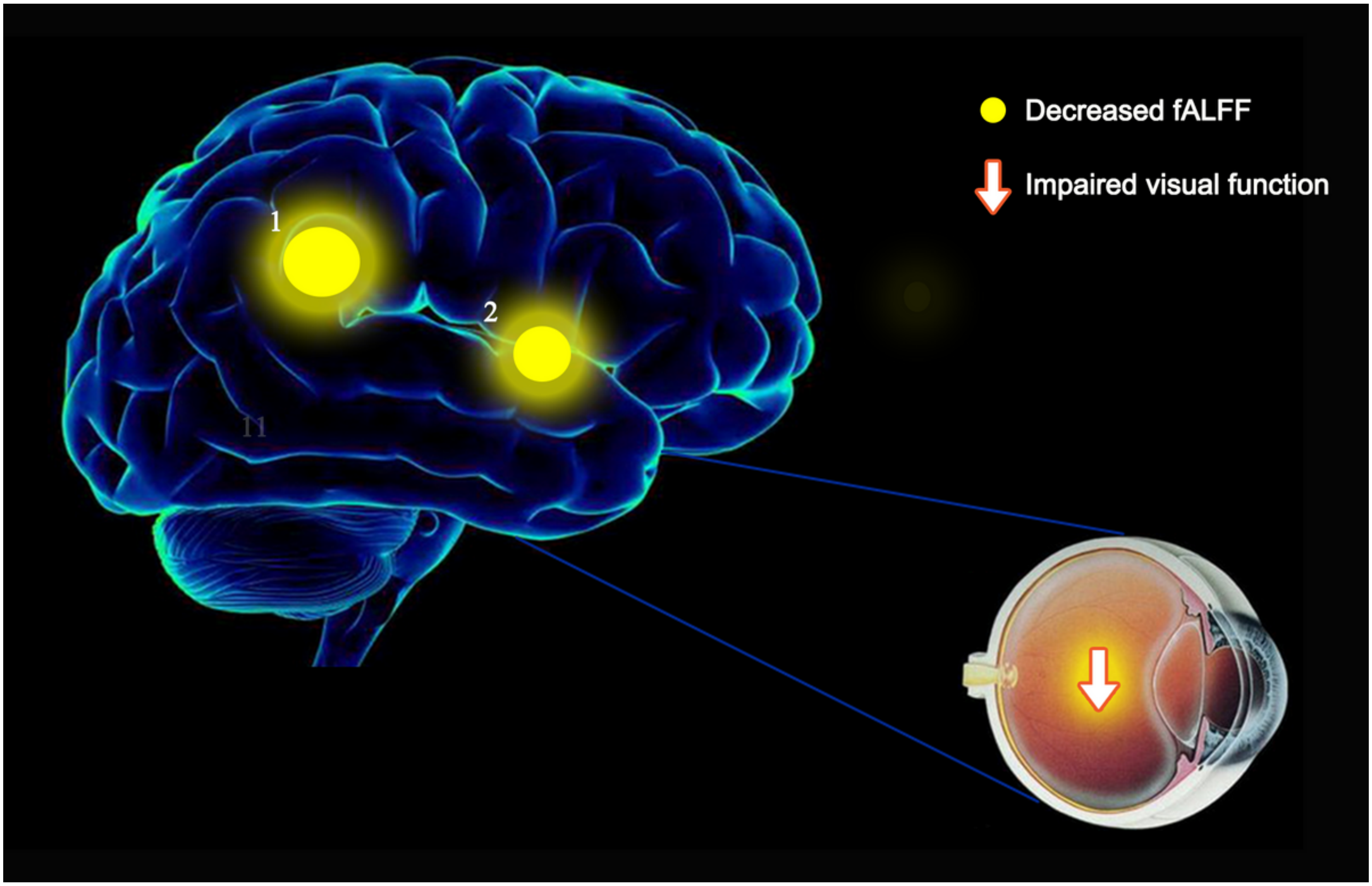

Figure 5

The correlations between average fALFF signal values and clinical manifestation of patients with OF. The OF patients have lower fALFF values and they are more likely to develop depressive symptoms. OF, orbital fractures.

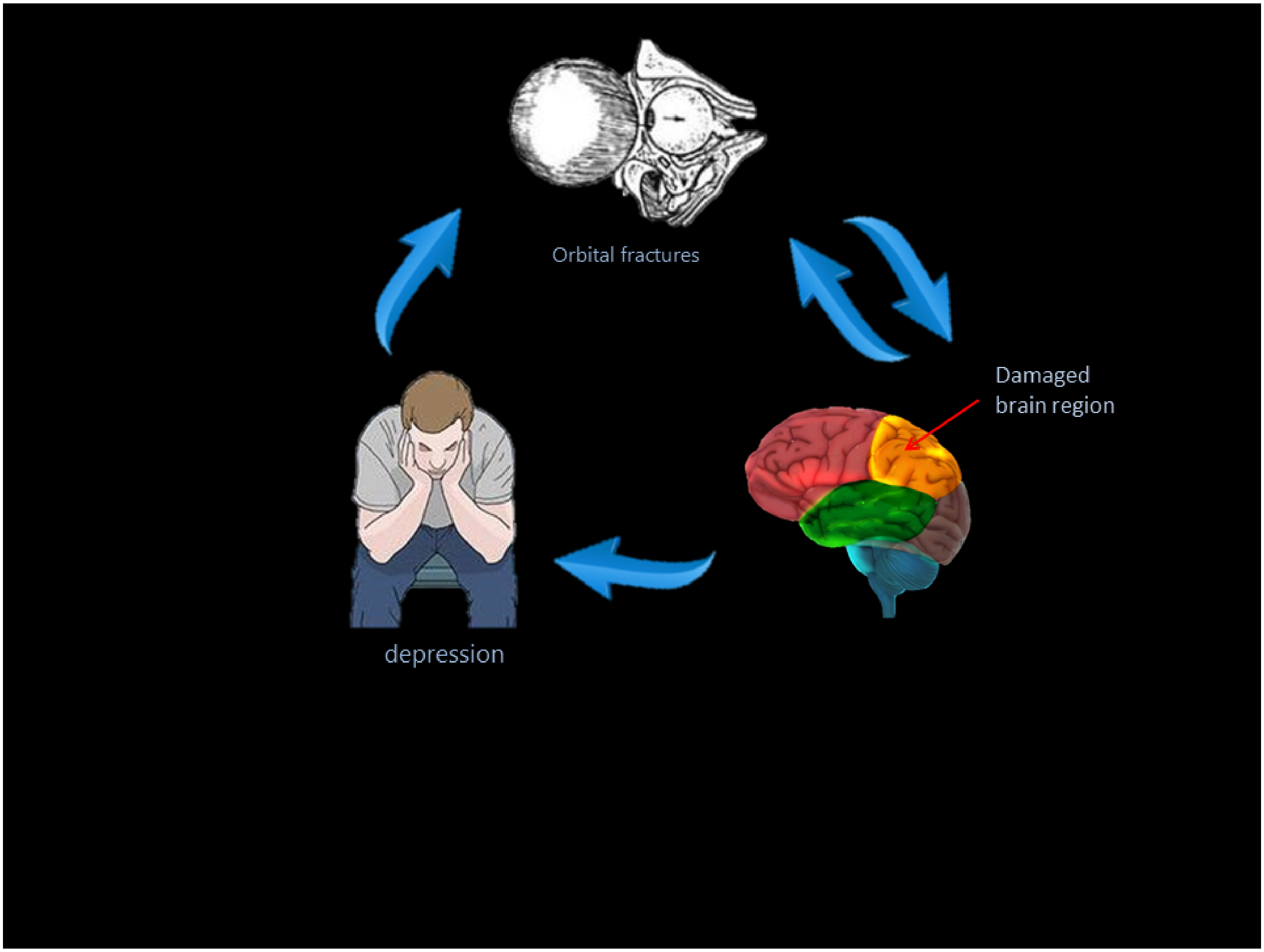

Figure 6

fALFF results of cerebral activity in OF group The fALFF values of the cerebral areas in OF group were in the following: 1- left anterior cingulate gyrus (t=-4.6941), 2- right superior temporal gyrus (t=-4.399). The intensity as well as the frequency of brain activity is reflected by the size of spots.