

Altered functional connectivity of primary visual cortex in adults with strabismus and amblyopia: a resting-state fMRI study

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Functional connectivity of the primary visual cortex was explored with resting functional magnetic resonance imaging among adults with strabismus and amblyopia and healthy controls. We used the two-sample test and receiver operating characteristic curves to investigate the differences in mean functional connectivity values between the groups with strabismus and amblyopia and healthy controls. Compared with healthy controls, functional connectivity values in the left Brodmann areas 17, including bilateral lingual/angular gyri, were reduced in groups with strabismus and amblyopia. Moreover, functional connectivity values in the right Brodmann area 17, including left cuneus, right inferior occipital gyrus, and left inferior parietal lobule, were reduced in adults with strabismus and amblyopia. Our findings indicate that functional connectivity abnormalities exist between the primary visual cortex and other regions. This may be the basis of the pathological mechanism of visual dysfunction and stereovision disorders in adults with strabismus and amblyopia.

Keywords

Strabismus; Amblyopia; Functional connectivity; Primary visual cortex; Spontaneous activity; Resting fMRI; Neuropathology; Ophthalmopathy

1. Introduction

Strabismus and amblyopia (SA) are visual developmental disorders, which may occur during childhood [1]. Strabismus is the relative deviation of the visual axis, and there are a variety of methods by which it can be classified. At present, the mainstream classification method is to categorize it as esotropia, exotropia, vertical rotary strabismus, or A-V pattern strabismus, according to the oblique direction of eye movement. It can also be classified according to abnormal eye movements [2].

During the critical period of visual development, the abnormal visual experience can cause developmental diseases of the visual system, including amblyopia. Amblyopia is characterized by reduced best-corrected vision in one or both eyes, without associated ocular organic lesions [3]. A series of studies have shown that ametropia, strabismus and ambly-

opia often influence each other [4–6]. Strabismus and amblyopia do not only affect visual function and appearance but can also seriously affect the psychosocial health of patients [7–9].

Strabismus is usually treated by surgery, while the removal mainly treats amblyopia of form deprivation, occlusion therapy, or depression therapy during the critical period [9]. Without treatment, SA can persist into adulthood [8]. Adults with SA may have permanent cortical changes due to disrupted functional connections in the brain, abnormal eye movements, loss of stereo vision, and interocular inhibition [10–13]. Neuroanatomically, the binocular provides two essentially independent information streams synthesized by the primary visual cortex (V1) [14]. After fusing images through the V1, the visual system produces a unified perception of the visual world. Simultaneously, the stereo parallax is used to perceive the distance information of the observed object [15].

Compared with magnetic resonance imaging (MRI), functional MRI (fMRI) can detect the fluctuation of blood oxygenation in specific cerebral regions to further explore the functional state of neuronal activity in these cerebral regions. It provides new neuroimaging and brain function studies [16–18]. Furthermore, fMRI can be used to determine the pathophysiological changes of brain function under resting-state conditions, which can be helpful for clinical diagnosis and treatment evaluation.

Comparisons facilitated by dynamic fMRI showed that healthy controls (HCs) participation is simpler and easier, with fewer influencing factors and more analytic data [19]. Our paper examines the functional connectivity (FC) of the V1 in adults with SA using resting fMRI. Our findings may be useful in determining the cause of visual impairment and visual fusion disorders among adults (>18+ years of age) with SA.

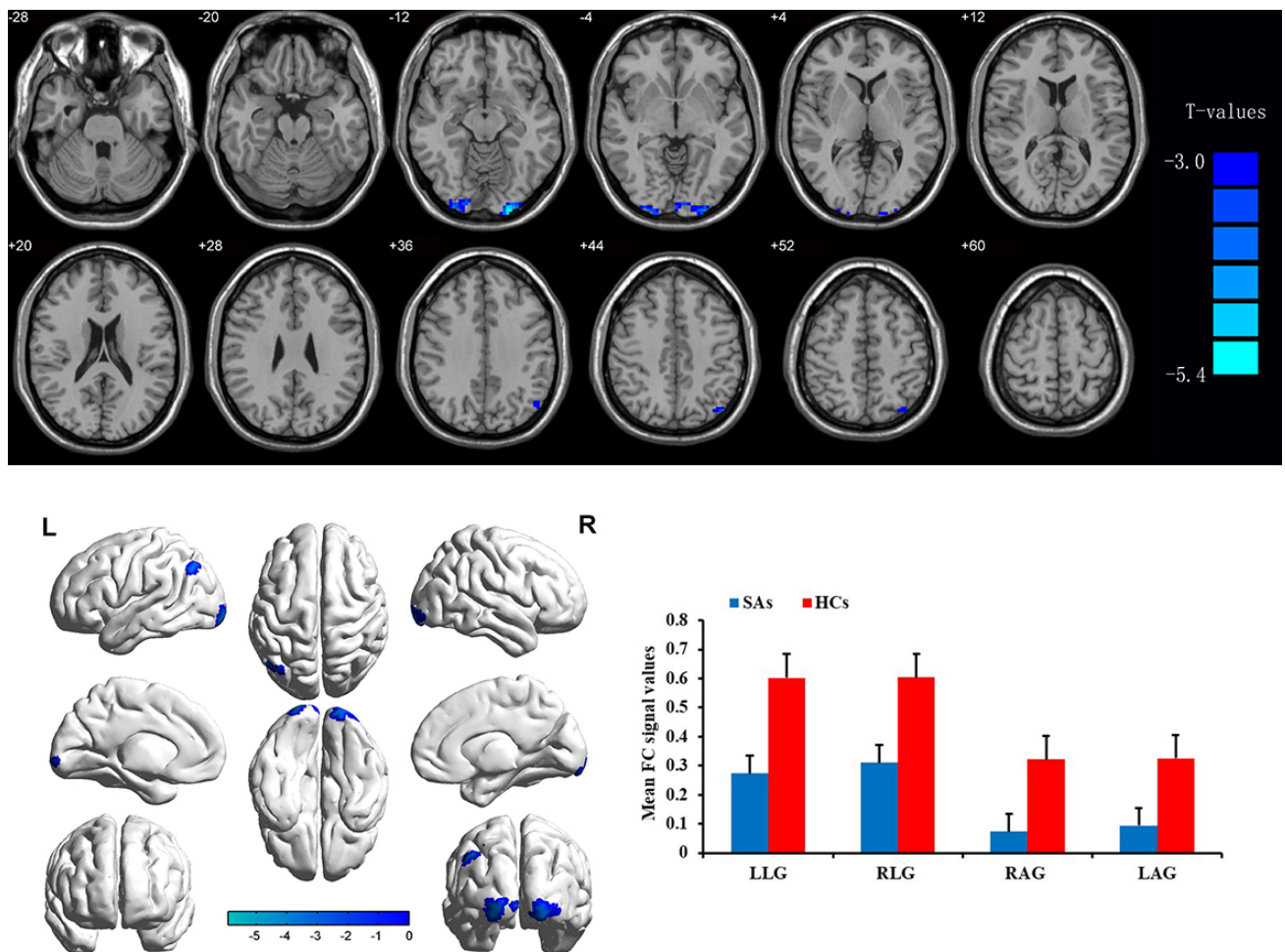


Fig. 1. Brain regions demonstrated statistically significant differences between two groups in FC in the left BA17. Significant FC differences were observed in the left lingual gyrus/right lingual gyrus and left angular gyrus/right angular gyrus, and the blue areas denote lower FC values. SAs, strabismus with amblyopia; HCs, healthy controls; BA, Brodmann area; FC, Functional connectivity.

2. Methods

With SA, sixteen adults (5 male and 11 female adults; mean age, 25.67 ± 4.91 years) participated at the Department of the Ophthalmology, the First Affiliated Hospital of Nanchang University in Jiangxi Province, China. And 16 HCs (5 males and 11 females; mean age, 24.98 ± 5.27 years) were also recruited who were similar in age to the SA group. The common inclusion criteria of the two groups were: (1) adult, over the age of 18 years; (2) availability of MRI scans (with no evidence of a pacemaker or metal implant, etc.). The unique inclusion criteria of the SA group were: (1) diagnosis of strabismus; (2) a difference of more than one line between the best-corrected visual acuity of amblyopia ($VA > 0.20$ logMAR units) and the fellow eye; (3) absence of eye trauma, glaucoma, cataract, and other eye diseases. The unique inclusion criteria of the HC group were: (1) normal brain parenchyma on MRI; (2) $VA > 1.0$, and the absence of eye disease; (3) absence of mental illness. The common exclusion criteria of the two groups were as follows: (1) the presence of other eye diseases or history of eye surgery; (2) mental illness, cardio-

vascular disease, or cerebral infarction; (3) drug or alcohol abuse. The unique exclusion criterion of the SA group was as follows: (1) acquired strabismus.

The age, weight, habitual hand and duration of strabismus amblyopia were collected routinely. The ophthalmologist determined the type of strabismus in adults with SA, measured the strabismus angle, and finally measured the binocular vision of all subjects. The work was approved by the Medical Ethics Committee of the First Affiliated Hospital of Nanchang University and followed the principles of the Declaration of Helsinki. All subjects voluntarily participated in the research and gave informed consent.

2.1 MRI parameters

A Trio 3-Tesla MRI scanner (Siemens AG) was used for the MRI scans. Subjects were told to close their eyes but remain awake during the scan of the resting-state fMRI (rs-fMRI). The parameters of T1 and T2 sequence imaging were as follows: repetition time (TR), 1900 ms; echo time (TE), 2.26 ms; flip angle (FA), 9° ; matrix, 256×256 ; field of view (FOV), 250×250 mm; thickness, 1.0 mm; gap, 0.5 mm; 176

sagittal slices. A three-dimensional spoiled gradient recalled-echo pulse sequence was used to obtain the functional data. The entire scanning procedure lasted approximately 8 min. In addition, 240 structural images were captured using the following settings: acquisition matrix, 64×64 ; FOV, 220×220 mm; thickness, 4.0 mm; gap, 1.2 mm; TR, 2000 ms; TE, 30 ms; FA, 90° ; and 29 axial images.

2.2 fMRI data processing

The data processing and analysis process used the Data Processing Assistant for rs-fMRI (DPARSF 2.3, <http://rfmri.org/DPARSF>) and the Matlab version 2014b software (Mathworks, Natick, MA, USA), as well as the Statistical Parametric Mapping software (SPM12, The Wellcome Centre for Human Neuroimaging, UCL Queen Square Institute of Neurology, London, UK, <http://www.fil.ion.ucl.ac.uk/spm>) and the rs-fMRI Data Analysis Toolkit (REST_V1.8.130615, The State key Laboratory of cognitive Neuroscience and learning Beijing Normal University, China, <http://www.restfmri.net>). The data preprocessing steps were as follows: (1) the first 10 time points were removed to eliminate the interference of slice timing effects. (2) Blood oxygenation level-dependent (BOLD) runs of 240 functional volumes were performed, and the images acquired were motion-corrected and converted to appropriate file formats [20]. The fMRI scans were discarded with an angular displacement or maximum displacement greater than 2 mm. (3) Images were spatially normalized (resampling to 3 mm isotropic voxels). Images were smoothed with a 6 mm full width at half maximum Gaussian kernel, linear detrending and temporal band-pass filtering was performed (0.01–0.08 Hz). The temporal covariates were later removed, as well as six head-motion parameters, white matter signals, and cerebrospinal fluid signals.

2.3 Definition of the region of interest in Brodmann area 17

The V1 is also referred to as Brodmann area 17 (BA17). We chose the WFU PickAtlas2.3 tool (The Functional MRI Laboratory, Wake Forest University School of Medicine, NC, USA) to select each side of V1 as the regions of interest (ROIs) (Table 1).

Table 1. Montreal Neurological Institute coordinates for selected seed regions.

ROI	Seed regions	X	Y	Z
1	L V1 (BA17)	−8	−76	10
2	R V1 (BA17)	7	−76	10

ROI, Region of interest.

2.4 Functional connectivity analysis

The FC analysis was performed on both the left and right BA17. The Data Processing & Analysis of Brain Imaging statistical module (<http://rfmri.org/dpabi>) analyzed the rs-fMRI data. The FC graph was constructed using age and sex as covariates. This part of data was analyzed by one-way anal-

ysis of covariance and generalized linear model.

2.5 Statistical analysis

To evaluate differences in demographic data with SA and HCs, we used the two-sample Student's *t*-test (SPSS software version 20.0, IBM Corp, Armonk, NY, USA). $p < 0.05$ was considered statistically significant. To know whether the difference in FC values of different cerebral regions was statistically significant, we used the independent sample *t*-test. The differences in FC between the groups with SA and HCs [at voxel level $p < 0.01$ and cluster level $p < 0.05$, Gaussian random field-corrected] were determined by applying the two-sample *t*-test. In data analysis, we have confirmed cerebral regions with significant differences in FC values between the two groups. On this basis, we assume that the FC value of the above cerebral regions can be used as a potential indicator for differential diagnosis of the SA group. Finally, we used the receiver operating characteristic (ROC) curve to analyze the potential differential diagnosis value of the above indicators.

3. Results

3.1 Statistical and behavioral changes

There were no significant differences in age and weight between the SA and HC groups ($p = 0.786$ in age; $p = 0.465$ in weight). Besides, there were significant differences in the best-corrected visual acuity between the two groups in the amblyopia eye ($p < 0.001$) and fellow eye ($p = 0.035$). See Table 2 for details.

3.2 Functional difference

The values obtained from the *t*-test of the two samples were used to determine the differences in FC mapping between the two groups. The FC values in the left BA17 and left lingual gyrus (BA18), right lingual gyrus (BA18), right angular gyrus (BA39), and left angular gyrus (BA39) were reduced in adults with SA ($n = 18$) compared with HCs (Fig. 1, Table 3). Moreover, the FC values in the right BA17 and left cuneus (BA18), right inferior occipital gyrus (BA18), and left inferior parietal lobule (BA39) were reduced (Fig. 2, Table 3). We found no significant correlations between the average FC value of specific brain areas in adults with SA and visual acuity ($p > 0.05$).

3.3 Analysis of receiver operating characteristic curves

We found significant differences in the FC values of different brain regions between groups with SA and HCs (Fig. 3). The areas under the curve were as follows: (A) left lingual gyrus, 0.910 ($p < 0.001$; 95% confidence interval [CI], 0.813–1.000); right lingual gyrus, 0.883 ($p < 0.001$; 95% CI, 0.758–1.000); right angular gyrus, 0.813 ($p = 0.003$; 95% CI, 0.652–0.973); left angular gyrus, 0.844 ($p = 0.001$; 95% CI, 0.709–0.979) (ROI in left BA17). (B) Left cuneus, 0.914 ($p < 0.001$; 95% CI, 0.815–1.000); right inferior occipital gyrus, 0.902 ($p < 0.001$; 95% CI, 0.791–1.000); left inferior parietal lobule, 0.816 ($p = 0.002$; 95% CI, 0.671–0.962) (ROI in right BA17).

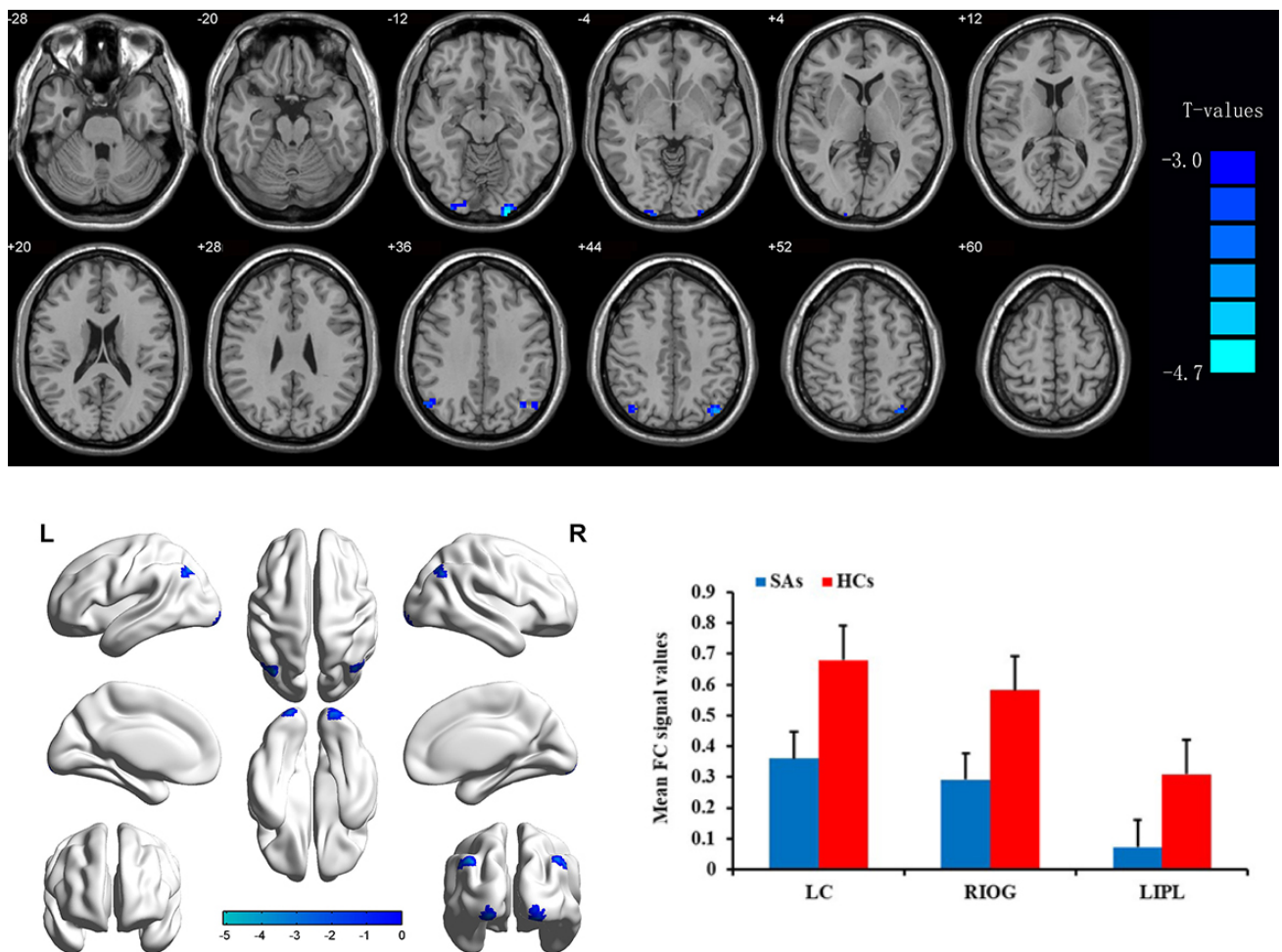


Fig. 2. Brain regions demonstrate statistically significant differences between two groups in FC in the right BA17. Significant FC differences were observed in the left cuneus, right Inferior Occipital Gyrus and left inferior parietal lobule, and the blue areas denote lower FC values. SAs, strabismus with amblyopia; HCs, healthy controls; BA, Brodmann area; FC, Functional connectivity.

Table 2. Demographics and clinical measurements of strabismus with amblyopia and healthy control groups.

Condition	SAs	HCs	<i>t</i> value	<i>p</i> -value
Male/female	5/11	5/11	N/A	>0.99
Age (years)	25.67 ± 4.91	24.98 ± 5.27	-0.243	0.786
Weight (kg)	61.22 ± 3.67	59.18 ± 3.65	-0.716	0.465
Handedness	16 R	16 R	N/A	>0.99
Duration (years)	23.57 ± 4.91	N/A	N/A	N/A
Esotropia/exotropia	6/10	N/A	N/A	N/A
Angle of strabismus (PD)	31.15 ± 11.65	N/A	N/A	N/A
VA-AE	0.15 ± 0.10	1.05 ± 0.25	6.136	<0.001
VA-FE	0.55 ± 0.05	1.00 ± 0.10	1.151	0.035

Independent *t*-tests comparing the two groups ($p < 0.05$ represented statistically significant differences). Data are shown as mean ± standard deviation or not applicable. SA, strabismus with amblyopia; HC, healthy control; R, right; PD, prism diopter; AE, amblyopic eye; FE, fellow eye; VA, Visual acuity.

4. Discussion

Adults with other eye diseases reportedly exhibit specific changes in FC of the V1 and other areas [21–32]. There was still a lack of understanding of the changes in cerebral func-

tion in adults with strabismus amblyopia. We found reduced FC values between the left BA17 and bilateral lingual/angular gyri in adults with SA compared with HCs. Similarly, the FC values between the right BA17 and left cuneus, right inferior occipital gyrus and left inferior parietal lobule are all reduced.

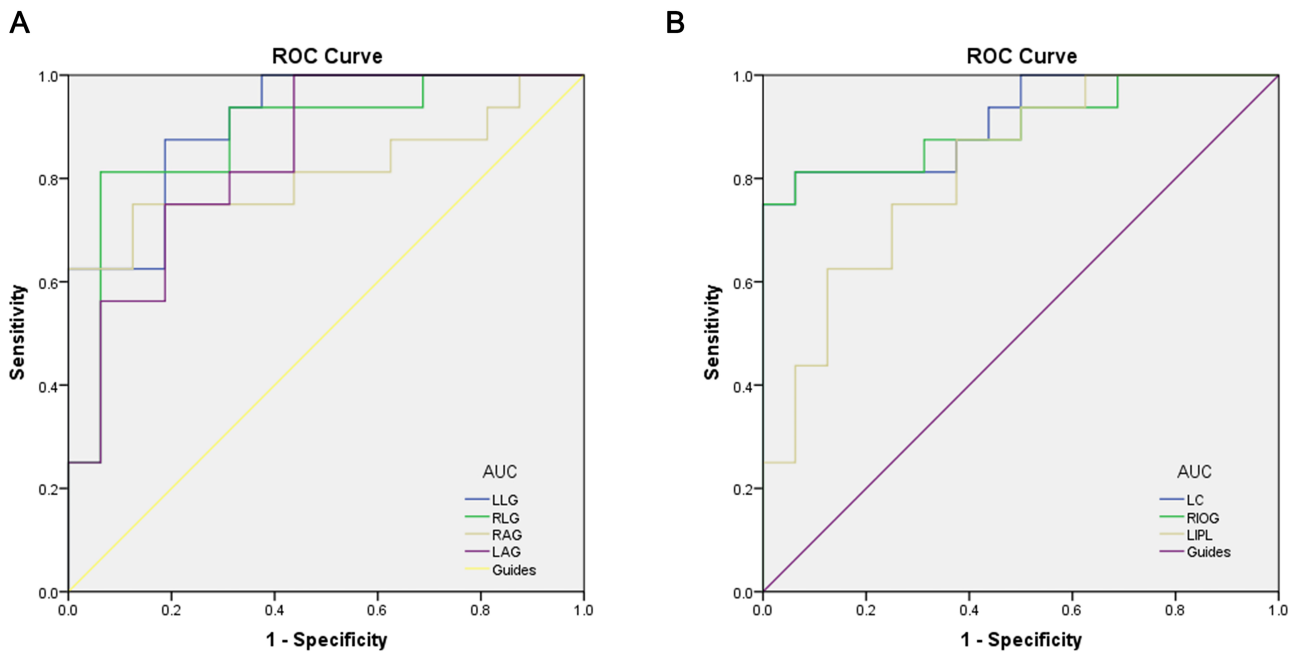


Fig. 3. ROC curve analysis of the mean FC values for altered brain regions. (A) ROI in left BA17. The AUCs of different brain regions were as follows: left lingual gyrus, 0.910 ($p < 0.001$; 95% confidence interval [CI], 0.813–1.000); right lingual gyrus, 0.883 ($p < 0.001$; 95% CI, 0.758–1.000); right angular gyrus, 0.813 ($p = 0.003$; 95% CI, 0.652–0.973); left angular gyrus, 0.844 ($p = 0.001$; 95% CI, 0.709–0.979). (B) ROI in right BA17. The AUCs of different brain regions were as follows: Left cuneus, 0.914 ($p < 0.001$; 95% CI, 0.815–1.000); right inferior occipital gyrus, 0.902 ($p < 0.001$; 95% CI, 0.791–1.000); left inferior parietal lobule, 0.816 ($s = 0.002$; 95% CI, 0.671–0.962). ROC, receiver operating characteristic; FC, Functional connectivity; CI, Confidence interval; SAs, strabismus with amblyopia; HCs, healthy controls; LC, left cuneus; RIOG, right Inferior occipital gyrus; LIPL, left inferior parietal lobule; LLG, left lingual gyrus; RLG, right lingual gyrus; RAG, right angular gyrus; LAG, left angular gyrus.

Table 3. Brain regions with significant differences in FC between SAs and HCs.

	Brain areas	MNI coordinates			BA	Peak voxels	<i>t</i> value	<i>p</i> -value
		X	Y	Z				
FC-L	ROI in left BA17							
	L Lingual Gyrus	−24	−102	−12	18	42	−5.1051	<i>p</i> < 0.005
	R Lingual Gyrus	24	−102	−6	18	37	−4.1837	<i>p</i> < 0.005
	R Angular Gyrus	54	−66	39	39	32	−3.8005	<i>p</i> < 0.005
	L Angular Gyrus	−39	−75	48	39	83	−4.169	<i>p</i> < 0.005
	Brain areas	MNI coordinates			BA	Peak voxels	<i>t</i> value	<i>p</i> -value
		X	Y	Z				
FC-R	ROI in right BA17							
	L Cuneus	−24	−102	−12	18	106	−5.9432	<i>p</i> < 0.005
	R Inferior Occipital Gyrus	24	−102	−6	18	84	−4.9365	<i>p</i> < 0.005
	L Inferior Parietal Lobule	−48	−72	42	39	42	−3.6918	<i>p</i> < 0.005

The statistical threshold was set at voxel level with $p < 0.005$ for multiple comparisons using Gaussian random field theory cluster level with $p < 0.05$ and cluster size > 40 voxels, AlphaSim corrected. *t* value was the statistical result obtained by the independent sample *t* test carried out by the Gaussian random field theory. FC, Functional Connectivity; SA, strabismus with amblyopia; HC, healthy control; L, left; R, right; MNI, Montreal Neurological Institute; BA, Brodmann area.

The lingual gyrus is connected to the fusiform gyrus and the parahippocampal gyrus and processed complex visual stimuli by identifying basic characteristics [21]. The lingual gyrus is also associated with processing overall visual stimuli.

When features such as visual contrast are increased, activation of the lingual gyrus is decreased [22].

The functional connection between the left BA17 and the bilateral lingual gyrus decreased. The lingual gyrus partici-

pated in several vision-related functional activities, so the reduced connectivity of functional activity in this part of the cerebrum can be seen to be a potential cause of visual fusion disorders in adults with SA. The angular gyrus activity is positively correlated with a delay in visual, auditory, and audiovisual actions; thus, differences between the predicted and actual results may be detected [23]. Block *et al.* [24] found that a specific region in the angular gyrus plays a positive mediating role between visual proprioception and rearrangement.

Ho *et al.* [25, 26] also found that the angular gyrus plays a key role in the lateralization of visual-spatial attention. Near and far spatial vision is reportedly altered in the right supramarginal gyrus under transcranial magnetic stimulation (TMS). In contrast, only “near space” vision is altered in the right angular gyrus under TMS [27]. These results indicate that the angular gyrus plays an important role in near-spatial visual processing and spatial attention.

The functional connection between left BA17 and bilateral angular gyrus is significantly reduced in adults with SA. The angular gyrus plays an important role in spatial visual processing, spatial attention, visual proprioception and audiovisual activities. Therefore, the decrease of functional connections between the angular gyrus and other cerebral regions could be one of the important pathological mechanisms of visual function decline in the SA group. Of course, the decrease of FC in this particular cerebral area may also result from visual dysfunction caused by strabismus amblyopia, which leads to significant changes in the functional activity of the cerebral cortex. Visual stimuli activated the primary posterior visual area and the anteromedial cuneus from the beginning of the cortical response. The anteromedial cuneus is in an appropriate temporal position to interact with the V1, thereby modifying the information transmitted by V1 to the outer cortex [28].

In addition, through the fMRI analysis of the amplitude of low-frequency fluctuation (ALFF) sequence, some scholars have pointed out that the ALFF value of the precuneus of adults with persistent postural-perceptual vertigo is significantly lower. We can infer that the precuneus played an important role in visual and vestibular information processing. We found that the FC value of the left cuneus of the SA group decreased significantly. The decreased functional connectivity of this cerebral region may be one of the important pathological mechanisms of visual fusion and vestibular dysfunction [29].

The FC values were reduced in the right BA17 and left cuneus group with SA, which may explain their visual deficits. Lu *et al.* [30] suggested that morphological abnormalities in the occipital, temporal, and frontal cortices of adults with amblyopia were due to early abnormal visual experience, which may cause neurodevelopmental processes to interfere with brain maturation. These changes may affect visual acuity and binocular vision.

Sato *et al.* [31] indicated that the degree of activation of the right inferior occipital gyrus increases, regardless of whether

the eyes are looking at a dynamic or a static pattern. This suggests that the right inferior occipital gyrus is early in visual processing. The results found that the functional connection between the right BA17 and the right inferior occipital gyrus was significantly decreased in adults with SA. The above discussion and analysis showed that the right inferior occipital gyrus played an important role in various visual modes. Therefore, a significant decrease in the functional connectivity of the right inferior occipital gyrus could be one of the potential auxiliary indicators for the differential diagnosis of SA.

The dorsal visual pathway starts from V1 and reaches the inferior parietal lobe through V2 and the medial temporal area, where the visual information is used to analyze and guide eye movement [32]. Yan *et al.* [33] have found that the structure of the inferior parietal lobe of patients with concomitant exotropia is abnormal. In addition, Ding *et al.* [34] indicated that the decreased FC values between the primary visual area and the inferior parietal lobule in a group with amblyopia might reflect functional deficits in the dorsal stream. Similarly, adults with SA had abnormal functional connections between the right BA17 and left inferior parietal lobe, leading to visual deficits.

Furthermore, we found the FC between the primary visual cortex and the medial/lateral occipitotemporal gyrus in SAs was not abnormal compared with healthy subjects. However, many scholars think the medial/lateral occipitotemporal gyrus in the role of vision cannot be ignored.

We further speculate that strabismus amblyopia can lead to significant changes in functional connection activity in specific brain regions. This change may be one of the potential neuropathological mechanisms of strabismus amblyopia. Of course, this inference requires further research. Through our above analysis and discussion, we have known that the occurrence and development of strabismus amblyopia are closely related to the complex brain network, especially the oculomotor neural network in the primary visual cortex [35]. The changes in neurological activity in the above brain areas may result from SA and the compensatory changes of cerebral cortex function caused by SA or its specific pathological mechanism. The changes in functional activities in the above brain regions may result from visual dysfunction caused by SA. They may be one of the potential neuropathological mechanisms of SA.

5. Conclusions

We can conclude that the functional connections of specific cerebral regions in adults with SA were significantly altered compared with those in normal adults. These include bilateral lingual gyrus, bilateral angular gyrus, left cuneus gyrus, right inferior occipital gyrus, and left inferior parietal lobule. The functional connection changes of the above cerebral regions may be the potential pathological mechanism of the occurrence and development of SA. The specific pathological mechanism of strabismus amblyopia needs to be fur-

ther studied. In addition, in clinical diagnosis, the above signal values of abnormal functional connectivity in brain areas may be used as indicators for the auxiliary diagnosis of SA diseases.

Abbreviations

ROI, region of interest; SA, strabismus with amblyopia; HC, healthy control; R, right; PD, prism diopter; AE, amblyopic eye; FE, fellow eye; VA, Visual acuity; FC, functional connectivity; MNI, Montreal Neurological Institute; BA, Brodmann area; ROC, receiver operating characteristic; CI, Confidence interval; LC, left cuneus; RIOG, right Inferior occipital gyrus; LIPL, left inferior parietal lobule; LLG, left lingual gyrus; RLG, right lingual gyrus; RAG, right angular gyrus; LAG, left angular gyrus.

Author contributions

LQL, QYL, ZHZ and YS conceived and designed the experiments; SNW and HYS performed the experiments; LJZ and RBL analyzed the data; YCP contributed reagents and materials; LQL and ZHZ wrote the paper.

Ethics approval and consent to participate

The study methods and protocols were approved by the Medical Ethics Committee of the First Affiliated Hospital of Nanchang University (Nanchang, China) (2015016) and followed the principles of the Declaration of Helsinki. All subjects were notified of the objectives and content of the study and latent risks, and then provided written informed consent to participate.

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Conflict of interest

The authors declare no conflict of interest.

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