Children with Strabismus and Amblyopia Presented Abnormal Spontaneous Brain Activities Measured Through Fractional Amplitude of Low-Frequency Fluctuation (fALFF)

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Research Article

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Abstract

Purpose

Based on fMRI technology, we explored whether children with strabismus and amblyopia (SA) showed significant alteration in fractional amplitude of low-frequency fluctuation (fALFF) values in specific brain regions compared with healthy controls, and whether this change could indicate the clinical manifestations and pathogenesis of children with strabismus to a certain extent.

Methods

23 children with strabismus amblyopia and same number matched healthy control was registered in the ophthalmology department of the First Affiliated Hospital of Nanchang University, and the whole brain was scanned by rs-fMRI. The fALFF value of each brain area was derived to explore whether there is a statistical difference in the two groups. Meanwhile, ROC curve was made in a view to evaluate whether this difference is of value as a diagnostic index. Finally, analyze whether the changes in the fALFF value of some specific brain regions are related to clinical manifestations

Results

report to HCs children with SA presented a decreased fALFF values in left temporal pole: the superior temporal gyrus, right middle temporal gyrus, right superior frontal gyrus, right supplementary motor area. Meanwhile, they also showed higher fALFF values in specific brain areas, which included left precentral gyrus, left inferior Parietal, left Precuneus.

Conclusion

Children with SA showed abnormal fALFF values in different brain regions. Most of these regions were allocated to the visual formation pathway. The eye movement-related pathway or other visual-related pathways, suggesting the pathological mechanism of the patient.

Introduction

Strabismus relates to the improper eye position, including esotropia and exotropia[1]. The prevalence of strabismus varies in different regions or nations, but what in common is that its incidence is increasing year by year[2]. Refractive differences between the eyes, hyperopia, related family history, and improper behaviors during the gestation period (drinking, smoking or drug dependence, etc.) are all clear risk factors for strabismus. Infants with congenital squint are often accompanied by the possibility of amblyopia, and the contemporary mainstream views are increasingly emphasizing the correction of amblyopia in children with strabismus. At the same time, strabismus represents one of the important reasons for the occurrence of amblyopia. The Preferred Practice Pattern (PPP) [3]also pointed out that the correction of strabismus can promote the treatment of amblyopia. The increasing number of children with strabismus and amblyopia (SA) has grown up to be done a serious public health problem. Eyes constitute an imperative tool for directly perceiving the world. Ophthalmic abnormalities and obstacles have a great influence on the growth process of children, and this impact is manifested in both physical and mental development[4]. Therefore, a comprehensive understanding of strabismus and amblyopia is extremely eminent.

Traditionally, the examinations prescribed for the diagnosis of SA were limited to optical function and acuity examinations, but large numbers studies have shown that patients with SA still have changes in the structure and function of the nervous system[5–7]. However, the evaluation of this part rarely participants in clinical work. The rapid development of the field of medical imaging in recent years suggests that we may make use of it to take a more intuitive and comprehensive view of SA. Among them, fMRI has become an important examination method for us to study the pathogenesis of SA patients at the neurological level and predict possible complications because it can evaluate the brain from many aspects such as morphology, metabolism, blood perfusion, and functional changes at the same time.

fMRI is a non-invasive post-processing imaging technology for functional brain areas. Blood-oxygen level dependent (BLOD) signals are obtained according to the differences in the metabolic levels of discrete brain regions. Among them, rs-fMRI is an examination, which was carried out when the subject is awake, closed eyes, resting, and shielded from external stimuli. The result of rs-fMRI can determine the spontaneous neural activity of subject's brain[8].

Low-frequency oscillations (LFOs) is deemed to be caused by the spontaneous activity of brain neurons[9]. When a person is in resting-state and not stimulated by peripheral environment, there will be synchronous low-frequency vibrations in specific brain areas. This vibration can be revealed by the BOLD signal, and moreover, be detected, recorded and presented by rs-fMRI. On this basis, ALFF was proposed as an index of rs-fMRI. ALFF defined as the disparity between low-frequency oscillation of BOLD signal and average fluctuation amplitude of the spontaneous brain neuron activity baseline in a specific time [10], which can be helpful to some researches to reprocess the rs-fMRI result data for the spontaneous activity of functional brain areas[11, 12]. However, in practical applications, the interference of physiological noise on the consequences of ALFF increases the uncertainty of the research results, and the improved fALFF based on ALFF can solve this problem and remove the signal artifacts caused by non-specific brain neuronal activities.

Due to its unique advantages, fALFF has been widely used in the research of many diseases, including pure major depression disorder[13], migraine[14], post-stroke depression[15], Parkinson disease[16], premenstrual syndrome[17].

There is still a lot of work in the study of SA in children. Therefore, this study adopted rs-fMRI to detect aberrant autogenic activities in specific brain areas of patients through fALFF to explore the possible neural mechanisms and potential pathological changes of the disease. As the best of we known, this study is the first time that this method has been used to study SA in children.

Materials And Methods

Subjects

The study included 23 patients (no more than18 years of age) which were diagnosed as strabismus and amblyopia and 23 healthy controls (HCs). All participants came from the Ophthalmology Department of the First Affiliated Hospital of Nanchang University.

The inclusion criteria of patients (PAT) were as following: 1) under18 years old; 2) being diagnosed as strabismus and amblyopia by a doctor who has obtained medical practitioner qualification strictly in accordance with the PPP diagnosis of strabismus and amblyopia (no distinction between monocular or binocular, esotropia and exotropia); 3) Ophthalmoscopy showed the suppression of the macular center; 4) lack of stereopsis.

The inclusion criteria of the healthy controls (HCs) included: 1) under 18 years old; 2) nonconforming the diagnostic criteria for strabismus and(or) amblyopia; 3) could cooperate with MRI examination; 4) no history of other ophthalmic diseases; 5) head MRI scanning showed no abnormality.

The exclusion criteria for all participants included: 1) had the history of surgery, especially eye surgery; 2) with the history of eye trauma; 3) born with abnormal neurological development; 4) have diseases that cannot cooperate with MRI examinations (from wearing a heart Pacemaker or severe mental illness)

The procedure for this study was approved by the Ethics Committee of the First Affiliated Hospital of Nanchang University. All participants had known the purpose, content, and risks of this research, and have obtained written informed consent before the experiment officially starts.

MRI parameters

The MRI scan was achieved by a 3.0T Siemens Trio Tim MRI scanners (Siemens, Munich, Germany). During the scanning, all participants kept their eyes closed and awake with relaxed breathing, and tried to avoid thinking on purpose or receiving external stimulation. Sustain the supine position throughout the scan. Scanning technical parameters were as presented: repetition time (TR) = 2000ms, echo time (TE) = 40ms, flip angle = 90°, acquisition matrix = 240×240, thickness = 4mm, field of view (FOV) = 240×240. Finally, 240 functional images were generated. The entire scanning time lasted for 8 minutes. The scanning range covered the entire brain.

fMRI data analysis

MRIcro software was adopted to classify, identify and delete incomplete data from the MRI scan for the integrity and validity of the data. The utilization of Statistical Parametric Mapping software8 (SPM8)was for data preprocessing, which includes: 1) Abandon the first 15 functional images, convert the remaining data to the NIFTI format, and perform time layer correction and head movement correction (retaining the data with head movement ≤ 1.5mm and head rotation ≤ 2°); 2) Taking into account the difference in brain volume of different subjects, the fMRI images are standardized using echo plane imaging templates (using the Montreal Institute of Neurology (MNI) spatial standard) and resembled (voxel = 3mm× 3mm×3mm); 3) Eliminate the linear trend of the time series and perform low-frequency filtering (0.01-0.08Hz) on it to reduce low-frequency drift and high-frequency noise; 4) Use full width and half height (FWHM: 6mm×6mm×6mm) Smooth the image.

The covariates referenced in the regression analysis includes the 6 parameters of head movement, the average frame displacement [FD], the overall brain signal, and the average signal of white matter and cerebrospinal fluid.

Calculation of fALFF values

The value of fALFF is equal to the ratio of the power spectrum in a specific low-frequency range of a certain brain area to the power spectrum of the entire frequency range, which can reduce the interference caused by the normal physiological activities of other brain areas to a certain extent. REST software was chosen for the calculation, conversion of time series data and a specific frequency range, and calculation of the power spectrum. The specific low frequency range is set to 0.01-0.08Hz, and the entire frequency range is set to 0-0.25Hz

Correlation analysis

Correlation analysis was performed to evaluate the relationship between atypical autonomous activities and clinical performance. Indexes we adopted included minimum resolution angle logarithmic vision (LogMAR), which based on the value of best corrected visual acuity (BCVA) and hospital anxiety and depression scale (HADS), which could quantify evaluate the level of anxiety. With the application of REST software, we defined brain regions in PAT with different fALFF values as regions of interest (ROI), and analysis the correlation between mean fALFF values of ROI and one of the indexes through linear correlation analysis ($\alpha = 0.05$, $P < \alpha$ is statistically significant).

Statistical analysis

The statistical analysis involved in the experiment was conducted using SPSS 20.0 (SPSS, IBM Corp, USA). General information and clinical characteristics of the subjects were statistically tested by independent sample t-test and chi-square test ($\alpha = 0.05$. $P < \alpha$ indicating that the difference is statistically significant). The difference of fALFF between PAT and HCs was verified by two independent sample t-tests to check if it is statistically significant, and the value of this difference as a diagnostic indicator was analyzed by ROC curve. The correlation analysis between the fALFF value and clinical manifestations of specific brain areas in the PAT group was performed by Pearson correlation analysis ($\alpha = 0.05$. $P < \alpha$ is statistically significant).

Results

Demographics and visual measurements

There were no significant differences in gender ($p > 0.99$), age ($p = 0.322$), BCVA ($p = 0.276$ for domain eyes and $P = 0.295$ for the fellow eye). More details were given in Table 1.

Table 1
The conditions of participants included in the study

Condition	SA	HCs	t-value	P-value*
Male/female	15/8	15/8	N/A	> 0.99
Age (years)	10.46 ± 1.29	11.61 ± 1.32	-1.056	0.322
Weight (kg)	28.53 ± 3.64	29.64 ± 3.54	-0.784	0.595
Handedness	23R	23R	N/A	> 0.99
Best-corrected VA-DE	1.15 ± 0.15	1.10 ± 0.10	1.875	0.276
Best-corrected VA-FE	1.10 ± 0.15	1.15 ± 0.10	1.864	0.295
Duration of SA (years)	10.46 ± 1.29	N/A	N/A	N/A
Esotropia/exotropia	13/10	N/A	N/A	N/A
Angle of strabismus (PD)	37.39 ± 9.24	N/A	N/A	N/A

Notes: Independent t-tests comparing two groups ($P < 0.05$ represented statistically significant differences).

Abbreviations: DE, dominant eye; FE, fellow eye; HCs, healthy controls; N/A, not applicable; PD, prism diopter; SA, strabismus and amblyopia; VA, visual acuity.

fALFF differences

Children with SA had a decreased fALFF values in Temporal-Pole-Sup-L, Temporal-Mid-R, Frontal-Sup-R, Supp-Motor-Area-R. Moreover, they also presented higher fALFF values in specific brain areas, which included Precentral-L, Precental gyrus, Parietal_Inf-L, Precuneus-L. More detailed information was shown in Fig. 1 **and** Table 2. In the meantime, Fig. 2 depicts the mean of changed spontaneous brain activity between PAT and HCs.

Table 2
Brain regions with significant differences in ALFF between PAT and HC groups

Brain areas	MNI coordinates			fALFF			ROI sequence
	X	Y	Z	BA	Peak voxels	t-value	
HCs > PAT							
Temporal_Pole_Sup_L	-15	9	-24	47	77	3.28	Cluster1
Temporal_Mid_R	60	-51	9	22	89	3.54	Cluster3
Frontal_Sup_R	21	33	45	8	65	5.49	Cluster5
Supp_Motor_Area_R	3	0	54	6	59	3.37	Cluster6
HCs < PAT							
Precentral_L	-30	-3	21	6	99	-4.23	Cluster2
Parietal_Inf_L	-39	-39	39	40	64	-4.16	Cluster4
Precuneus_L	-9	-60	60	7	66	-3.2	Cluster7

Notes: α=0.05 for multiple comparisons through Gaussian random field theory (z>2.3, P<0.01, cluster size>40 voxels, Alphasim corrected)

Abbreviations: PAT, patients; HCs, healthy controls; MNI, Montreal Neurological Institute; BA, Brodmann area; ROI, region of interest; L, left; R, right; Temporal-Pole-Sup, Temporal pole: superior temporal gyrus; Temporal-Mid, Middle temporal gyrus; Frontal-Sup, Superior frontal gyrus; Supp-Motor-Area, Supplementary motor area; Precentral, Precentral gyrus; Parietal_Inf, Inferior parietal, but supramarginal and angular gyri.

ROC analysis

Due to the difference in fALFF values in some brain regions between PAT and SA, we wonder whether this discrepancy could be considered as a diagnostic criterion for SA, thus we chose receiver operating characteristic (ROC) curve as a common method to explore the diagnostic value of this difference. We concentrated on the area under the curve (AUC) of the ROC curve, because this indicator can simultaneously take sensitivity and specificity into account. We divide the accuracy into low (AUC0.5 ~ 0.7) and high (AUC0.7-0.9) levels to assess its diagnostic value more accurate. The area under curve is 0.745 for Temporal-Pole-Sup-L (P = 0.005); 0.755 for Temporal-Mid-R (P = 0.003); 0.887 for Frontal-Sup-R (P < 0.001); 0.773 for Supp-Motor-Area-R (P = 0.002); 0.69 for Precentral-L (P = 0.001,); 0.68 for Parietal-L (P < 0.001); 0.73 for Precuneus-L (P = 0.003). (Fig. 3)

Correlation analysis

Mean fALFF values of temporal-pole-sup-L showed a negative correlation with log MAR (r=-o.665, P = 0.001), meanwhile, familiar correlation was observed in temporal-mid-R and HADS (r=-0.535, P = 0.009).

(Fig. 4)

Discussion

Analysis of the increased fALFF in children with SA

The superior temporal gyrus is linked with language comprehension [18], visual search[19] and other functions. The bilateral superior temporal gyrus and middle temporal gyrus are also known as the V5/MT area (visual area 5/middle temporal gyrus), and the hippocampus there are functional connections that play an important role in visual memory[20]. In addition, the V5/MT area is also the core area of the global motion perception, GMP[21], that is, in a specific visual scene, the motion trajectory of a single element is integrated to form a comprehensive three-dimensional stimulus. In many diseases, there are certain pathological changes in the superior temporal gyrus, including schizophrenia[22], Alzheimer's disease[23], adult common exotropia[24]and unilateral acute open eye injury[25]. Wang et al[26]found that the thickness of the cerebral cortex in the V5/MT area of patients with high intraocular pressure glaucoma was reduced, which may be related to the decrease of high intraocular pressure and visual stimulation caused by the disease[27, 28]. The study of Cai[29] et al showed that the stimulation of the V5/MT area may cause the subjects to discriminate the overall direction of movement. Similar to this result, the increase in the fALFF value in this experiment indicates that the V5/MT area of SA patients is overactive, which may be related to the compensatory overactivation of this area caused by the obstacle of SA patients' judgment of spatial location.

The frontal lobe is one of the main functional areas of the cerebral hemisphere, and there are abnormal pathological changes in the superior frontal gyrus in many ophthalmological diseases. Huang[30] et al showed that the ALFF value of the superior frontal gyrus of patients with primary angle-closure glaucoma (POAG) decreased, and the increase of the ALFF value of the superior frontal gyrus was also discovered in patients with corneal ulcer[31], and adults with strabismus and amblyopia also showed The ALFF on the right forehead is worth increasing[6]. This phenomenon may be due to the frontal eye field (FEF)[32] [23] formed by the participation of the frontal gyrus, which is related to saccade movement, visual perception[32]and pain[33]. In this study, children with strabismus and amblyopia also showed an increase in the fALFF value of right superior frontal gyrus, suggesting that compared with HCs, the spontaneous activities of right superior frontal gyrus of PAT were more active, and the patients with strabismus and amblyopia caused eye movement disorders and vision. The ability to receive and integrate stimuli decreases, so this may be the result of compensatory hyperfunction of the superior frontal gyrus.

The supplementary motor area (SMA) includes a part of the side of Brodmand 6 and 8. The anterior extremity is the supplementary eye field(SEF), and is adjacent to the supplementary sensory area. Stimulating SEF under laboratory conditions could cause eye movement and combined eye movement[34]. It shows that spontaneous brain activities of SEF could be detected before the movement of unilateral eyeball[35], and there will be SMA activation after showing the intention to change the existing combined eye movement state[36]. Discrete lesions of SEF and SMA can cause abnormal eye movements in patients[37]. In addition, activation of SMA can also be observed in sequence learning[38]. Studies believe that this activation is explained by the visual cues and responses required during the learning process[39]. At present, it is believed that the post-spinal inhibition of the supplemental exercise area involved in exercise is closely related to diseases such as Parkinson disease[40]. The SMA area, especially the SEF area, is closely connected with the movement of the eyeball. In this study, we found that there is a decrease in fALFF value in the SMA area in children with SA, which may indicate that in the early stages of the course of strabismus in children, there is a functional compensation in this brain area due to abnormal eye movements, thus showing unusually active.

Analysis of the decreased fALFF in PAT

The precentral gyrus is part of the primary motor cortex[41], which receives proprioception and regulates autonomous movement. Studies have found that in many ophthalmological diseases, changes in the structure of function of precentral can be observed. Huang[30] et al found that the ALFF value of precentral in PACG patients decreased, and analogously, Chan[42] et al showed that the gray matter volume (GMV) of the right precentral gyrus was increased in patients with strabismus. The study by Lin [43]et al observed more active spontaneous brain activities in precentral gyrus in anisometropia patients. Those conclusions are compatible with the results of our study, suggesting that children with SA have spontaneous eye movement disorders.

The parietal lobe is related to higher cognitive functions and thinking processing[44], while the inferior parietal lobules are thought to be related to the oculomotor nerve, the forming and maintaining of attention, hand-eye coordination recalibration[45], and language learning in real life[46]. Meanwhile it also be reported to be greatly helpful to choose of information, which is related to visual space[47]. In this study, the fALFF value of inferior parietal decreased, which may be related to the abnormal visual function increasing the obstacles of language learning of children, which leading to the lack of reading and spelling ability.

Default mode network (DMN) refers to a functional network composed of brain regions that are spatially separated but show a high degree of temporal correlation at rest. DMN involves many brain regions, including the subcortex of parietal lobe, middle frontal gyrus, and frontal gyrus and precuneus[48].

The precuneus plays a key role in DMN and participates in the formation of visual network pathways. It also plays an irreplaceable role in visual spatial imaging[49], self-processing[50], episodic memory extraction[51], spatial position coding[52], etc. We reviewed the studies of other researches and found that many eye diseases have been observed to changed structure or connection function and spontaneous activity of the precuneus. In patients with binocular blindness, the volume of local gray matter in the precuneus is reduced[53]. Other studies have shown that in normal-tension glaucoma[54], diabetic retinopathy[55], primary angle-closure glaucoma[30] and other diseases, the precuneus shows spontaneous reduction of brain activity, which is consistent with our research. The conclusions are the same, and the results of the study are also consistent with the clinical manifestations of SA children with eye movement disorders and abnormal visual spatial imaging. However, Tan[56] et al found that with acute open globe injury (OGI), the ALFF value of the precuneus was increased, which was negatively related to the duration of OGI. This result strongly suggested that in the early stage of eye injury, the damage will be compensated by more active spontaneous brain activities of precuneus. However, as the course of the disease continues, this compensatory effect may be weakened. This hypothesis can also explain the results of some similar studies that are contrary to the results of our study[30].

In addition, due to the superficial anatomical position of the eyes. It is easy to be noticed in daily life and interpersonal communication. Therefore, some scholars believe that strabismus is actually a cosmetic disease[57], and childhood is an important period of character formation and interpersonal communication. Therefore, congenital SA may influence the physical and mental health of children. Studies have shown that SA may cause patients to discover negative emotions such as low self-esteem and anxiety[58]. In our study, HADS was used to evaluate the anxiety of children, and it was found that the HADS score of SA patients was negatively correlated with the spontaneous brain activity of the middle temporal gyrus. This anxiety may be secondary to the decreased activity of the middle temporal gyrus area in SA disease, or it may be caused by disease making children become unconfident and anxious in daily life and social activities. (Table 3)

Table 3
The function of brain regions with altered fALFF values and its clinical significance

Brain region	Experiment result	Function	Anticipated results
Temporal-Pole-Sup-L	HC > PAT	Auditognosis; Language; emotion processing.	Depression; anxiety; visual impairment.
Temporal-Mid-R	HC > PAT	Forming DMN; recognition and processing of color and shape.	Depression; anxiety.
Frontal-Sup-R	HC > PAT	Memory; processing of cognitive information.	Damaged spatial cognitive ability and eye-hand coordination.
Supp-Motor-Area-R	HC > PAT	Action inhibition; modulating interhemispheric interactions.	Epilepsy; depression; motor neglect.
Precentral-L	HC < PAT	Somatic movement controlling.	Damaged visual function.
Parietal-Inf-L	HC < PAT	Part of DMN; Advanced cognitive function.	Depression; anxiety.
Precuneus-L	HC < PAT	Visuospatial imagery; attention; episodic memory; Functional core of DMN; consciousness.	Pain felling; dysfunction of spatial orientation.

Abbreviation: PAT, patient; HC, healthy controls; DMN, default-mode network.

Limitations

It should be noted in particular that there are still some deficiencies in this study, including: 1) samples included in the study are not adequate; 2) The subjects were younger, there may be a low degree of coordination in the process of fMRI examination; 3) Mixed bias is unavoidable.

Conclusion

In this study, we found that children with SA presented abnormal spontaneous brain activities in the visual pathway or visual-related brain regions. These abnormal spontaneous activities may have a bearing on the patient's clinical manifestations or be attributed to compensatory of eye movement dysfunction. Moreover, correlation analysis also showed that SA in childhood may cause undesirable emotions in patients.

Declarations

Ethics approval All research methods were approved by the committee of the medical ethics of the First Affiliated Hospital of Nanchang University and were in accordance with the 1964 Helsinki declaration and its later amendments or comparable ethical standards. Parents (or legal guardians) of all subjects were explained the purpose, methods, potential risks, and gave their consent to this study.

Consent to participate All data generated or analyzed during this study from patients are included in this published article. All Patients and guardians were provided consent to publish these pictures.

Consent for publication All authors have read and agreed to the published version of the manuscript.

Availability of data and material Data used to support the findings of this study are available from the corresponding author upon request.

Competing interests This was not an industry supported study. The authors report no conflicts of interest in this work.

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Figures

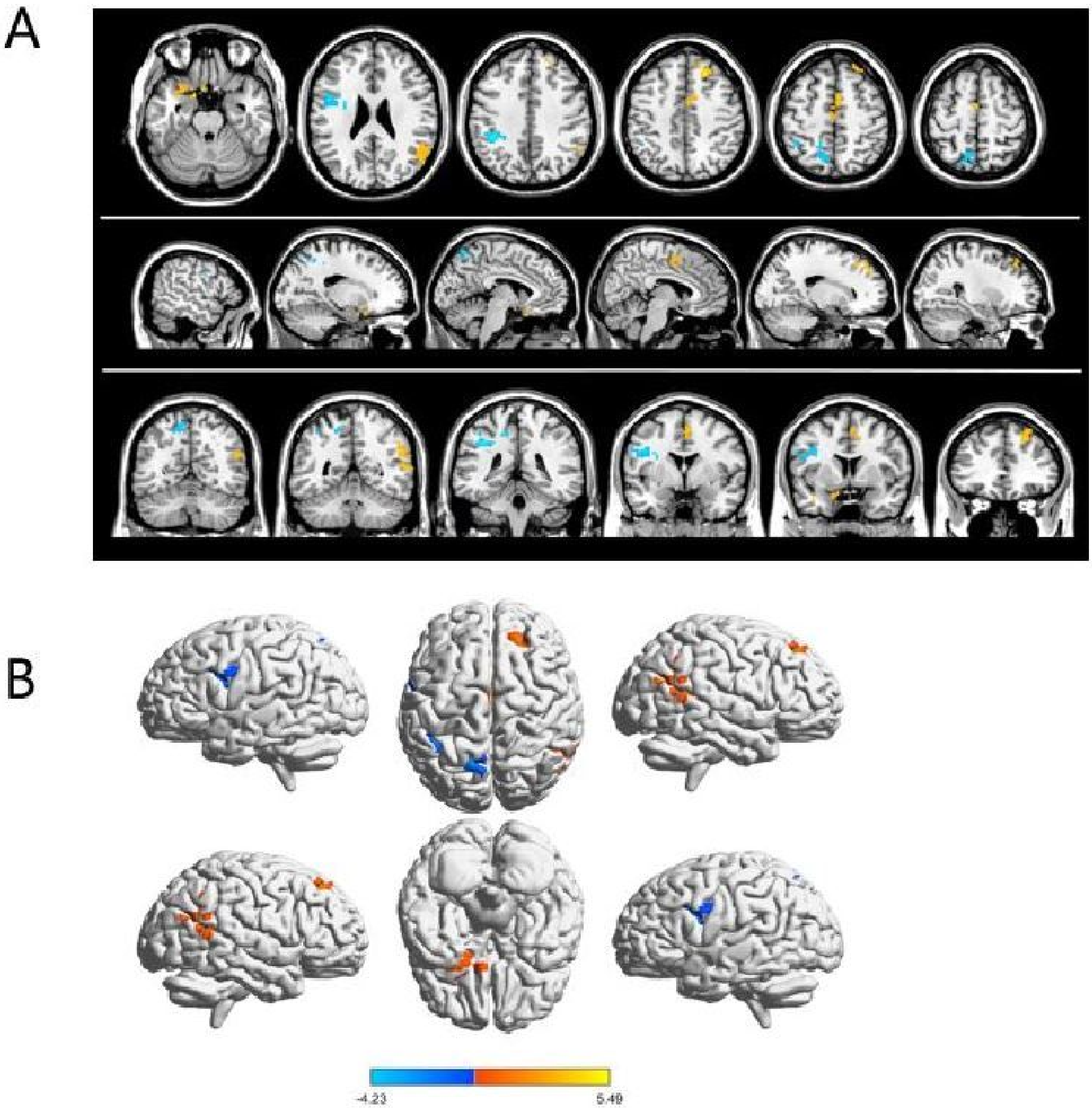

Figure 1

Spontaneous brain activity in children and HCs. Notes:(A) The brain regions presented sensible differences in fAlFF values between SA and HCs. (B) Children with SA would be observed some abnormal brain activities in specific regions. Compared with HCs, red regions trend to mean higher fALFF values. Regions marked by blue presented delegated region presenting decreased fALFF values. Abbreviation: fALFF, fractional amplitude of low-frequency fluctuation; HCs, healthy controls; SA, strabismus and amblyopia.

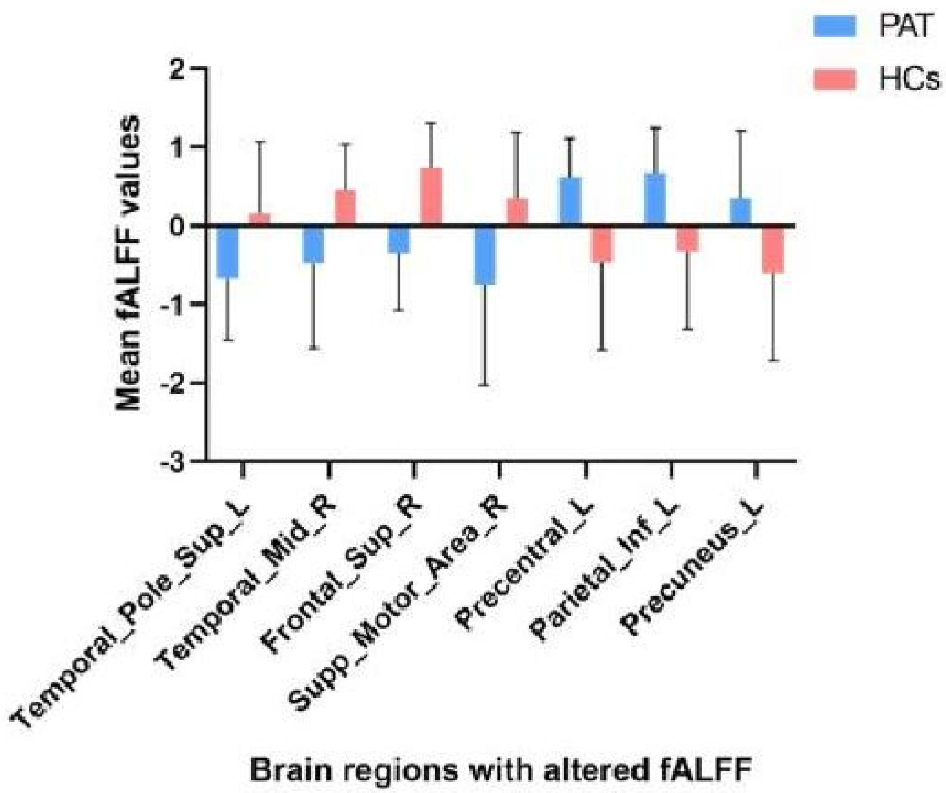

Figure 2

The mean fALFF values between children with SA and HCs

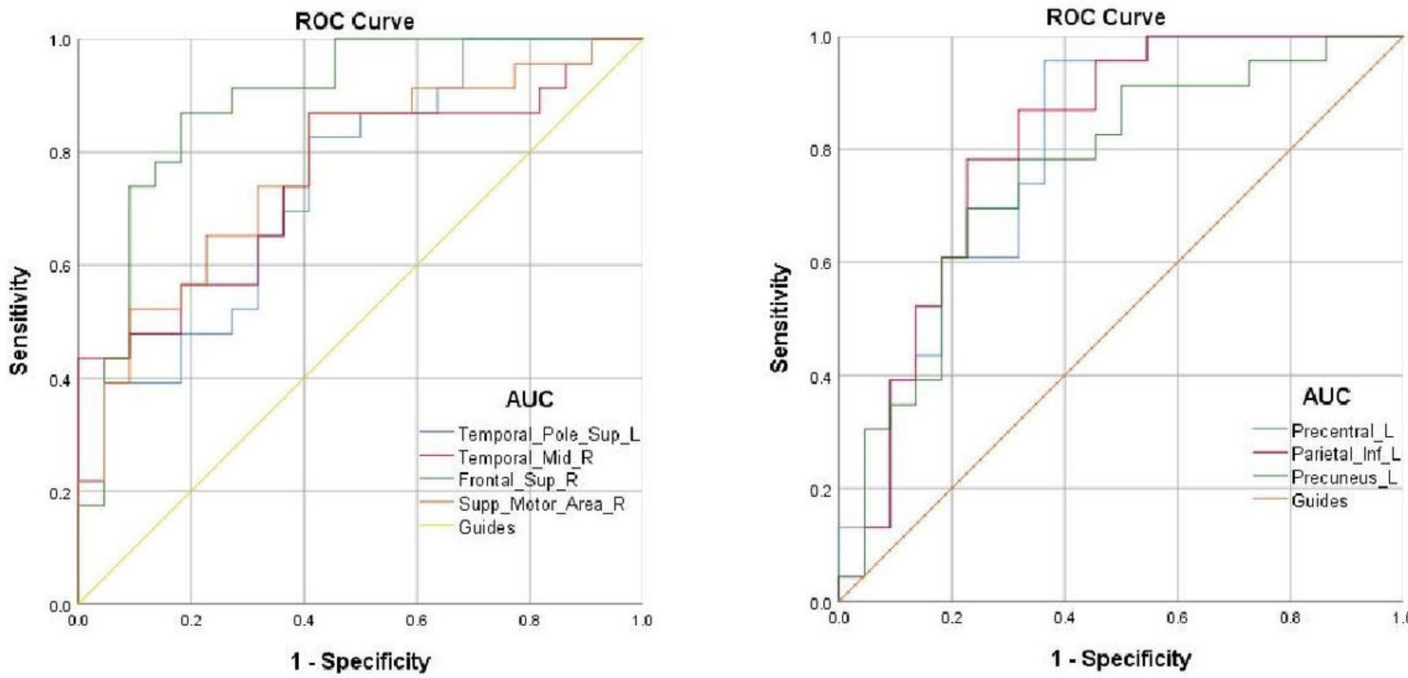

Figure 3

ROC curve analysis for the mean fALFF values of altered brain regions Notes: (A)The area under ROC curve was 0.745 for Temporal-Pole-Sup-L (P=0.005, 95%CI:0.603-0.887); 0.755 for Temporal-Mid-R (P=0.003, 95%CI:0.621-0.898); 0.887 for Frontal-Sup-R (P<0.001, 95%CI:0.787-0.988); 0.773 for Supp-Motor-Area-R (P=0.002, 95%CI:0.635-0.910). (B)The area under ROC curve was 0.69 for Precentral-L (P=0.001, 95%CI:0.659-0.930); 0.68 for Parietal-L (P<0.001, 95%CI:0.675-0.941); 0.73 for Precuneus-L (P=0.003, 95%CI: 0.616-0.902).

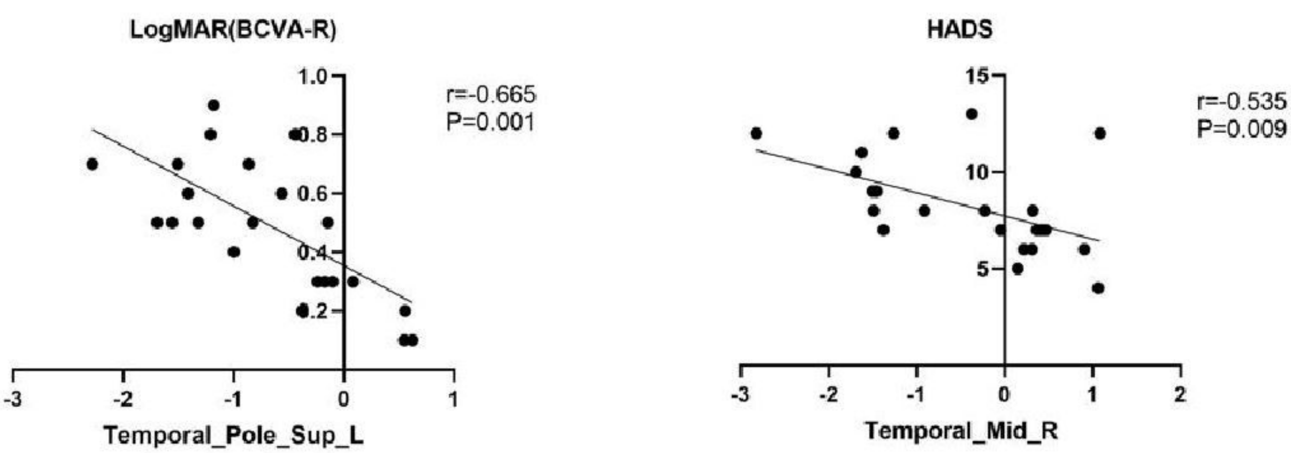

Figure 4

The result of correlation analysis. Notes: The values of LogMAR(BCVA-R) of PAT presented significant correlation with the fALFF values of Temporal-Pole-Sup-L. The scores of HADS showed a negative correlation with fALFF values of temporal_mid_R (r=-0.535, P=0.009)