

Altered spontaneous brain activity pattern in patients with high myopia using amplitude of low-frequency fluctuation: a resting-state fMRI study

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Objective: Many previous reports have demonstrated significant neural anatomy changes in the brain of high myopic (HM) patients, whereas the spontaneous brain activity changes in the HM patients at rest are not well studied. Our objective was to use amplitude of low-frequency fluctuation (ALFF) method to investigate the changes in spontaneous brain activity in HM patients and their relationships with clinical features.

Methods: A total of 38 patients with HM (17 males and 21 females) and 38 healthy controls (HCs) (17 males and 21 females) closely matched in age, sex, and education underwent resting-state functional magnetic resonance imaging scans. The ALFF method was used to assess local features of spontaneous brain activity. The relationship between the mean ALFF signal values in many brain regions and the clinical features in HM patients was calculated by correlation analysis.

Results: Compared with HCs, the HM patients had significantly lower ALFF in the right inferior and middle temporal gyrus, left middle temporal gyrus, left inferior frontal gyrus/putamen, right inferior frontal gyrus/putamen/insula, right middle frontal gyrus, and right inferior parietal lobule and higher ALFF values in the bilateral midcingulate cortex, left postcentral gyrus, and left precuneus/inferior parietal lobule. However, no relationship was found between the mean ALFF signal values of the different areas and the clinical manifestations in HM.

Conclusion: The HM patients were affected with brain dysfunction in many regions, which may indicate the presence of neurobiological changes involving deficits in language understanding and attentional control in HM patients.

Keywords: ALFF, high myopic, resting state, functional magnetic resonance imaging

Introduction

High myopia (HM) is a common eye disorder which has become a public health problem globally.¹ The prevalence of myopia is 70% among teenagers in Hong Kong.² The occurrence of HM is associated with many factors such as genetic variants,³ education factors,⁴ and season of birth.⁵ Clinically, HM is often associated with low best-corrected visual acuity (VA). Besides, HM may lead to macular complications,⁶ chorioretinal atrophy,⁷ and retinal detachment.⁸ Currently, the important methods for HM correction include among other excimer laser⁹ and orthokeratology.¹⁰

Optical coherence tomography (OCT) is a noninvasive, high-resolution method that can measure the structure of the eye accurately. A previous study demonstrated using OCT method that the HM eyes have less retinal nerve fiber thickness compared with emmetropic eyes.¹¹ Another study reported that the OCT examinations could reveal the types of abnormalities around the optic disc in HM eyes.¹² Meanwhile, OCT

can evaluate HM-related complications such as choroidal neovascularization.¹³ High-resolution magnetic resonance (MR) also has been used to evaluate the eye shape in HM. MR could make correct assessment of the shape of eye in HM patients.¹⁴ The aforementioned inspection methods focus merely on the pathological changes of ocular trauma in HM. However, other visual systems, including the visual pathways and the visual cortex, are often overlooked.

Functional magnetic resonance imaging (fMRI) has been used to evaluate the brain functional connectivity in HM patients. Zhai et al reported that HM patients showed decreased short- and long-range functional connectivity density in the posterior cingulate cortex/precuneus.¹⁵ However, there are only a few studies on the changes of spontaneous brain activity in HM patients at rest. The blood oxygenation level dependent signal changes can reflect the changes in the neuronal and physiological activities to some extent. Amplitude of low-frequency fluctuation (ALFF) can be used to detect the spontaneous neuronal activity in blood oxygenation level dependent signal. The ALFF is a reliable relevant amplitude measure which can be detected in the human resting brain.¹⁶ The ALFF has been widely applied to detect the brain function within a specific frequency range (0.01–0.08 Hz).¹⁷ In our previous studies, the ALFF method was successfully used to assess the neurological conditions in some eye diseases such as optic neuritis,¹⁸ glaucoma,¹⁹ and comitant strabismus.²⁰ Our study is the first to use the ALFF method to investigate the spontaneous brain activity in HM patients and investigate its relationship with the behavioral performances.

Materials and methods

Subjects

A total of 38 patients with HM (17 males and 21 females) were recruited from the ophthalmology department of the First Affiliated Hospital of Nanchang University. The inclusion criteria of the study were: 1) HM patients with binocular refractive errors; 2) binocular refractive diopter –6.00 to –7.00 D and corrected VA >1.0; and 3) absence of ocular diseases (cataracts, glaucoma, optic neuritis, retinal degeneration) in both eyes. The exclusion criteria were: 1) refractive diopter –1.00 to –6.00 D; 2) monocular HM; 3) congenital HM; 4) HM with amblyopia and related complications (retinal detachment, retinal atrophy degeneration, macular hole); 5) long-term medical treatment of HM; and 6) psychiatric disorders and cerebral infarction diseases (cerebral hemorrhage, cerebral infarction, cerebral vascular malformations).

Thirty-eight healthy controls (HCs; 17 males, 21 females) who were matched in age, sex, and educational

status to subjects in the HM group were also recruited for this study. All healthy subjects met the following criteria: 1) no ocular disease with uncorrected or corrected VA >1.0; 2) no psychiatric disorders (depression, bipolar disorder, sleep disorder); and 3) could be scanned with MRI (eg, no cardiac pacemaker or implanted metal devices). All research methods followed the Declaration of Helsinki and the study protocol was approved by the ethics committee of the First Affiliated Hospital of Nanchang University. All volunteers participated voluntarily and were informed of the purposes, methods, and potential risks before they signed an informed consent form.

MRI parameters

MRI scanning was performed on a 3 T MR scanner (Trio; Siemens, Munich, Germany). The functional data were obtained with spoiled gradient-recalled echo sequence with the parameters (repetition time =1,900 ms, echo time =2.26 ms, thickness =1.0 mm, gap =0.5 mm, acquisition matrix =256×256, field of view =250×250 mm, flip angle =9°). We also obtained 240 functional images (repetition time =2,000 ms, echo time =30 ms, thickness =4.0 mm, gap =1.2 mm, acquisition matrix =64×64, flip angle =90°, field of view =220×220 mm, 29 axial).

fMRI data analysis

Functional data were classified by MRICro software (www.MRICro.com) and incomplete data were removed. The first ten volumes were discarded due to magnetization equilibration. The rest of the data was preprocessed by Data Processing Assistant for Resting-State fMRI, version 2.3 (<http://rfmri.org/DPARSF>) software, including slice timing, head motion correction, spatial normalization, and smoothing with a Gaussian kernel of 6×6×6 mm³ full width at half maximum. The fMRI images were spatially normalized to the Montreal Neurological Institute space criteria using the standard echo-planar imaging template and resampling the images at a resolution of 3×3×3 mm. After preprocessing, the ALFF of each voxel was divided by the global mean ALFF value for each participant. More details of ALFF calculation have been reported in our previous study.¹¹

Statistical analysis

A one-sample *t*-test was performed to extract the ALFF results across the subjects within each group ($P<0.05$). Statistical analysis was performed with a general linear model analysis using the Statistical Parametric Mapping 8 (SPM8) toolkit to investigate the ALFF signal group differences in the resting state between the two groups, after controlling

for the effects of age and sex ($P < 0.01$ for multiple comparisons using Gaussian random field theory) ($z > 2.3$, $P < 0.01$, cluster > 40 voxels, AlphaSim corrected).

Brain–behavior correlation analysis

Brain areas with different ALFF findings between the two groups were classified as regions of interest with the Resting-State fMRI Data Analysis Toolkit version 1.8 software. The relationship between the mean ALFF value in different brain regions in the HM group and the behavioral performances was calculated with correlation analysis ($P < 0.05$ was considered statistically significant difference).

Clinical data analysis

The cumulative clinical measurements, including the duration of the onset of HM, refractive diopter, and best-corrected VA, were recorded and analyzed in the study with independent sample *t*-test ($P < 0.05$ was considered statistically significant difference).

Results

Demographics and visual measurements

There were no marked differences in weight ($P = 0.972$), age ($P = 0.856$), best-corrected VA-right ($P = 0.705$), and best-corrected VA-left ($P = 0.940$) between the two groups (Table 1).

ALFF differences

A one-sample *t*-test was performed to extract the ALFF results across the subjects within each group ($P < 0.05$). Intragroup comparison within the HM and HC groups is shown in Figure 1. Compared with HCs, HMs had significantly lower ALFF in the right inferior and middle temporal gyrus (MTG), left MTG, left inferior frontal gyrus (IFG)/putamen, right IFG/putamen/insula, right middle frontal

gyrus, and right inferior parietal lobule (IPL) (Figure 2, blue areas; Table 2). In contrast, higher ALFF values were observed in the bilateral midcingulate cortex (MCC), left postcentral gyrus, and left precuneus/IPL in the HM group (Figure 2, red areas; Table 2). The mean values of altered ALFF between the two groups are shown in Figure 3. In the HM group, there was no significant correlation between the mean ALFF values in different brain regions and the clinical manifestations ($P > 0.05$).

Receiver operating characteristic (ROC) curve

We hypothesized that the ALFF differences between the HM and HC groups might be useful diagnostic markers. Besides, the mean ALFF values in different brain regions were analyzed by ROC curve method. The areas under the ROC curve for the ALFF values were as follows: right inferior and MTG (0.744), left MTG (0.734), left IFG/putamen (0.713), right IFG/putamen/insula (0.725), right middle frontal gyrus (0.783), right IPL (0.729) (HMs $<$ HCs) (Figure 4A); bilateral MCC (0.643), left postcentral gyrus (0.679), left precuneus/IPL (0.659) (HMs $>$ HCs) (Figure 4B).

Discussion

In our study, the HM patients had significantly lower ALFF in the right inferior and MTG, left MTG, left IFG/putamen, right IFG/putamen/insula, right middle frontal gyrus, and right IPL and higher ALFF values in the bilateral MCC, left postcentral gyrus, and left precuneus/IPL.

Analysis of the decreased ALFF values in HM

The IFG is a part of the frontal lobe which plays an important role in language comprehension.²¹ A previous study showed that the left IFG is a critical brain area in reading the mind in the eyes.²² The triangular part of the IFG is the grammar center.²³

Table 1 Demographics and clinical measurements by group

Variable	HM	HC	t-test	P-value*
Male/female, n	17/21	17/21	N/A	> 0.99
Age (years), mean \pm SD	22.76 \pm 1.28	22.71 \pm 1.23	0.183	0.856
Weight (kg), mean \pm SD	65.21 \pm 6.89	65.26 \pm 6.31	-0.035	0.972
Handedness, n	38R	38R	N/A	> 0.99
Duration of HM (years), mean \pm SD	6.34 \pm 1.12	N/A	N/A	N/A
Refractive diopter-right (D), mean \pm SD	-641.05 \pm 37.04	N/A	N/A	N/A
Refractive diopter-left (D), mean \pm SD	-643.68 \pm 37.59	N/A	N/A	N/A
Best-corrected VA-right eye, mean \pm SD	1.15 \pm 0.16	1.13 \pm 0.15	0.381	0.705
Best-corrected VA-left eye, mean \pm SD	1.14 \pm 0.14	1.14 \pm 0.16	-0.076	0.940

Note: * $P < 0.05$, independent *t*-tests for comparing two groups.

Abbreviations: HC, healthy control; HM, high myopia; N/A, not applicable; R, right; VA, visual acuity.

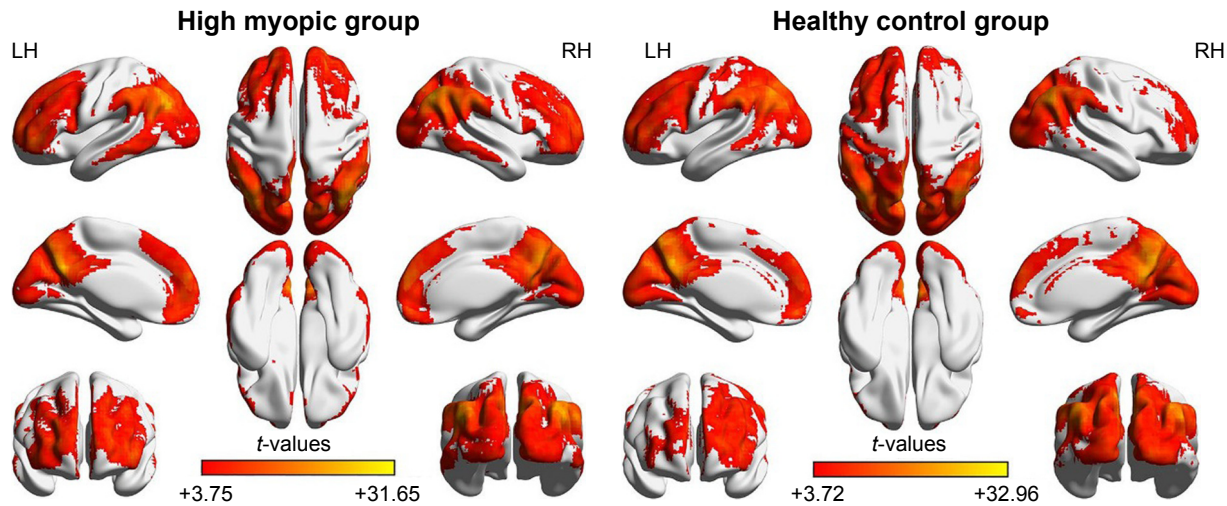


Figure 1 One-sample t-test results. Within-group ALFF maps within the HM (left) and HC (right) groups ($P < 0.001$, FDR corrected).
Abbreviations: ALFF, amplitude of low-frequency fluctuation; FDR, false discovery rate; HC, healthy control; HM, high myopia; LH, left hemisphere; RH, right hemisphere.

Besides, another study reported that there were changes in morphology of the IFG in language-disordered subjects.²⁴ Meanwhile, the right IFG plays a vital role in inhibition and attentional control.²⁵ A previous research showed that stimulation of the right IFG may improve attention in patients with early Alzheimer’s disease.²⁶ Li et al demonstrated that patients with HM showed smaller white matter volume in the prefrontal area, compared with HCs.²⁷ In support of these findings, we observed that HM patients had significantly lower ALFF in the bilateral IFG. We surmised that HM may lead to dysfunction of the bilateral IFG, which might indicate that HM patients suffer from impairment of language understanding and attentional control.

The putamen is located in the forebrain, which connects to the substantia nigra and globus pallidus. The putamen is a part of the dorsal striatum. It is also one of the structures

that comprise the basal ganglia. A previous study demonstrated that the putamen was involved in processing the motor information in monkeys.²⁸ Another study reported that macaque monkey showed increased activity of neurons in the putamen during a visuomotor task.²⁹ Apart from its involvement in motor skills, the putamen also plays an important role in learning.^{30–32} In addition, dysfunction of the putamen was associated with many diseases such as schizophrenia,³³ pain,³⁴ and Parkinson disease.³⁵ In our study, we found that HM patients had significantly lower ALFF in the bilateral putamen. We speculated that HM may lead to dysfunction of the putamen, which may be reflected as defective movement and learning in HM patients.

MTG is located in the middle of superior temporal gyrus and inferior temporal gyrus, and is involved in speed of word recognition.³⁶ Besides, the MTG includes middle temporal

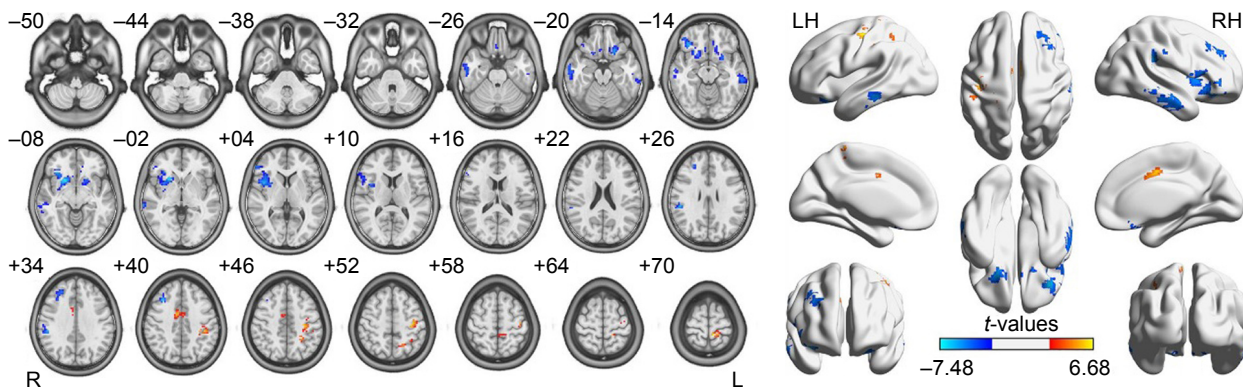


Figure 2 Spontaneous brain activity in the monocular blindness and healthy control groups.
Notes: Significant differences in activity were observed in the right inferior and middle temporal gyrus, left middle temporal gyrus, left inferior frontal gyrus/putamen, right inferior frontal gyrus/putamen/insula, right middle frontal gyrus, right inferior parietal lobule, bilateral midcingulate cortex, left postcentral gyrus, and left precuneus/inferior parietal lobule. The red or yellow areas denote higher ALFF values and the blue areas indicate lower ALFF values ($P < 0.01$ for multiple comparisons using GRF theory) ($z > 2.3$, $P < 0.01$, cluster > 40 voxels, AlphaSim corrected).
Abbreviations: ALFF, amplitude of low-frequency fluctuation; GRF, Gaussian random field; L, left; LH, left hemisphere; R, right; RH, right hemisphere.

Table 2 Brain areas with significantly different ALFF values between the groups

Brain areas	MNI coordinates			Voxels	BA	L/R	Peak t-values
	x	y	z				
HM < HC							
Inferior and middle temporal gyrus	60	-27	-18	147	20.21	R	-5.323
Middle temporal gyrus	-63	-33	-15	68	21	L	-5.681
Inferior frontal gyrus/putamen	-21	24	-21	119	47	L	-5.975
Inferior frontal gyrus/putamen/insula	21	15	-6	450	47.13	R	-7.484
Middle frontal gyrus	33	24	39	86	9	R	-6.986
Inferior parietal lobule	51	-33	30	60	40	R	-6.631
HM > HC							
Midcingulate cortex	9	-3	39	59	24	B	5.874
Postcentral gyrus	-39	-15	54	159	3	L	6.679
Precuneus/inferior parietal lobule	-27	-48	48	37	40.7	L	6.479

Note: The statistical threshold was set at the voxel level with $P < 0.05$ for multiple comparisons using GRF theory ($z > 2.3$, $P < 0.01$, cluster > 40 voxels, AlphaSim corrected).

Abbreviations: ALFF, amplitude of low-frequency fluctuation; B, bilateral; BA, Brodmann area; GRF, Gaussian random field; HC, healthy control; HM, high myopia; L, left; MNI, Montreal Neurological Institute; R, right.

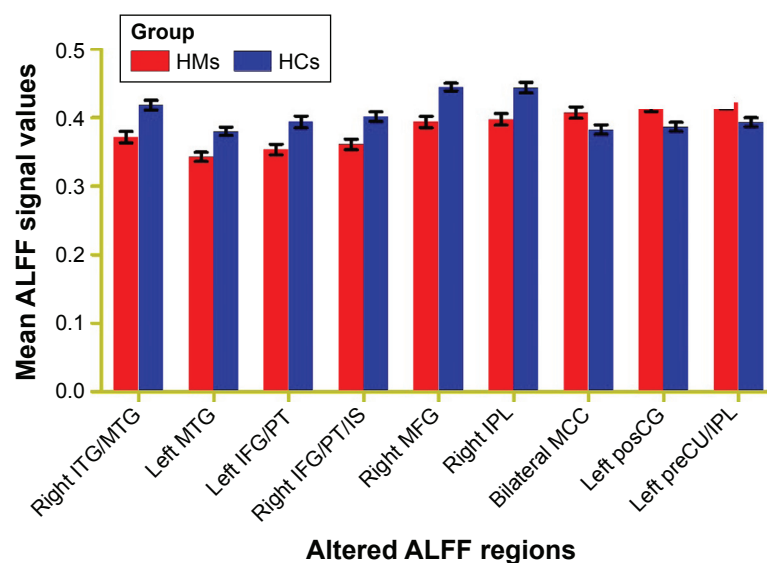
visual area (V5), which plays an important role in visual motion.^{37,38} In addition, the MTG is responsible for the pursuit eye movements.³⁹ In our study, we found that HM patients had significantly decreased ALFF values in the bilateral MTG, indicating the impairment of the MTG. We speculated that HM may be associated with deficits in visual motion and word recognition.

Analysis of the increased ALFF values in HM

The IPL is located behind the lower part of the postcentral sulcus. It is involved in the encoding of spatial location.⁴⁰ Besides, the IPL is responsible for the spatial attention

or motor attention.⁴¹ Meanwhile, the IPL is involved in the auditory motion.⁴² In our study, we found that HM patients had significantly higher ALFF values in the left IPL, which indicated increased activities in the left IPL in them. We speculated that the higher ALFF in the left IPL may indicate reinforcement of the spatial attention in HM patients.

The cingulate cortex is located in the middle of the cerebral cortex, which is a part of limbic cortex. The MCC plays an important role in cognitive control.⁴³ Besides, the MCC may be involved in negative emotion and motor control.^{44,45} Dysfunction of the MCC leads to many diseases such as pain⁴⁶ and autism.⁴⁷ In our study, we found that there were

**Figure 3** The mean values of altered ALFF values between the HM and HC groups.

Abbreviations: ALFF, amplitude of low-frequency fluctuation; HC, healthy control; HM, high myopia; IFG, inferior frontal gyrus; IPL, inferior parietal lobule; IS, insula; ITG, inferior temporal gyrus; MCC, midcingulate cortex; MFG, middle frontal gyrus; MTG, middle temporal gyrus; posCG, postcentral gyrus; preCU, precuneus; PT, putamen.

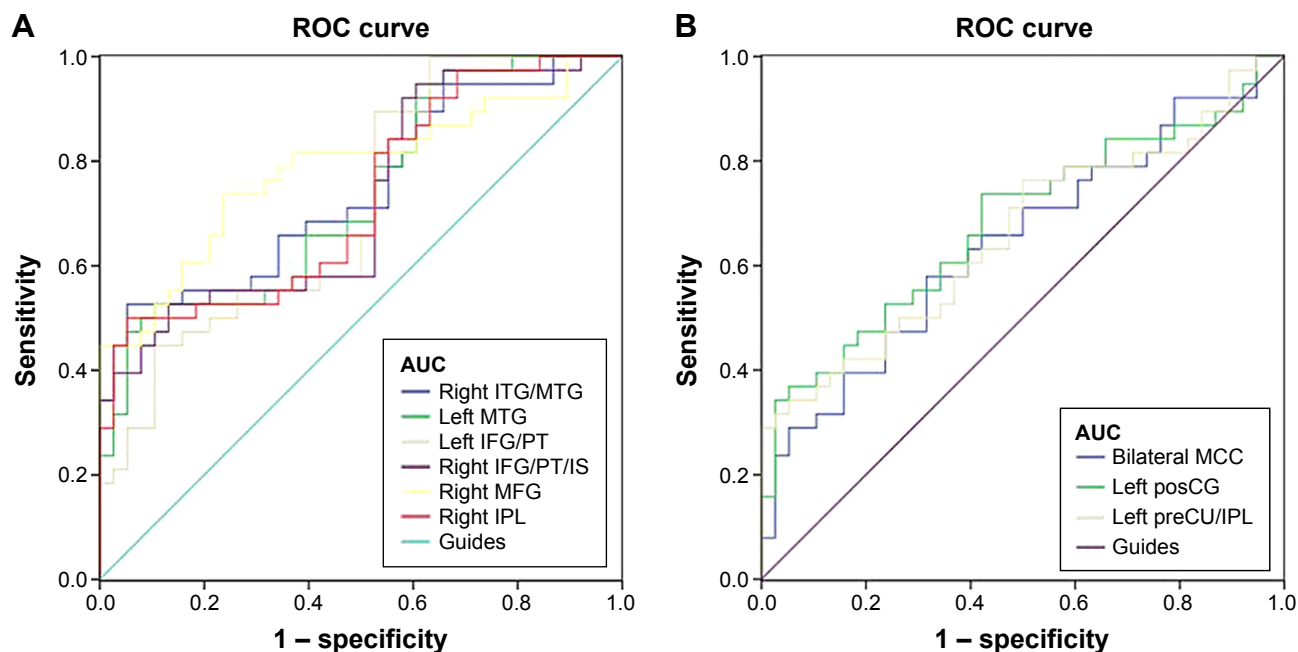


Figure 4 ROC curve analysis of the mean ALFF values for altered brain regions.

Notes: The AUCs were: 0.744 ($P < 0.001$; 95% CI: 0.634–0.855) for the right ITG/MTG, 0.734 ($P < 0.001$; 95% CI: 0.634–0.845) for the left MTG, 0.713 ($P = 0.001$; 95% CI: 0.598–0.828) for the left IFG/PT, 0.725 ($P = 0.001$; 95% CI: 0.611–0.839) for the right IFG/PT/IS, 0.783 ($P < 0.001$; 95% CI: 0.677–0.888) for the right MFG, and 0.729 ($P = 0.001$; 95% CI: 0.616–0.841) for the right IPL (HMs < HCs) (A). The AUCs were: 0.643 ($P = 0.032$; 95% CI: 0.519–0.768) for the bilateral MCC, 0.679 ($P = 0.007$; 95% CI: 0.558–0.801) for the left posCG, 0.659 ($P = 0.017$; 95% CI: 0.536–0.783) for the left preCU/IPL (HMs > HCs) (B).

Abbreviations: ALFF, amplitude of low-frequency fluctuation; AUC, area under the curve; CI, confidence interval; HCs, healthy controls; HM, high myopia; IFG, inferior frontal gyrus; IPL, inferior parietal lobule; IS, insula; ITG, inferior temporal gyrus; MCC, midcingulate cortex; MFG, middle frontal gyrus; MTG, middle temporal gyrus; posCG, postcentral gyrus; preCU, precuneus; PT, putamen; ROC, receiver operating characteristic.

significantly higher ALFF values in the bilateral MCC in HM patients, which indicated enhanced activities in bilateral MCC. We surmised that the HM may lead to the hyperfunction of emotion and attention.

Limitations

However, there are some limitations in our study, such as the relatively small sample size and the differences in refractive diopter in HM patients. Besides, the duration of the onset of HM is not exactly the same, which may have a bad effect on the accuracy of the results.

Conclusion

In summary, our results showed that there were abnormal spontaneous activities in many brain regions, which may indicate that neurobiological changes associated with deficits in language understanding and attentional control are found in HM patients.

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Disclosure

The authors report no conflicts of interest in this work.

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