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Abnormal Fractional Amplitude of Low-Frequency Fluctuation Changes in Patients with Monocular Blindness: A Functional Magnetic Resonance Imaging (MRI) Study

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Background: We used fractional amplitude of low-frequency fluctuation (fALFF) technology to investigate spontaneous cerebral activity in patients with monocular blindness (MB) and in healthy controls (HCs).

Material/Methods: Thirty MB patient and 15 HCs were included in this study. All subjects were scanned by resting-state functional magnetic resonance imaging (rs-fMRI). The independent sample *t* test and chi-squared test were applied to analyze demographics of MB patients and HCs. The 2-sample *t* test and receiver operating characteristic (ROC) curves were applied to identify the difference in average fALFF values between MB patients and HCs. Pearson's correlation analysis was applied to explore the relationship between the average fALFF values of brain areas and clinical behavior in the MB group.

Results: MB patients had lower fALFF values in the left anterior cingulate and higher fALFF values in the left precuneus and right and left inferior parietal lobes than in HCs. Moreover, the mean fALFF values of MB patients in the left anterior cingulate had negative correlations with the anxiety scale score ($r=-0.825$, $P<0.001$) and the depression scale score ($r=-0.871$, $P<0.001$).

Conclusions: Our study found that MB patients had abnormal spontaneous activities in the visual and vision-related regions. The finding of abnormal neuronal activity helps to reveal the underlying neuropathologic mechanisms of vision loss.

MeSH Keywords: **Anxiety • Blindness • Depression • Magnetic Resonance Imaging**

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Background

Worldwide, there are estimated to be 285 million people with impaired vision; of these, 39 million are considered blind [1]. Blindness is related to several different diseases. If not be treated in a timely manner, it may result in permanently impaired vision and adversely affect patients' quality of life. Blindness has become a serious global social problem. The common causes of blindness include trachoma [2], glaucoma [3], cataracts [4], diabetic retinopathy [5] (DR), and age-related macular degeneration [6] (AMD). Monocular blindness (MB) is a severe ocular condition that affects patients of all age and can cause vision loss in 1 eye and visual interference in stereovision, field coverage, and exteroception of shape and color, thereby affecting the performance of visuomotor tasks [7]. Ocular trauma is the leading cause of MB worldwide [8]. MB is likely to develop into binocular blindness. The ideal treatment of irreversible blindness has been unclear. Determining the potential pathology leading to blindness is crucial to discover a cure for diseases leading to blindness [9].

The visual system is associated with transmission of visual signals, and destruction of the visual pathway can result in blindness. Therefore, it is important to explore whether the visual system of MB patients has substantial changes. Functional magnetic resonance imaging (fMRI), as an imaging technology, is commonly used to detect diseases of the brain and abnormal metabolism of the nerves [10]. The stimulation of neural activity can be a task-based neural response or spontaneous brain activity fluctuations in an unconscious state ("resting state"). fMRI has been used to assess neural activities in blind patients. Dormal et al. [11] used fMRI analysis to assess the effect of sound and external stimuli on the brain of patients with early blindness. Chan et al. [12] used blood-oxygenation-level-dependent (BOLD) fMRI to compare congenital versus acquired blindness to understand brain visual cortex activity and response during sensory replacement tasks and rest. Previous studies have shown that blindness can induce changes to the occipital cortex. The occipital cortex of early blind (EB) patients were thicker than those of normal people [13]. Furthermore, resting-state fMRI (rs-fMRI) showed the change of functional connectivity between visual cortex and cognitive control networks in EB patients [14]. The abovementioned studies were focused on brain network changes in blindness. However, the effect of MB on brain activities remains unknown.

Low-frequency oscillations (LFOs, typically in the 0.01–0.08 Hz frequency band) are linked to brain neuronal activity. rs-fMRI is considered a useful tool to study brain function to investigate brain development, aging, and diseases [15]. The brain exerts synchronous low-frequency fluctuations in particular areas when the brain is quiet without any form of activity such as cognitive or language actions [16]. The use of rs-fMRI

allows researchers to investigate functional connectivity in the brain based on low-frequency fluctuations in the BOLD signal [16]. Amplitude of low-frequency fluctuation (ALFF) is an rs-fMRI indicator of partial change resulting from cerebral activity [17]. ALFF is an effective tool; it is easy to calculate and reliably analyzes rs-fMRI data [18]. ALFF has been used to study neurological conditions, such as optic neuritis [19], Parkinson's disease [20], epilepsy [21], bipolar disorder [22], and schizophrenia [23]. ALFF also has been used widely in research on ocular diseases, such as MB [24], high myopia [25], glaucoma [26], optic neuritis [27], and diabetic retinopathy [28].

Fractional ALFF (fALFF) is a relatively new method to detect ALFF for rs-fMRI. The fALFF approach effectively restrains non-specific signals in rs-fMRI, which increases the sensitivity and specificity of studying neural activities [17]. In our research, rs-fMRI was used through the fALFF approach to assess regional spontaneous cerebral activity in MB patients and in sighted subjects.

Material and Methods

Subjects

This study included 30 MB patients (18 caused by ocular trauma, 12 caused by keratitis), and 15 healthy controls (HCs). All MB patients were enrolled from the Department of Ophthalmology, the First Affiliated Hospital of Nanchang University. The diagnostic criteria for MB patients were: 1) one eye with no light perception and 2) healthy other eye without any diseases such as glaucoma or cataracts. The exclusion criteria were patients with: 1) a history of eye surgery, 2) severe mental health conditions such as schizophrenia, bipolar disorder, or other complex nervous system diseases, or 3) those that had undergone a long therapeutic procedure for blindness.

The HCs were matched by sex and age with MB patients. The procedures of this research were approved by the First Affiliated Hospital of Nanchang University Ethics Committee. All participants were acquainted with the purposes, contents, and risks of the research, and signed the informed consent form.

MRI parameters

The MRI scans were performed using the same 3-Tesla MR scanner (Trio; Siemens, Munich, Germany). A three-dimensional metamorphic gradient echo pulse sequence was used to get the functional data. The following scanning parameters were used: repeat time=2,000 ms, echo time=40 ms, flip angle=90°, slice thickness/gap=4.0/1 mm, field of view=240×240 mm, and plane resolution=64×64. Overall, 30 axial slices covering the brain were recorded, and 240 functional images were finally obtained. The entire scanning process was completed in 8 min.

Table 1. Demographics and clinical measurements of MB and HC groups.

Condition	MB	NCs	t	P-value*
Male/Female	22/8	11/4	N/A	N/A
Age (years)	56.23±6.45	54.32±7.34	0.376	0.712
Weight (kg)	67.18±11.49	68.42±12.43	0.473	0.765
Handedness	30R	15R	N/A	N/A
Best-corrected VA, right	0.24±0.12	1.05±0.15	-4.524	0.008
Best-corrected VA, left	0.15±0.05	1.05±0.20	-4.174	0.006
Duration of MB (years)	1.05±0.45	N/A	N/A	N/A
IOP-L	13.73±4.32	15.24±4.32	0.275	0.748
IOP-R	13.36±5.05	16.71±3.88	0.294	0.783

Independent *t* tests comparing the two groups ($P < 0.05$ represented statistically significant differences). Data shown as mean standard deviation or n. HC – healthy control; L – left; MB – monocular blindness; N/A – not applicable; VA – visual acuity; R – right; IOP – intraocular pressure.

fMRI data analysis

MRICro software (<http://www.MRICro.com>) was used to classify functional data and eliminate incomplete data. The Statistical Parametric Mapping software (SPM8, <http://www.fil.ion.ucl.ac.uk/spm/>) was used, as indicated below, to pretreat fMRI images: 1) The first 10 time-points are removed to balance the signal, and then slice timing and motion correction were performed. For head motion parameters, it does not include more than 2 mm or rotation more than 1.5° during the process. 2) All realigned data were then spatially homogenized into a standard Montreal Institute of Neurology (MNI) EPI template and resampled to 3×3×3-mm cubes. 3) Covariates (6 head movement parameters, mean framewise displacement [FD], global brain signal, and the average signal from white matter signal and cerebrospinal fluid) were used for regression analysis. 4) Blunt trends were removed and filtered (0.01–0.08 Hz). Finally, the regression image is smoothed with a full width at half maximum (FWHM) of 6 mm to weaken spatial noise.

fALFF analysis

The fALFF value is calculated on the trend data by REST software. REST has a built-in fast Fourier transform function that converts time series data into the frequency domain and calculates the power spectrum. Using the ratio of each frequency in the low-frequency range (0.01–0.08 Hz) to the power in the whole frequency range (0–0.25 Hz), fALFF was obtained. Then, a band-pass filtering of 0.01–0.08 Hz was used to ensure that the influence of low-frequency drift and high-frequency physiological noise such as from heartbeats and the respiratory rhythm is small.

Statistical analysis

SPSS 17.0 (SPSS, IBM Corp, USA) was used to determine differences in clinical features by independent sample *t* test and chi-squared test. *P* values < 0.05 indicated statistically significant differences. The 2-sample *t* test and receiver operating characteristic (ROC) curves were applied to identify the difference in average fALFF values between MB patients and HCs. Pearson's correlation analysis was applied to explore the relationship between the average fALFF values of brain areas and clinical behavior in the MB group. For all statistical analyses, $P < 0.05$ indicated statistically significant differences.

Results

Demographics and visual measurements

There were no significant differences in age ($P = 0.721$), weight ($P = 0.765$), or intraocular pressure of 2 eyes ($P = 0.748$, $P = 0.783$, respectively) between MB patients and HCs. The differences in best-corrected VA – right ($P = 0.008$) and best-corrected VA – left ($P = 0.006$) between the 2 groups were significant. More information is shown in Table 1.

fALFF differences

MB patients had lower fALFF values in the left anterior cingulate and higher fALFF values in the left precuneus and right inferior parietal lobe and left inferior parietal lobes than in the HC group (Figure 1, Table 2). The result of the 2-sample *t* test revealed that the difference in mean fALFF values between MB patients and HCs was significant ($P < 0.001$) (Table 3).

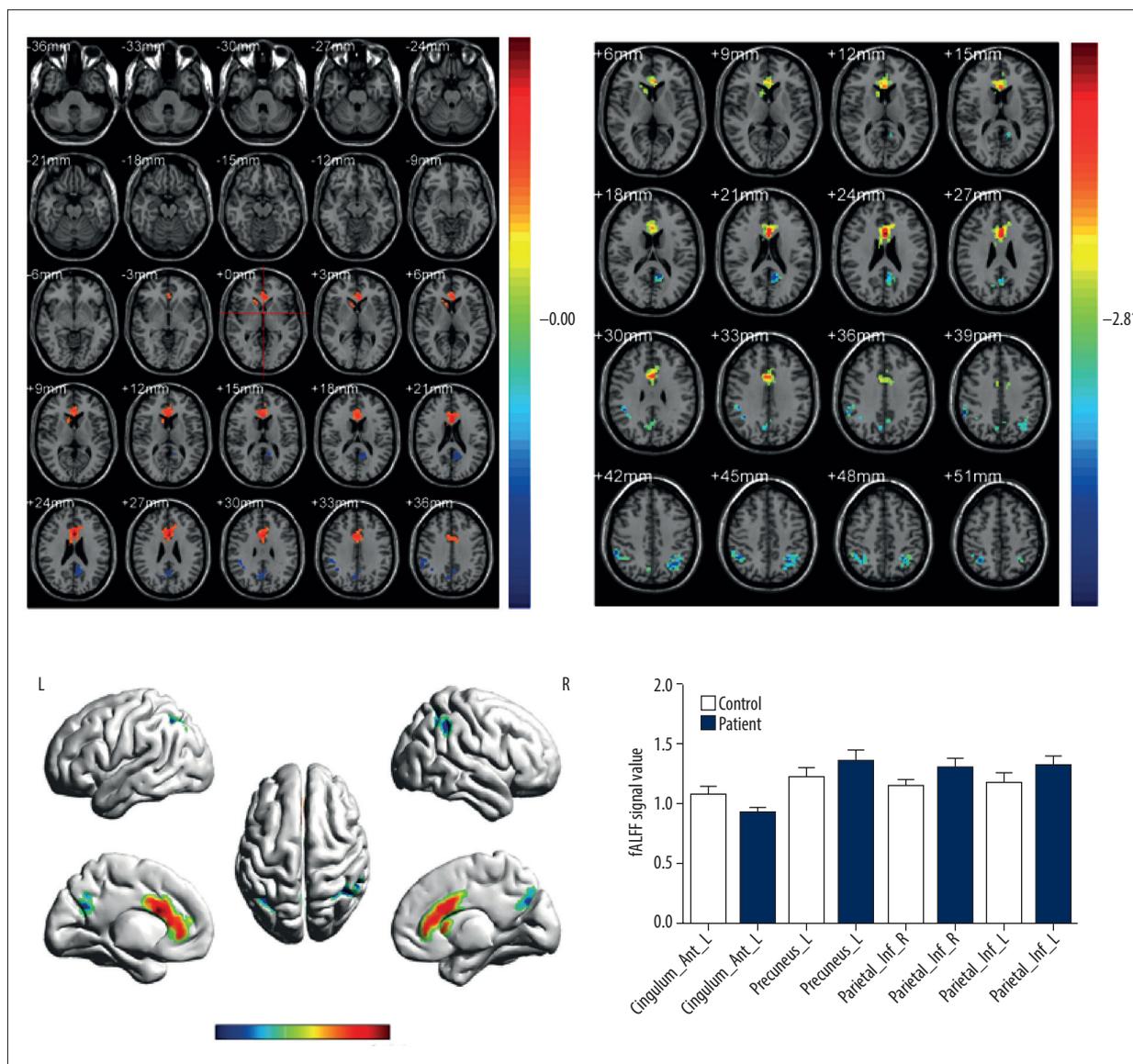


Figure 1. Spontaneous cerebral activity in MB patients and HCs. Significant brain activity differences were observed in the left anterior cingulate and paracingulate gyri, left precuneus, right inferior parietal, but supramarginal and angular gyri and left inferior parietal, but supramarginal and angular gyri. The red or yellow denotes increased fALFF values, and the blue areas indicate decreased fALFF values, respectively ($P < 0.01$ for multiple comparisons using Gaussian random field theory [$z_{2.3}$, $P < 0.01$, cluster: 40 voxels, Alphasim corrected]). MB – monocular blindness; HCs – healthy controls; fALFF – fractional amplitude of low-frequency fluctuation; L – left; R – right.

Receiver operating characteristic curve

The mean fALFF values in these regions were evaluated by ROC curves. The AUCs of fALFF values were as follows: left anterior cingulate (0.969) (Figure 2A), left precuneus (0.887), right inferior parietal lobe (0.936), and left inferior parietal lobe (0.911) (Figure 2B).

Correlation analysis

The mean fALFF values of MB patients in the left anterior cingulate had negative correlations with the score of anxiety scale ($r = -0.825$, $P < 0.001$) and depression scale ($r = -0.871$, $P < 0.001$) (Figure 3).

Table 2. Brain areas with significantly different fALFF values between MB and HCs groups.

Brain areas	MNI coordinates			BA	Number of voxels	T value
	X	Y	Z			
HC>MC						
Cingulum_Ant_L	-3	15	24	0	431	6.1548
HC<MC						
Precuneus_L	-9	-51	21	23	101	-4.0416
Parietal_Inf_R	48	-51	45	40	133	-4.1100
Parietal_Inf_L	-27	-66	42	7	122	-3.9046

A P-value <0.05 was significantly different for multiple comparisons using Gaussian random field theory (z.2.3, P,0.01, cluster .40 voxels, Alphasim corrected). fALFF – fractional amplitude of low-frequency fluctuation; MB – monocular blindness; HCs – healthy controls; MNI – Montreal Neurological Institute; Cingulum_Ant_L – left anterior cingulate; Precuneus_L – left precuneus; Parietal_Inf_R – right inferior parietal lobe; Parietal_Inf_L – left inferior parietal lobe.

Table 3. Two sample t tests between mean fALFF values between MB patients and HCs-related brain regions.

	MB	HCs	t	P
Cingulum_Ant_L	0.923±0.045	1.076±0.065	9.237	<0.001
Precuneus_L	1.360±0.093	1.218±0.082	-5.013	<0.001
Parietal_Inf_R	1.302±0.079	1.149±0.060	-6.614	<0.001
Parietal_Inf_L	1.322±0.079	1.172±0.092	-5.687	<0.001

Two sample t tests were compared between the two groups (P<0.05 represents a statistically significant difference). fALFF – fractional amplitude of low-frequency fluctuation; MB – monocular blindness; HCs – healthy controls; Cingulum_Ant_L – left anterior cingulate; Precuneus_L – left precuneus; Parietal_Inf_R – right inferior parietal lobe; Parietal_Inf_L – left inferior parietal lobe.

Discussion

The fALFF approach has been used to study neurological conditions (Table 3). The objective of this study was to use the fALFF method to investigate the effect of MB on spontaneous neuronal activity. MB patients showed obviously higher fALFF values in left precuneus, right inferior parietal lobe, and left inferior parietal lobe, but lower fALFF values in the left anterior cingulate compared to HCs (Table 4).

Analysis of the increased fALFF values in MB patients

As a portion of the superior parietal lobule forward of the occipital lobe (cuneus), the precuneus has a significant role in the visuospatial imagery [29], episodic memory retrieval [30], and consciousness [31]. A study found that blind patients had less local gray matter in the precuneus than sighted individuals [32]. However, MB patients in our study had increased fALFF values in the left precuneus. The compensation mechanism is crucial for monocular vision loss. We speculated that the high activity of the anterior wedge may reflect obstacles of the visual space perception, as well as compensated vision loss and visual field defects in MB patients.

The parietal lobe supports higher cognitive functions, including mathematical cognition, semantics, and thought processing [33]. The function of the inferior parietal lobule (IPL) is associated with oculomotor and attentional mechanisms and the adaptive recalibration of eye-hand coordination [34]. The angular (ANG) and supramarginal (SMG) gyri of the left IPL make significant functional contributions to visual word recognition [35]. Normally, ANG plays an important role in semantic processing, whereas SMG is essential in phonological processing during reading. A previous fMRI study found that EB patients had more spatial variability in a bilateral parietal network than normal sighted individuals when at rest or listening to a vocal drama [36]. In our research, MB patients had increased fALFF values in the right inferior parietal lobe and left inferior parietal lobe, which may indicate the functional improvement to compensate for impaired visual acuity.

Analysis of the decreased fALFF values in MB patients

The anterior cingulate cortex (ACC) is a portion of the limbic system located anterior to the corpus callosum and posterior to the prefrontal cortex. The ACC is involved in movement [37]. Patients with increased ACC activity may have spasms, compulsive behaviors, and abnormal social behavior, while reduced ACC activity

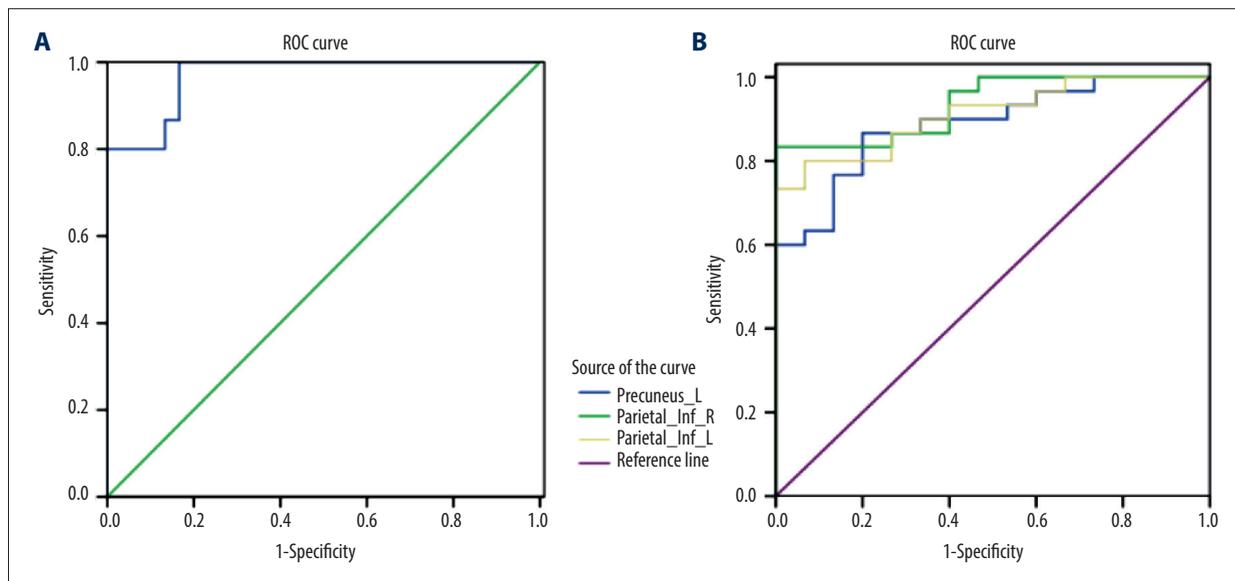


Figure 2. ROC curve analysis of the mean fALFF values for changed areas. The AUCs of fALFF values were as follows: left anterior cingulate (0.969) (A); left precuneus (0.887), right inferior parietal lobe (0.936), and left inferior parietal lobe (0.911) (B). ROC – receiver operating characteristic; AUC – area under the curve; fALFF – fractional amplitude of low-frequency fluctuation; MB – monocular blindness; HCs – healthy controls; Cingulum_Ant_L – left anterior cingulate; Precuneus–L – left precuneus; Parietal_Inf_R – right inferior parietal lobe; Parietal_Inf_L – left inferior parietal lobe.

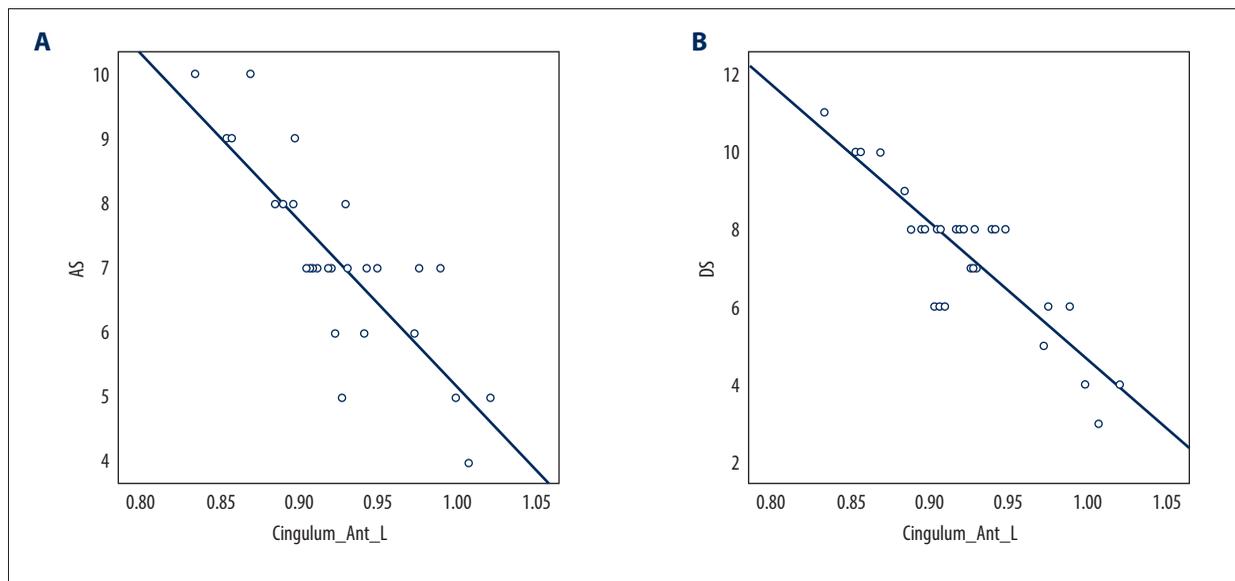


Figure 3. Correlations between the mean fALFF signal values of the Cingulum_Ant_L and score of anxiety scale and score of depression scale in MB patients. The mean fALFF signal value of the Cingulum_Ant_L showed negative correlations with the score of anxiety scale ($r=-0.825$, $P<0.001$) (A); The mean fALFF signal value of the Cingulum Ant L showed negative correlations with the score of depression scale ($r=-0.871$, $P<0.001$) (B). fALFF – fractional amplitude of low-frequency fluctuation; Cingulum_Ant_L – left anterior cingulate; MB – monocular blindness; AS – anxiety scale; DS – depression scale.

may result in disturbance of behavior such as lower self-consciousness and depression, motor neglect and impaired motor initiation, and aberrant social behavior [37]. The ACC is regarded as a monitoring center that is in charge of online detection of response conflicts [38]. Accordingly, the conflict signal sensed

by the ACC is transmitted to other brain regions to trigger compensatory adjustments in cognitive control [39], such as the dorsal part of the lateral prefrontal cortex, to elevate the level of cognitive control. Abnormalities in the ACC have been associated with many diseases [40] such as depression, schizophrenia,

Table 4. The fALFF applied in neurodegenerative diseases.

Author	Year	Disease	Brain areas	
			fALFF increased	fALFF decreased
Lai CH, et al. [28]	2015	Pure major depressive disorder	Left temporal subgyral region	Right frontal subcallosal gyrus and right parietal postcentral gyrus
Wang JJ, et al. [29]	2016	Migraine	Bilateral insular and left orbital cortex	Left occipital lobe and bilateral cerebellum posterior lobe
Egorova N, et al. [30]	2017	Post-stroke depression	DLPFC, right precentral gyrus and left insula	–
Tang Y, et al. [31]	2017	Parkinson's disease	–	Right cerebellum posterior lobe
Duan G, et al. [32]	2017	Premenstrual syndrome	Left hippocampus	–

fALFF – fractional amplitude of low-frequency fluctuation.

Table 5. Brain regions alternation and its potential impact.

Brain regions	Experimental result	Brain function	Anticipated results
Anterior cingulate cortex	MB <HCs	Movement, affect and social behaviors	Behavioral disorders, depression, schizophrenia, and autism
Paracingulate cortex	MB <HCs	Cognitive and affective regulation	Bipolar disorder
Inferior parietal, but supramarginal and angular gyri	MB >HCs	Part of the default model network and higher cognitive functions	Depression, anxiety, alexia and agraphia
Precuneus	MB >HCs	Visuospatial imagery, episodic memory retrieval, and consciousness	Depression, anxiety and impaired consciousness

MB – monocular blindness; HCs – healthy controls.

and autism. The paracingulate cortex (PaC) is an adjacent and functionally relevant area of the ACC. The PaC has cognitive and affective regulatory function and is related to varied conditions such as psychosis and neurological conditions [41]. Our results showed that the fALFF values of the left anterior cingulate in MB patients were lower than in the HCs. This likely reflects the dysfunction of the ACC and PaC in MB patients.

Mental health comorbidities are common among patients with visual impairment [42]. In our study, the result showed that the mean fALFF values of MB patients in the left anterior cingulate had negative correlations with the scores of the anxiety and depression scale. Hence, we speculated that the cause of anxiety and depression may be related to the inhibition of the left anterior cingulate (Table 5).

Limitations

Our study has some limitations. First, the sample size was relatively small, and, despite our best efforts, there were fewer

HC patients than MB patients. Second, our inclusion criteria were not rigid, because patients with MB in the right or left eye were both included in our study, and the causes of MB were diverse. Third, during the scanning process, physical movement of patients might have had an effect on the scanning results. Lastly, further research is needed to verify our results.

Conclusions

MB patients in our study exhibited abnormal fALFF values in the visual cortices and vision-related areas, suggesting dysfunction of visual processing caused by vision loss. The finding of abnormal neuronal activity helps to reveal the underlying neuropathologic mechanisms of vision loss.

Conflict of Interest

None.

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