

Resting State Functional Magnetic Resonance Study Based on Amplitude of Low-Frequency Fluctuation in Patients with Acute Angle-Closure Glaucoma

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Abstract

Objective: To investigate the altered brain spontaneous activity in acute angle-closure glaucoma (AACG) using resting-state amplitude of low-frequency fluctuation (ALFF).

Methods: Eighteen AACG patients and eighteen age, gender-matched healthy controls (HC) were included in the rs-fMRI scans. Two sample t tests were performed to observe the ALFF changes between AACG and HC. The correlations between ALFF values and the ophthalmologic measurements were analyzed.

Results Compared with HC AACG patients showed decreased ALFF in the right lingual gyrus, right supra marginal gyrus, left precuneus, left medial superior frontal gyrus, left inferior parietal gyrus, left middle frontal gyrus. Meanwhile AACG patients showed increased ALFF in the right lobule crus2 of cerebellar hemisphere, left V1, right cuneus. In this study, no correlation between brain regions with abnormal ALFF value and intraocular pressure was found.

Conclusion: AACG patients have abnormal brain spontaneous activity in the visual, sensual, motional and emotional areas, which provides a new insight into the neuropathological mechanism and treatment of AACG.

1. Introduction

Glaucoma is a group of disease characterized by retinal ganglion cells apoptosis and progressive loss of optic axons [1]. It is the leading cause of blindness [2]. Glaucoma is classified on the basis of the morphology of the anterior chamber angle as primary open angle glaucoma (POAG) or primary angle-closure glaucoma (PACG). The prevalence of PACG was approximately double that of POAG in adult Chinese [3]. Among them, acute angle-closure glaucoma (AACG) occupies a large proportion in PACG [4]. AACG is characterized by a sudden onset of severe blurring followed by excruciating pain, halos, and nausea and vomiting [5]. Examination revealed obvious increase of intraocular pressure, shallow anterior chamber, corneal edema, moderately dilated pupil and other characteristics [6]. However, patients are often mistaken for acute gastrointestinal diseases, leading to delayed treatment, So it's very important for AACG patients to correct diagnosis and assessment their condition properly.

In recent years, glaucoma is considered to be a group of neurodegenerative diseases similar to Alzheimer's disease and Parkinson's disease [7, 8]. Blood oxygen level dependent-functional magnetic resonance imaging (BOLD-fMRI), which is widely used in various neurodegenerative diseases is also appropriate for exploring the mechanism of AACG [9]. Amplitude of low frequency fluctuation (ALFF) is the most widely used method of rs-fMRI [10, 11]. ALFF study detected changes in low-frequency oxygen signals in the resting brain, it reflects the activity intensity of autonomic nerves in brain regions [12, 13]. In this study, based on rs-fMRI, BOLD imaging technology was used to study the spontaneous neuron activity in the brain of AACG patients by using ALFF analysis method.

2. Materials And Methods

2.1 Subjects

All subjects participated voluntarily and were informed of the purpose, methods, and the potential risks; All subjects signed informed consent.

Eighteen AACG patients and 18 gender and age-matched healthy volunteers were enrolled in the study. AACG patients were recruited at the Second Affiliated Hospital of Shandong First Medical University and Taian City Central Hospital. The mean age of the AACG group was (68 ± 8.88) and that of the healthy control group was (66.11 ± 10.36).

Inclusion criteria for the AACG group were as follows: (1) history of acute attack, (2) both eyes were found shallow anterior chamber and narrow corner signs by gonioscope and slit lamp, (3) at least one of the eye suffered from elevated IOP (larger than 21 mmHg), (4) varying degrees of optic disc depression, (5) varying degrees of visual field defects. Exclusion criteria were: (1) secondary glaucoma, angle-opening glaucoma, chronic angle-closing glaucoma and other eye diseases that may affect visual pathway, (2) patients with glaucoma after surgery, (3) hypertension, impaired glucose tolerance, diabetes or other metabolic disease according to clinical record, (4) history of psychiatric or neurological illnesses, (5) MRI contraindications such as heart pacemaker, metal denture.

Inclusion criteria for normal control group: (1) naked eye or corrected visual acuity > 1.0 , (2) gender, age and education level were consistent with the AACG group, (3) no neurological or eye diseases, (4) no MRI contraindications: such as pacemaker, metal denture, etc.

2.2 Data acquisition

2.2.1 MRI

Magnetic resonance imaging data were acquired using a 3.0T MR scanner (Siemens Magnetom Skyra 3.0T). Subjects were scanned in the supine position. The patients were instructed to stay awake during the scan, the operation was completed by the radiologist and the subjects were closely observed until the scan was completed successfully. Conventional T1W1 were conducted using the following parameters: repetition time (TR)/ echo time (TE)/ inversion time (TI) = 2300 / 2.29 / 900 ms, field of view (FOV) = 240 mm \times 240 mm, slice thickness = 1 mm, slice gap = 0 mm, matrix = 256 \times 256, number of signal averages (NEX) = 1, flip angle = 8°, bandwidth = 123.36 Hz.

Echo planar imaging (EPI) sequence was used to obtain fMRI with the following parameters: TR/ TE = 2000/30 msec, FOV = 240 mm \times 240 mm, matrix = 64 \times 64, slice number = 33, slice thickness = 3 mm, slice gap = 1 mm, flip angle = 90°, scan duration time = 480s (240 volume).

2.2.2 Data processing

In order to reduce the influence of machine instability and subject's acclimatization, the first 10 time points of rs-fMRI data were eliminated. The preprocessing of the remaining 230 points were as follows : (1) DICOM format of the functional images was converted to NIFTI format .(2) Slice timing. (3) Head motion correction, realigned. (4) All the tested data was then normalized to Montreal Neurological Institute (MNI) space. (5) Linear trends were removed. (6) Nuisance covariates such as head motion parameters, whole brain, white matter and cerebro-spinal fluid signal were removed by regression approach.

The functional images were preprocessed using Statistical Parametric Mapping (SPM8) and the toolbox for Data Processing and Analysis for Brain Imaging (DPABI) software implemented in Matrix Laboratory platform (MATLAB 2013b).

2.2.3 ALFF calculation

The ALFF calculation was as follows: power spectrum of a given voxel was obtained by converting the time sequence of a given voxel into the frequency domain by fast Fourier transform, and then the square root of the power spectrum was calculated, the square root was averaged in the frequency range from 0.01 to 0.1 HZ, the square root value of the averaged power spectrum was called the voxel ALFF value.

2.4 Statistical analysis

Two sample t-test was used to compare ALFF values in the whole brain between AACG group and HC. When p value is less than 0.05, the difference is considered to be statistically significant. The correlation between ALFF values in different brain areas and clinical data of patients with AACG was analyzed by Pearson's correlation analysis.

3. Results

3.1 Demographic and clinical measures

There was no statistical significance in age between AACG group and HC group ($P = 0.593 > 0.05$). The IOP of the left eyes were 39.72 ± 14.04 mmHg and the IOP of the right eyes were 15.94 ± 2.53 mmHg for AACG patients. For HC, the IOP of the left eyes were 15.94 ± 2.53 mmHg and the IOP of the right eyes were 15.00 ± 2.72 mmHg. The difference of between the two groups was statistically significant ($P < 0.05$, as shown in the Table 1).

Table 1
Comparison of clinical data between AACG group and HC group

	AACG	HC	p-value
Age (years old)	68 ± 8.88	66.11 ± 10.36	0.593
Sex (M / F)	9/ 9	7 / 11	0.468
IOP_L (mmHg)	39.72 ± 14.04	15.94 ± 2.53	< 0.001
IOP_R (mmHg)	15.94 ± 2.53	15.00 ± 2.72	0.033

3.2ALFF and brain regions

Compared with HCs, the right lingual gyrus, right supra marginal gyrus, left precuneus (BA7), left medial superior frontal gyrus, left inferior parietal gyrus and left middle frontal gyrus showed decreased ALFF in AACG patients, meanwhile, the right lobule crus2 of cerebellar hemisphere, left V1, right cuneus showed increased ALFF in AACG patients ($P < 0.05$, FDR corrected, extent threshold > 20 voxels, as shown in the Table 2 and Fig. 1).

Table 2

Two sample ALFF t-map between acute angle-closure glaucoma (AACG patients and healthy controls (HC) ($P < 0.05$, FDR corrected, extent threshold > 20 voxels).

Conditions	Brain region	BA	Cluster volume (mm ³)	MNI coordinates			Tvalue
				X	Y	Z	
AACG > HC	Cerebelum_Crus2_R	NA	567	12	-90	-33	4.4295
AACG > HC	left V1	17	1296	-24	-51	12	6.3407
AACG > HC	Cuneus_R	18	756	12	-75	24	5.3268
AACG < HC	Lingual_R	18	540	24	-93	-15	-4.9835
AACG < HC	SupraMarginal_R	48	1566	63	-18	24	-5.8647
AACG < HC	Precuneus_L	7	675	-12	-66	39	-6.0604
AACG < HC	Frontal_Sup_Medial_L	10	729	-6	66	30	-5.4403
AACG < HC	Parietal_Inf_L	2	1242	-57	-27	48	-6.4715
AACG < HC	Frontal_Mid_L	32	864	-12	12	48	-5.1307

BA: Brodmann Atlas, MNI: Montreal Neurological Institute, Cerebelum_Crus2: the lobule crus2 of cerebellar hemisphere, Precuneus: precuneus gyrus, Cuneus: cuneus gyrus, Lingual: lingual gyrus, SupraMarginal: supra marginal gyrus, Frontal_Sup_Medial: the medial superior frontal gyrus, Parietal_Inf_L: the inferior parietal gyrus, Frontal_Mid: the middle frontal gyrus, NA represents not applicable, L and R represent left and right.

In this study, no correlation between brain regions with abnormal ALFF value and intraocular pressure was found.

4. Discussion

AACG causes irreversible damage to the optic nerve by increasing intraocular pressure, numerous studies have shown that glaucoma not only causes visual nerve damage, but also affects visual pathways, including the optic tract, optic chiasma, lateral geniculate body, visual radiation, and visual cortex (V1) [14, 15, 16]. However, conventional MRI is of limited value in the diagnosis of optic nerve and can only show changes in optic nerve morphology [17]. fMR technology based on BOLD effect has been widely used in the study of human brain function[18]. In terms of AACG, little has been published regarding its effect on the whole brain.

Right lobule crus2 of cerebellar hemisphere, is located in the cerebellar inferior lobe, the cerebellum is often considered as a link to involve in the regulation of body movement and balance function[19]. Meanwhile, the cerebellum is also involved in cognitive and emotional processing[20], study has reported that even subtle abnormalities in cerebellar volume may have functional impact on cognition[21]. Sang et al. found that there was a functional connection between the cerebellar hemispheric crus2 and the fronto-parietal network, which is very important for visual memory, language, cognition and other aspects [22]. In this study, decreased ALFF values in right lobule crus2 of cerebellar hemisphere may be a result of reduced visual signals from the primary and higher visual cortex to the cerebellum, which may be related to increased intraocular pressure and decreased vision in AACG patients. This may be related to the functional connection between the cerebellar hemispheric crus2 and the fronto-parietal network. Of course, this also suggests that AACG patients have dysfunction in emotional cognition and pain regulation, which provides a pathological basis for the occurrence of negative emotions and pain in PACG patients .

(V1) BA17 is defined as primary visual cortex (primary visual cortex, PVC), which receives visual input from the retina. Glaucoma retinal injury results in decreased visual stimulation received by PVA, resulting in neurodegeneration of visual cortex in glaucoma patients [23]. In the present study, The increase of spontaneous neural activity in BA17 indicated that the function of primary visual cortex was impaired.

The precuneus is involved in the visuospatial imagery, episodic memory retrieval, self-processing, and consciousness [24, 25]. BA18 and BA19 are defined as higher visual cortices that receive input information from PVC. The PVC receives informations from the lateral geniculate nucleus and then sends it out through two distinct anatomical streams[26]. The former involves the parietal gyrus and responds to spatial information and motional orientation; the latter pathway extends into the temporal lobe and responds to color and shapes[27]. Precuneus (BA7) is part of parietal lobe, which belongs to the dorsal visual network pathway. Previous studies on functional imaging of glaucoma have also shown that the visual dorsal and ventral pathways of glaucoma patients show dysfunction in both task and resting states [28]. In this study, ALFF value of left precuneus (BA7) decreased. This result can be explained as the primary visual cortex and dorsal visual pathway damage caused by glaucoma, resulting in decreased visual information transmission, and then caused by glaucoma Changes in cortical structure and function occurred in the relevant brain regions.

Cuneus(BA18) belongs to the higher visual cortex, the increase of spontaneous neural activity in BA18 indicated that the function of higher visual cortices were impaired.

The fissura calcarina is the concentrated region of the primary visual cortex and is involved in the construction of visual field. The lingual gyrus is located below the fissura calcarina and is the site that receives the fibers of the lateral geniculate body. Jiang et al. found that brain regions showed a significant main effect for group included the right inferior occipital gyrus (Brodmann area [BA] 18) and right superior frontal gyrus (BA 10) [29]. Chen et al reported that POAG patients showed significant reduction of gray matter volumes in bilateral visual cortex using an optimized VBM analysis method [30]. Previous study have found that glaucomatous neuropathy from POAG may lead to decreased cortical activity in the visual cortex even in the visual field defined as the normal central area [16]. In this study, the decrease in spontaneous activity in the right lingual gyrus was consistent with previous studies. The pathophysiological change of glaucoma is the apoptosis of retinal ganglion cells, thus, we speculated that visual information is transmitted backward from the visual pathway, decreased retinal input and synaptic degeneration lead to visual network dysfunction.

The supra marginal gyrus is associated with language perception and processing [31]. The inferior parietal lobule (IPL) is the terminal of the dorsal stream, which plays an important role in the coordination of the visual-motor function and is a core component of the parieto-occipital pathway [29]. It participates in a wide spectrum of highly integrated tasks, such as oculomotor, visuospatial imagery [13]. Therefore, decrease spontaneous activity in the right supra marginal gyrus and the inferior parietal gyrus could reflect impaired visual function in the AACG group.

The frontal lobe area, known as the "frontal eye area". The frontal lobe is involved in optical positioning, eye rotation adjustment, fixing point determination and spatial information processing. It is an important area for eye movement tracking. The superior frontal gyrus is associated with language perception and processing, and with self-awareness [32]. A study found that the gray matter volume of the superior frontal gyrus was decreased in POAG patients [33]. Chen et al. found a significant decrease in the bilateral gray matter volume in the superior frontal gyrus, postcentral gyrus, Rolandic operculum, and inferior frontal gyrus, which may indicate abnormalities in the CNS other than the visual cortex. In this study [30]. The decrease of ALFF in the right medial superior frontal gyrus and the left Medial frontal gyrus in AACG group was consistent with previous studies, thus, our results suggest that AACG may cause dysfunction in the frontal network. In addition, abnormal frontal lobe function is one of the important characteristics of the development of depression [34]. George et al. [35] believed that the frontal lobe was closely related to emotional and memory processes, and some scholars believed [36] that various emotional disorders such as depression were related to frontal lobe dysfunction, changes in frontal lobe function may be related to depression in patients with acute angle-closure glaucoma. This abnormal activation of the frontal lobe may lead to an increased risk of depression in patients with acute angle-closure glaucoma.

In conclusion, this study found that patients with acute angle-closure glaucoma had abnormal ALFF in brain areas such as vision, sensorimotor and emotion. It provides a new idea for further research on the neuropathological mechanism and treatment of AACG.

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Figures

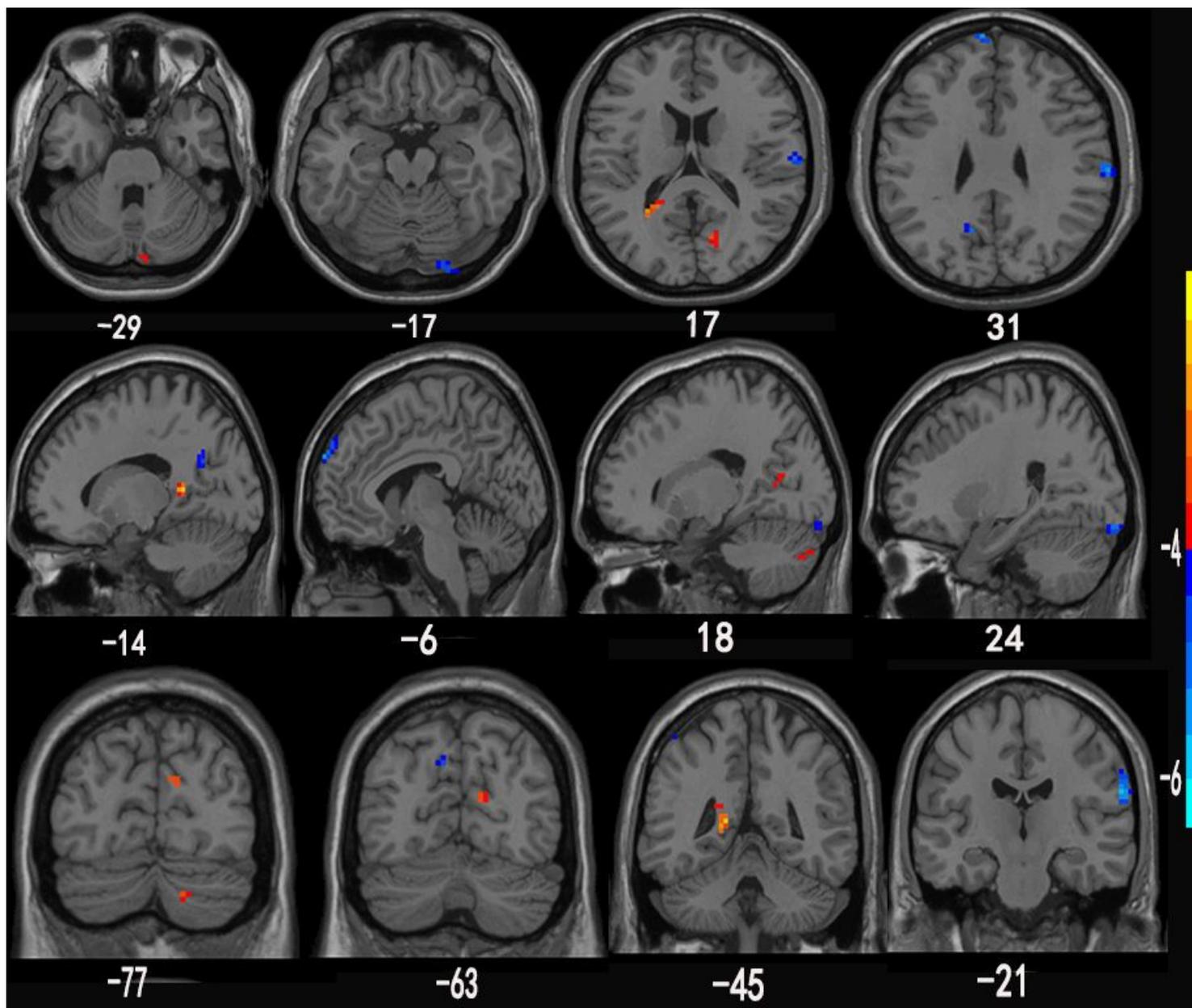


Figure 1

Regions showing significant ALFF differences between AACG patients and healthy controls at $p < 0.05$ (FDR corrected, $p < 0.05$, extent threshold > 20 voxels)