Altered Brain Network Centrality in Patients with Adult Strabismus with Amblyopia: A Resting-State Functional Magnetic Resonance Imaging (fMRI) Study

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Background:
The aim of this study was to explore potential changes in brain function network activity in patients with adult strabismus with amblyopia (SA) using the voxel-wise degree centrality (DC) method.

Material/Methods:
We enrolled 15 patients with SA (6 males, 9 females) and 15 sex-matched healthy controls (HCs). All subjects completed resting functional magnetic resonance imaging scans. Independent-sample t tests and receiver operating characteristic (ROC) curves were used to assess DC value differences between groups, and Pearson correlation analysis was performed to evaluate correlations between DC-changed brain regions and clinical data of patients with SA.

Results:
Compared with the HC group, DC values that were lower in patients with SA included the left middle frontal gyrus and bilateral angular gyri. Increases were observed in the left fusiform gyrus, right lingual gyrus, right middle occipital gyrus, right postcentral gyrus, and left paracentral lobule. However, DC values were not correlated with clinical manifestations. ROC curve analysis showed high accuracy.

Conclusions:
We found abnormal neural activity in specific brain regions in patients with SA. Specifically, we observed significant changes in DC values compared to HCs. These changes may be useful to identify the specific mechanisms involved in brain dysfunction in SA.

MeSH Keywords:
Amblyopia • Magnetic Resonance Imaging • Neuroimaging • Strabismus

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CLINICAL RESEARCH

Background

Strabismus is a common eye movement disorder, and the prevalence among Asian children is 3.35% [1]. In Iran and Singapore, exotropia is the main type of strabismus [2]. Strabismus can lead to vision loss in both eyes [3]. Clinically, it can roughly be divided into concomitant and non-concomitant strabismus, and surgery is the main treatment [4]. Eye muscle malformation is an important factor underlying the condition. Defective extraocular muscle traction plays an important role in the development of non-concomitant strabismus [5], which is usually accompanied by an unstable traction force by the rectus muscle [6]. Abnormal extraocular muscle action can cause vertical strabismus [7]. The close connection between the visual and motor systems of the eyes and brain is an important condition for the best possible visual acuity (VA). Therefore, the normal functional activity of the corresponding neurons is essential for visual formation and eye activity. The frontal eye field (FEF) is involved in controlling eye movements [8] and may also participate in conjugate eye movements [9]. One study reported increased gray matter volume of the FEF in adult strabismus [10]. This suggests that in addition to eye muscle abnormalities, strabismus is related to changes in the brain's eye movement center.

Amblyopia, also called lazy eye, occurs without obvious organic lesions, and subjects with this condition have monocular or binocular best-corrected VA that is low for their age, or have an interocular difference of 2 lines or more in acuity [11]. This eye disease is closely related to visual development. It manifests as varying degrees of visual loss during the development of the visual system [12]. Monocular strabismus, refractive error, high refractive error, and deprivation are the common pathogenic factors. Amblyopia can cause serious damage to visual function in children, but some can be cured with treatment over time. A prompt diagnosis improves the prognosis. If not treated in time, the condition can be aggravated and even lead to blindness. It is generally believed that the visual cortex is the principle site of vision deficits in the visual pathway in amblyopia [13]. Previous studies have also observed functional deficits and morphological changes at the level of the lateral geniculate nucleus (LGN) in anisometropic amblyopia [14].

Resting-state functional magnetic resonance imaging (rs-fMRI) is a new imaging technology that reflects anatomical connections and also integrates functions and images [15]. rs-fMRI has been used in the histological and pathological studies of central nervous system diseases and related brain functional diseases, which greatly expands the scope of imaging. fMRI includes blood oxygenation level-dependent imaging (BOLD), diffusion tensor imaging (DTI), and magnetic resonance spectrum analysis [16]. BOLD-fMRI technology can be used to observe the hemodynamic effects of changes in neural activity in specific brain regions. Activity causes increased blood flow in corresponding functional areas, which leads to higher local oxyhemoglobin levels compared with other areas, and this reflects regional activity [16,17]. DTI can noninvasively assess the neural fiber structures of the brain by observing the movement route and density of water molecules in the tissue.

fMRI has been used successfully in the study of strabismus. It was reported that there is low metabolic activity in visual-predominant regions in early strabismus in monkeys [18]. There are also reports of primary visual cortex suppression in patients with strabismus [19]. Moreover, patients with strabismus have a low fractional anisotropy in the middle occipital gyrus. Although the above reports indicate morphological neuron changes in patients with strabismus, the neuro-mechanical changes in concomitant strabismus remain unclear [20].

Degree centrality (DC) is a measurement index used to describe the importance of nodes in different brain networks [21]; it can be used to analyze the energy network and identify the important nodes in information transmission. The voxel-based DC analysis method regards each voxel in the brain as a brain network node and calculates the correlation between each node and other nodes in the whole brain [22]. The size reflects the functional connection characteristics at the brain voxel level, and the voxel DC value is positively correlated with its importance in the functional network. The DC method has been used to reveal the importance of this graph theory index to study the brain network in patients with SA. Using rs-fMRI technology, DC analysis at the combination level, and pattern recognition algorithm, the present study assessed changes of brain network DC in patients with SA. The DC calculation formula [23] was as follows:

$$DC(i) = \Sigma rij \ (rij > r0; \ j = 1, 2, \ldots, N; i \neq j),$$

where rij is the Pearson correlation coefficient between voxel I and j, N is the number of total brain voxels, and R0 is a baseline threshold associated with the elimination of possible false values. Only values with a correlation coefficient >0.2 are used for superposition calculation [24].

Material and Methods

Subjects

A total of 15 adult SA patients (6 males and 9 females) treated at the First Affiliated Hospital of Nanchang University in Jiangxi province were enrolled in this prospective study.

The inclusion criteria of SA patients were: 1) strabismus with uncorrected and corrected VA >1.0, 2) equal deviation degrees,

3) visual development period, 4) abnormal visual experience, 5) corrected VA lower than that of normal children at the same age, 6) no organic eye lesions, and 7) and including hyperopia and myopia patients. The exclusion criteria were: 1) acquired strabismus, 2) patients with a history of previous ocular surgery, including intraocular and extraocular surgery, and 3) mental illness, diabetes, coronary heart disease, or intracranial disease. HCs had: 1) no eye diseases with uncorrected and corrected VA >1.0, 2) no mental illness (depression, paranoia), and 3) could undergo MRI scanning (no implanted metal devices).

All study methods were in accordance with the Helsinki Declaration, and all subjects participated voluntarily and signed informed consent forms after being informed of the study purpose, content, and risk.

MRI parameters

A 3.0-Tesla MR scanner was used for data acquisition. The following parameters were used for the T1 and T2 sequences: repetition time (TR) 1900 ms, echo time (TE) 2.26 ms, thickness 1.0 mm, clearance 0.5 mm, field of view (FOV) 250×250 mm, matrix 256×256, flip angle (FA 9°), and a total of 176 sagittal sections. Next, 240 functional images were obtained using the gradient echo plane image sequence in the static scanning session: TE 30 ms, section clearance 1 mm, matrix 64×64, and FA 90°. We collected 35 oblique slices. We used a sagittal fast spoiled gradient echo-bravo sequence to obtain T1-weighted images: TR 8.208 s, inversion time 450 ms, TE 3.22 ms, FOV 240×240 mm; voxel size 0.5 mm×0.5 mm×1 mm, FA 12°.

fMRI data processing

MRIcro software was used to process the information. The first 10 images were deleted to minimize instability. The remainder were preprocessed using the brain imaging data processing and analysis box (DPABI2.1) based on MATLAB2010a software (MathWorks, Inc., Natick, MA, USA). Subjects were asked to remain still during scanning. We used the Friston 24-head motion parameter higher-order model to reduce effects of head movement (Satterthwaite TD, 2013; Yan CG, 2013). Next, linear regression was used to correct head motion to normalize the functional image space to the Montreal Neurological Institute space. Finally, 0.01–0.1 Hz band pass filtering was performed for the time series of every voxel to reduce the influence of other factors such as low-frequency drift, respiration, and linear attenuation.

Statistical and data analysis

SPSS 16.0 software (SPSS, Chicago, IL, USA) was used to analyze the clinical variables. DC values in the SA and HC groups were compared with independent-sample t tests. Two-sample t tests were used to evaluate differences between cerebral blood flow maps (voxel level $P<0.01$, corrected by Gaussian random field). The linear model was built using the SPM8 toolkit. Receiver operating characteristic (ROC) curves were generated to analyze between-group differences in average DC values. Pearson correlations were used to assess relationships between SA patient clinical characteristics and DC values. For all analyses, differences were considered significant at $P<0.05$.

Results

Demographics and visual measurements

There were no significant differences in age or best-corrected VA of the fellow eye between the SA and HC groups. There was a statistically significant difference in the best-corrected VA of the amblyopic eye ($P<0.001$) between the 2 groups (Table 1, Figure 1).

DC values in different brain area regions

Compared with the HC group, the DC values of the left middle frontal gyrus and bilateral angular gyri were significantly lower in the SA group. Conversely, DC values were significantly higher in the left fusiform gyrus, right lingual gyrus, right middle occipital gyrus, right postcentral gyrus, and left paracentral lobule (Table 2, Figure 2).

ROC curves

Significant differences in DC values between the SA and HC groups would suggest that they could be useful diagnostic biomarkers. ROC curves were generated, and areas under the curve (AUCs) were calculated. A value of 0.5–0.7 indicates low precision, 0.7–0.9 indicates medium precision, and > 0.9 indicates high precision. (Figure 3).

Discussion

We used the DC method to study brain activity changes in functional networks in patients with SA. Compared with HCs, DC values of the left middle frontal gyrus and bilateral angular gyri were significantly lower. However, SA patients had significantly higher DC values in the left fusiform gyrus, right lingual gyrus, right occipital gyrus, right postcentral gyrus, and left paracentral lobule (Figure 4, Table 3). The DC method has been successfully applied in glaucoma [10], strabismus [15], and open-globe injury [18] and could be useful for understanding other eye disorders (Table 4).

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

	SA	HC	t-Value	p-Value
Male/Female	6/10	6/10	N/A	>0.99
Age (years)	24.50±5.91	24.94±5.23	−0.222	0.615
Handedness	16 R	16 R	N/A	>0.99
Duration (years)	18.19±9.85	N/A	N/A	N/A
Esotropia/exotropia	5/11	N/A	N/A	N/A
Spherical equivalent refractive error (Diopters)	1.22±0.56	1.25±0.67	−0.365	0.741
Mean±SD (range)	−2.75~1.75	−2.75~2.00	N/A	N/A
Angle of strabismus(PD)	26.25±12.71	N/A	N/A	N/A
Best-corrected VA-AE	0.77±0.53	−0.05±0.08	6.149	<0.001
Best-corrected VA-FE	−0.03±0.09	−0.01±0.07	−0.651	0.185

Independent *t* tests comparing the 2 groups (*P*<0.05 indicates statistically significant differences). Data shown as mean standard deviation or n. SA – strabismus with amblyopia; HC – healthy control; N/A – not applicable; PD – prism diopter; VA – visual acuity; AE – amblyopic eye; FE – fellow eye; R – right.
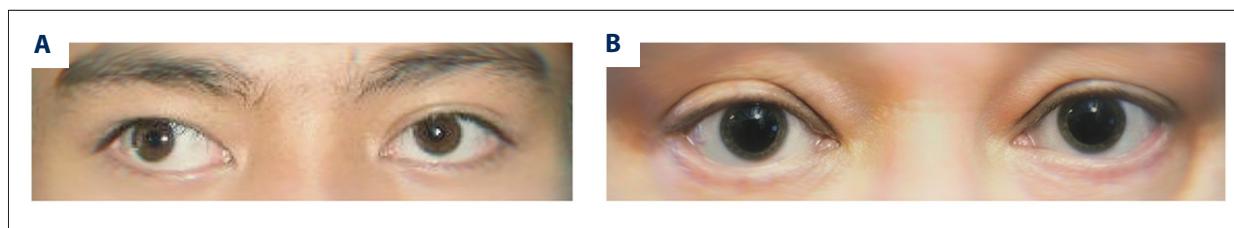

Figure 1. An example of SA patients and HC groups. (**A**) An adult strabismus with amblyopia patient. (**B**) An adult healthy control. SA – strabismus with amblyopia; HC – healthy control.

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

Conditions	L/R	Brain regions	BA	MNI coordinates			Peak voxels	t-Value
				X	Y	Z		
SAs >HCs								
1	L	Fusiform gyrus	19	−27	−78	−6	201	7.6374
2	R	Lingual gyrus	19	39	−75	−9	169	4.6259
3	R	Middle occipital gyrus	18	24	−90	12	45	5.6222
4	R	Postcentral gyrus	3	36	−36	60	46	4.1174
5	L	Paracentral lobule		−6	−27	60	43	5.1415
SAs <HCs								
1	L	Middle frontal gyrus	10	−39	57	15	29	−4.0959
2	L	Angular gyrus	39	−45	−78	30	79	−4.4390
3	R	Angular gyrus	39	42	−78	42	71	−5.2001

The statistical threshold was set at the level of voxel, and multiple comparisons were made using gaussian random field theory (z> 2.3, corrected column by column *P*<0.05), *P*<0.05. DC – degree centrality; BA – Brodmann area; SA – strabismus with amblyopia; HC – healthy control; MNI – Montreal Neurological Institute; R – right; L – left; B – bilateral.
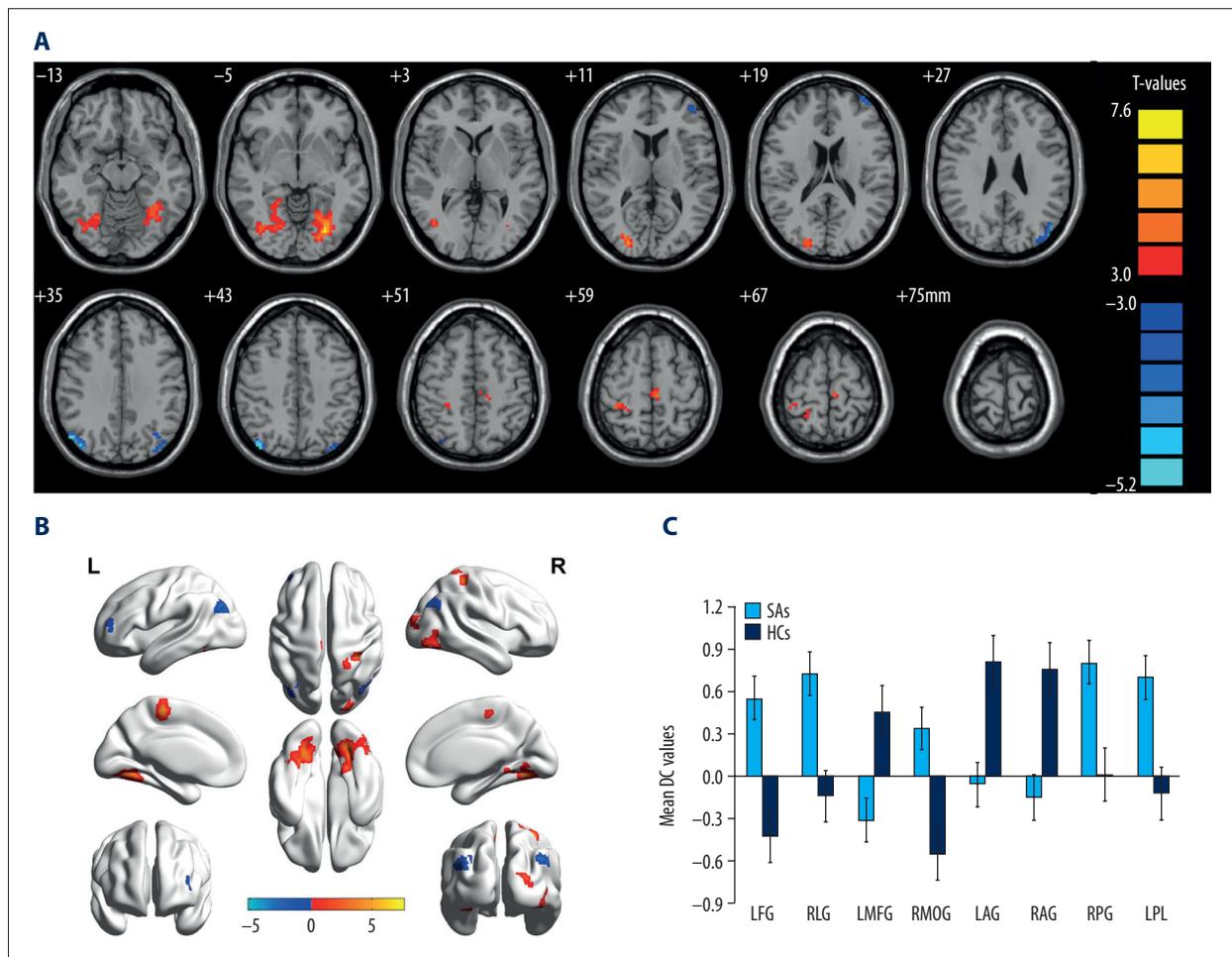
Figure 2. Comparison of DC in adult strabismus with amblyopia patients and HC groups. (**A, B**) Notable differences in DC of the brain were observed. Significant differences in DC were observed in the left fusiform gyrus, right lingual gyrus, left middle frontal gyrus, right middle occipital gyrus, left angular gyrus, angular gyrus, right postcentral gyrus, and left paracentral lobule. The red area represents higher DC value, while the blue area represents lower DC value. Multiple comparison using gaussian random field (GRF) theory (Z >2.3, column by column $P<0.05$). (**C**) The mean DC values of the brain between the adult strabismus with amblyopia patients and HC groups. DC – degree center; SAs – strabismus with amblyopia; HCs – healthy control groups; LFG – left fusiform gyrus; RLG – right lingual gyrus; LMFG – left middle frontal gyrus; RMOG – right middle occipital gyrus; LAG – left angular gyrus; RAG – angular gyrus; RPG – right postcentral gyrus; LPL – left paracentral lobule; R – right; L – left.

The FEF [25] is at the back of the frontal cortex and is involved in eye movement [26]. Previous studies showed that the FEF controls eye movement [27], triggers cross-eye movement [28], and is involved in the visual search process [29]. FEF lesions can cause eye movement disorders [30]. We found that patients with SA had significantly lower DC values in this region, suggesting frontal dysfunction. We speculate that these lower values may underlie eye movement disorders in patients with SA. In addition, medial frontal gyrus abnormalities are known to be associated with depression and anxiety. According to our linear regression study, middle frontal gyrus values in the SA group were positively correlated with anxiety and depression scores (Figure 5). Based on this, we speculate that SA is correlated with anxiety and depression.

The angular gyrus is in the parietal lobe above Wernicke's area. If the angular gyrus is lesioned, the visual and auditory images of words will be disconnected, and reading will be impaired. This causes auditory-visual aphasia, in which the subject is unable to understand the meaning of a word because of a perceived disconnect with the object seen and the sound heard. Angular gyrus damage can also cause dyslexia and dysgraphia (inability to write properly). In our study, DC values in the bilateral angular gyri of subjects with SA were significantly decreased. Dysfunction of the angular gyrus may contribute to eye movement disorders in SAs.

The visual center is located in the occipital cortex on both sides of the talus fissure and includes the upper cuneus and lower
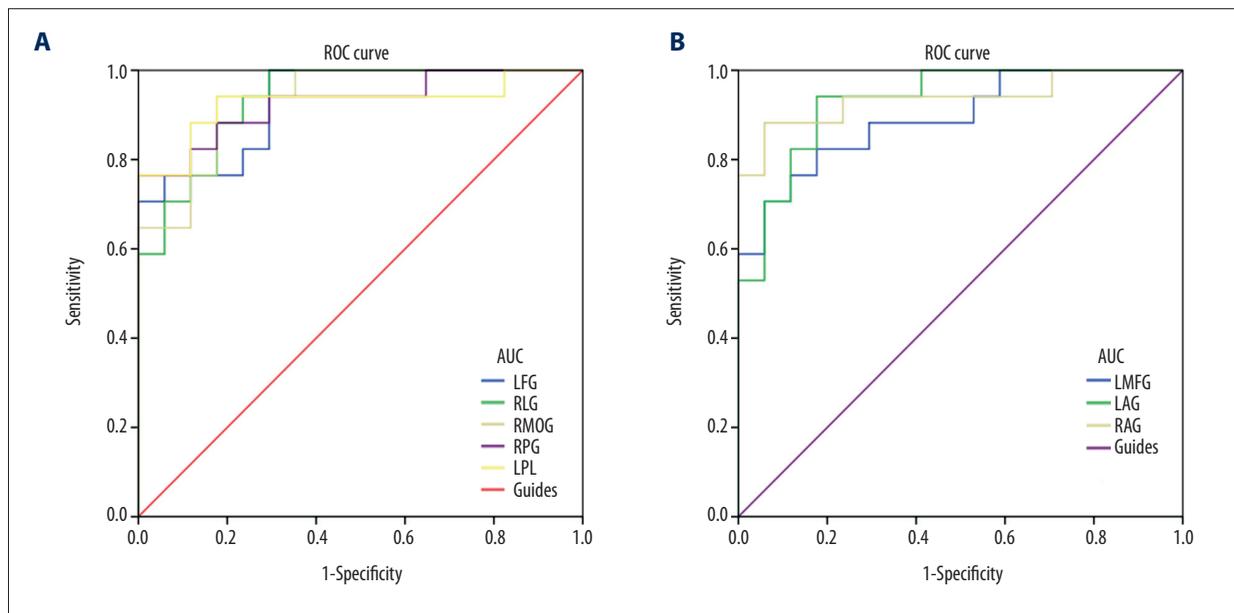
Figure 3. ROC curve analysis of the DC values for altered brain regions. (**A**) The area under the ROC curve were 0.931, (*P*<0.001; 95% CI: 0.851–1.000) for LFG, RLG 0.934 (*P*<0.001; 95% CI: 0.857–1.000), RMOG 0.934 (*P*<0.001; 95% CI: 0.857–1.000), RPG 0.927 (*P*<0.001; 95% CI: 0.838–1.000), LPL 0.927 (*P*<0.001; 95% CI: 0.828–1.000). (**B**) The area under the ROC curve were 0.893 (*P*<0.001; 95% CI: 0.786–0.999) for LMFG, LAG 0.931 (*P*<0.001; 95% CI: 0.849–1.000), RAG 0.938 (*P*<0.001; 95% CI: 0.850–1.000). DC– degree centrality; ROC – receiver operating characteristic; LFG – left fusiform gyrus; RLG – right lingual gyrus; LMFG – left middle frontal gyrus; RMOG – right middle occipital gyrus; LAG – left angular gyrus; RAG – angular gyrus; RPG – right postcentral gyrus; LPL – left paracentral lobule.
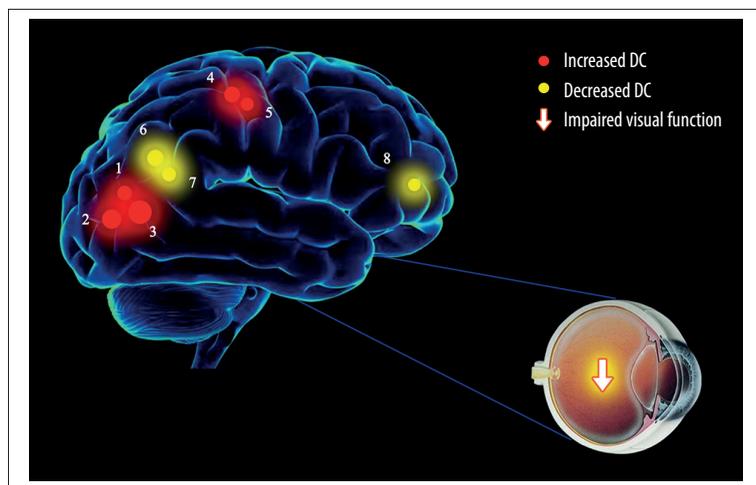

Figure 4. The DC results of brain activity in the SA group. Compared with the HCs, the DC of the following regions were increased to various extents: 1 – right lingual gyrus (t=4.6259); 2 – right middle occipital gyrus (t=5.6222); 3 – left fusiform gyrus (t=7.6374); 4 – left paracentral lobule (t=5.1415); 5 – right postcentral gyrus (t=4.1174); 6 – right angular gyrus (t=–5.2001); 7 – left angular gyrus (t=–4.439); 8 – left middle frontal gyrus (t=–4.0959) in SA patients. The sizes of the spots denote the degree of quantitative changes. DC – degree centrality; SA – strabismus with amblyopia; HC – healthy control.

lingual gyrus. Due to the special structure of this part of the brain, it contains white fine lines and is therefore called the striate cortex. The visual centers of each hemisphere are associated with one half of each eye's field of vision, and complete blindness occurs when the visual centers of both hemispheres are completely damaged. We found that SA patients had significantly higher DC values in the right lingual gyrus, suggesting that SA may lead to functional impairment of this brain region.

The occipital lobe, at the back of the brain, contains the primary visual cortex (Brodmann area 17), which processes visual information and control related to eye movement and pupil reflex activity. Stimulating a certain point can cause a response to a specific visual field, and retinal stimulation can induce a response in a single cell in the striate cortex. One side of the occipital cortex is mainly associated with the retina on the same sides of both eyes, and therefore with vision on the opposite sides of both eyes. We found decreased DC in the right occipital gyrus in SA patients, indicating that SA may cause abnormalities in this brain region.

Table 3. Brain regions alternation and its potential impact.

Brain regions	Experimental result	Brain function	Anticipated results
Fusiform gyrus	SAs >HCs	Face recognition, secondary object classification recognition	Mental visual impairment, visual distortion or agnosia
Lingual gyrus	SAs >HCs	Visual processing, vocabulary processing	Blindness, vision losing
Middle frontal gyrus	SAs <HCs	Writing center	Agraphia
Angular gyrus	SAs <HCs	The production, expression and reception of language	Reading and writing disorder

HCs – healthy controls; SA – strabismus with amblyopia.

Table 4. DC method applied in ophthalmological diseases.

Author	Year	Disease	Increase DC	Decrease DC
Wang et al. [34]	2017	Acute unilateral open globe injury	Bilateral primary visual cortex (V1/V2) and left PCUN	Right insula, left insula, RIPL/SMG, IPL/SMG, right supplementary motor area and right postcentral gyrus.
Tan et al. [33]	2018	Adult comitant exotropia strabismus	Right superior temporal gyrus, bilateral anterior cingulate, right superior temporal gyrus, and left inferior parietal lobule	Right cerebellum posterior lobe, right inferior frontal gyrus, right middle frontal gyrus and right superior parietal lobule/primary somatosensory cortex (S1)
Hu et al. [35]	2018	High myopia	Right cerebellum posterior lobe, left precentral gyrus/postcentral gyrus, and right middle cingulate gyrus	Right inferior frontal gyrus/ insula, right middle frontal gyrus, and right supramarginal/ inferior parietal lobule
Zhu et al. [36]	2019	Trigeminal neuralgia	Right lingual gyrus, right postcentral gyrus, left paracentral lobule, and bilateral inferior cerebellum.	/
Wang et al. [37]	2019	Diabetic nephropathy and retinopathy	BP	RITG, LSG
Liu et al. [38]	2020	Exophthalmos of Primary Hyperthyroidism	/	Cerebellum posterior lobe
Zhang et al. [39]	2020	Ophthalmectomy	Left cerebellum posterior lobe, left middle frontal gyrus1, right supramarginal gyrus, left middle frontal gyrus2, right middle frontal gyrus	Left lingual gyrus, bilateral lingual lobe, left cingulate gyrus

PCUN – precuneus; RIPL – right inferior parietal lobule; SMG – supramarginal gyrus; BP – bilateral precuneus; RITG – right inferior temporal gyrus; LSG – left subcallosal gyrus regions.

The postcentral gyrus, also known as the primary somatosensory cortex (S1), is in the lateral parietal lobe of the human brain and is thought to play acritical roles in nociception and the sense of touch [31]. A voxel-based morphology analysis revealed smaller white-matter volumes in the left postcentral gyrus of adults with strabismus. Tan et al. demonstrated that the DC value of S1 was decreased in patients with adult comitant *vs.* concomitant exotropia [32]. However, a recent study on anisometropic amblyopia found increased regional homogeneity in the postcentral and precentral gyri [33]. In the present work, we found
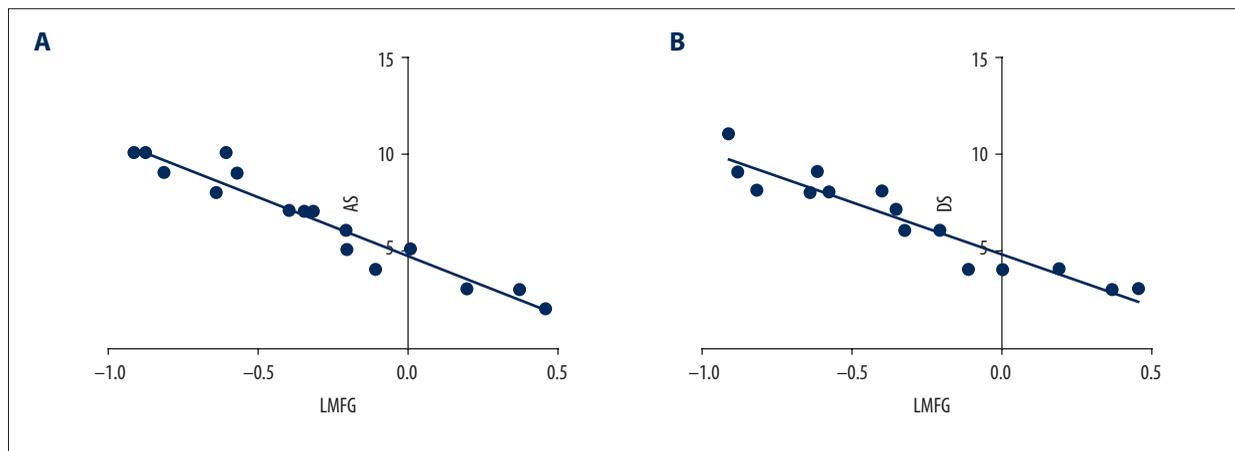
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Figure 5. (**A, B**) Correlation between the average DC values of the whole brain in SA patients and AS and DS. There was a negative correlation with the DC values of left middle frontal gyrus. Therefore, we concluded that SA can lead to dysfunction of the left middle frontal gyrus, resulting in depression and anxiety (r=−0.9640, R squared=0.9292, $P<0.0001$; r=−0.9473, R squared=0.8973, $P<0.0001$). The decrease in DC value reflects the severity of nerve injury. DC – degree centrality; DS – depression scores; AS – anxiety scores.
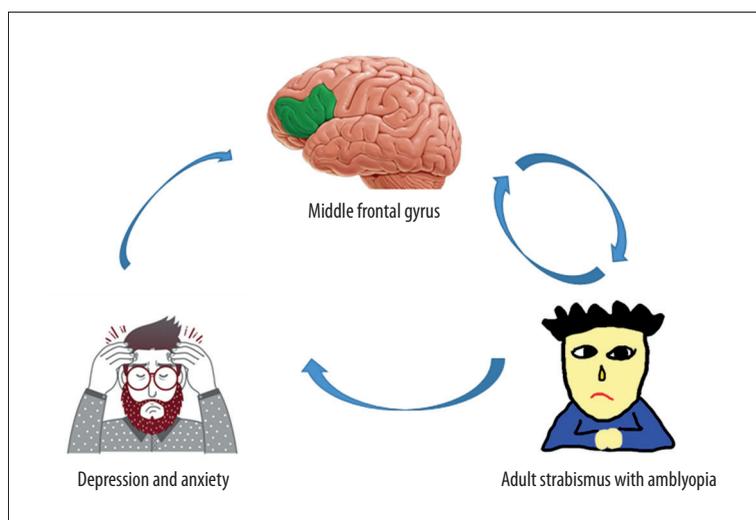

Figure 6. A schematic diagram of the relationship between adult strabismus with amblyopia and eye pain and anxiety.

a higher DC value in the right postcentral gyrus, suggesting S1 hyperactivity. This indicates that SA might be associated with functional reorganization in this brain region. During the follow-up treatment of patients with strabismus and amblyopia, clinicians can also evaluate the changes in the treatment effect and clinical performance through changes in the DC value of the corresponding brain areas. In the present study, most of the patients showed similar clinical manifestations, consistent with the clinical symptoms corresponding to changes in brain activity.

Conclusions

In conclusion, we applied the DC method of fMRI to investigate intrinsic brain activity in SA patients and HCs. From the perspective of brain function changes, SA is associated with central nervous system abnormalities, and it is important to explore the mechanism of these changes (Figure 6). We found significant changes in the middle frontal gyrus, angular gyrus, fusiform gyrus, lingual gyrus, middle occipital gyrus, postcentral gyrus, and paracentral lobule in SA patients. These results provide insight into the neural variation in SA patients and could help reveal the mechanisms of SA pathogenesis.

Conflict of interest

None.

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