Research Paper

Altered brain function in children with strabismic amblyopia: an fMRI study using a voxel-wise degree centrality approach

Running head: Synchronous neural activity changes in children with SA

Yi-Xin Wang[1], Wen-Qing Shi[2], Pei-Wen Zhu[2], Yen-Po Chen[1], Jeremy A Guggenheim[1]

[1]School of Optometry and Vision Sciences, Cardiff University, Cardiff , CF244HQ, United Kingdom

[2]Department of Ophthalmology, Fudan University School of Medicine, Shanghai 200080, China；

#Correspondence to: Jeremy A Guggenheim, **email:** guggenheim@cf.ac.uk;

Keywords： Internet game addiction, Ocular surface disease, Psychological health, Physical health, Dream Anxiety

Received: February 11, 2024 **Accepted:** November 11, 2024 **Published:** December 7, 2024

ABSTRACT

Objective: The purpose of this study was to investigate the intrinsic spontaneous alterations in brain activity of children with SA, using the voxel-wise degree centrality (DC) technique. A total of 23 children with SA (15 boys and eight girls), as well as 23 healthy controls (HCs), including 15 boys and eight girls were closely matched in sex and age. All children were examined using resting-state functional magnetic resonance imaging (fMRI). The DC method was applied to evaluate spontaneous variations in cerebral activity between the children with SA and the HCs. The data were evaluated using receiver operating characteristic (ROC) curves. Furthermore, the correlations between the DC values of distinct brain regions and clinical manifestations in patients with SA were evaluated using Pearson's correlation. Remarkably reduced DC values were observed in the left cerebellum and left precuneus of children with SA, compared with HCs. In contrast, mean DC values in children with SA were higher in the left middle temporal gyrus, left superior parietal gyrus, right superior parietal gyrus, right orbital superior frontal gyrus, right superior frontal gyrus, and right medial superior frontal gyrus. These findings may indicate changes in neural activity in related brain regions. However, no linear correlation was observed between the mean DC values in brain regions and clinical features. Our study suggests that various brain regions, including vision-related and motion-related areas, exhibit aberrant intrinsic brain activity patterns, which indicate the neuropathologic mechanisms of oculomotor disorders and vision deficits in pediatric patients with SA.

Keywords: strabismus; amblyopia; functional MRI; voxel-wise degree centrality; spontaneous brain activity

INTRODUCTION

Strabismus and amblyopia are two common eye diseases, especially in children. Strabismus refers to a condition in which one eye cannot achieve binocular vision with the other eye owing to an imbalance in the extraocular muscles (Figure 1). Strabismus includes two broad categories, one is concomitant strabismus, and the other is paralytic strabismus. The former is regarded as the more common category, in which the eye position has a temporal bias, without any eye movement disorders or reversion. Paralytic strabismus is characterized by limited eye movement[1], diplopia[2], and may be accompanied by ocular vertigo and gait instability.

Amblyopia suggests that there are no obvious organic lesions in the eye, or there may be organic changes and ametropia; however, vision loss is not compatible with the lesion and continuous correction or corrected vision of less than 0.9 can occur in one or both eyes. The most important manifestation of amblyopia is strabismus with amblyopia (SA). More than half of all cases of amblyopia are related to refractive errors[3].

From a symptomatic point of view, strabismus is regarded as abnormal eye position, and amblyopia is regarded as abnormal vision. Thus, SA often exhibits a wide range of visual defects, including abnormal spatial summation[4], impaired vision, contrast sensitivity[5], and balance control[6]. However, the specific cause of SA is still unclear. Related studies have shown that the severity of white matter damage of immaturity (WMDI) is significantly positively related to the incidence of strabismus, and the prevalence of strabismus in children with WMDI is higher than that in healthy people[7].

The treatment measures adopted for children with SA include surgical treatment of strabismus; drug treatments, such as atropine drops, patch treatment, optical treatment[8]; and unilateral glasses combined treatment and repair. After surgery, the central adaptive mechanism is also important for reconstructing and maintaining the eye's ability to converge on the target. The earlier the treatment time, the better the treatment effect achieved in the patient. In recent years, there has been strong evidence that the use of iPad-based dichoptic training provides interesting and promising data to support vision improvement in amblyopic patients[9-12].

Functional magnetic resonance imaging (fMRI) neurofeedback is a form of biofeedback that uses real-time online fMRI signals to regulate brain function. Since its introduction in 2003, the technology has made considerable progress. As a non-invasive neuroimaging technique, fMRI is based on cerebral blood flow and metabolic analysis, and has been widely used in studies of the neurological status of specific brain areas[13]. Researchers can detect activation of specific brain regions, and thereby explore the spatial organization of the brain, including visual pathways from the retina to the corresponding cerebral cortex, and discover the mechanisms of specific pathological changes in eye diseases.

The latest research on strabismus and amblyopia has also extensively adopted fMRI technology. Some researchers have compared the similarities and differences of functional connections between the cerebral hemispheres of anisometropic amblyopia and SA[14, 15]. Other researchers conducted a comparative study of the long-range intraocular suppression in adults with SA and the control group, and concluded that no significant differences were found[16]. Furthermore, some researchers have used regional homogeneity (ReHo) to analyze fMRI data and suggest that visual information processing in patients with SA may be impaired in the visual areas V1 and V2, while adults with SA show specific patterns of brain plasticity to compensate for some defects in visual movement[17].

Nevertheless, research on the effects of SA has been limited mainly to the reduction or even loss of vision, and studies on the changes in brain functional status of patients with SA are still just a few. Generally, previous studies have been focused on either strabismus or amblyopia. In this study, we used fMRI technology to conduct a controlled study on changes in brain function in children with SA. The data were analyzed by voxel-wise degree centrality (DC), and the results were displayed as receiver operating characteristic curve (ROC) analysis output.

The DC is a resting-state fMRI analysis method, which is applied to reveal the connectivity of the brain network at the voxel level. The DC method is a measure of the importance of a single node. It can reflect the characteristics of a functional brain network "hub" and has a high reliability of retesting[18]. The higher the voxel expression score of a specific brain region, the higher the importance of nodes in the functional network of that brain region.

On the other hand, compared with the ReHo and

amplitude of low frequency fluctuation methods, the DC method can study the entire brain at the functional level, and has advantages over other methods without defining specific regions[19]. At the same time, the DC method is also widely used in the research of various ophthalmological diseases (Table 1) [19-25]. Here, we proved that the DC method plays an important role in revealing changes in brain regions of children with SA. To our knowledge, this study is the first to use the DC method to analyze the fMRI data of children with SA.

PATIENTS AND METHODS

Patients

Children with SA, including 15 boys and eight girls, were recruited as study participants from the Ophthalmology Department of Cardiff University. The inclusion criteria were as follows: (i) children under 12 years of age; (ii) diagnosed with SA; (iii) with a best-corrected visual acuity (VA) ≥ 0.20 logMAR units, and central fixation of both eyes with greater than one line difference; and (iv) no other eye diseases (such as optic neuritis, glaucoma, or cataracts, etc.). Patients meeting the following criteria were excluded: (i) history of ocular surgery, including intraocular or extraocular surgery; (ii) other disorders besides eye disease, such as ischemic disease, inflammation, or infection; (iii) mental disease or cerebral infarction; (iv) either addicted to illicit drugs or an alcoholic.

Twenty-three HCs matched for sex and age also participated in the study, including 15 boys and eight girls. All HCs conformed to the following standards: (i) an absence of abnormal MRI in the brain parenchyma; (ii) no history of ophthalmic surgery and best-corrected VA not greater than 0 logMAR units; (iii) a state of sanity; (iv) no contraindications for MRI examination, such as implanted metal devices or a cardiac pacemaker.

The Medical Ethics Committee of the Cardiff University approved the study, and the protocol was in accordance with the principles of the Declaration of Helsinki. All participants, including the children and their parents, gave informed consent and details of the objectives of the research, as well as the latent danger to patients, were explained in detail.

Table 1 DC method applied in ophthalmology-related diseases.

Authors	Year	Diseases
Wang et al [19]	2017	Acute unilateral open globe injury
Hu et al [20]	2018	High myopia
Tan et al [21]	2018	Adult comitant exotropia strabismus
Zhang et al [22]	2019	Ophthalmectomy
Cai et al [23]	2015	Primary angle-closure glaucoma before and after surgery
Zhang et al [24]	2019	Primary open-angle glaucoma
Wang et al [25]	2019	Diabetic nephropathy and retinopathy

Abbreviation: DC, degree centrality.

Figure 1. Compare the eyes of strabismic and amblyopic children with normal children

Notes: Figure 1A shows the binocular conditions of children with strabismic and amblyopic, Figure 1B shows the binocular conditions of normal children.

Correlation analysis

All participants were subjected to measurements of deviation associated with esotropia and the Hospital Anxiety and Depression Scale. We then used the GraphPad Prism 8 software to analyze the linear correlation between the DC values of the left cerebellum and esotropic deviation. Moreover, we used the same software for linear analysis of DC values of the right medial superior frontal gyrus and anxiety scores (AS). Furthermore, the depression scores (DS) and DC values of the right orbital superior frontal gyrus were also subjected to linear regression analysis.

MRI parameters

The MRI scanning was performed using a 3-T magnetic resonance scanner (Trio, Siemens, Munich, Germany). During the entire scanning process, all participants were required to remain awake, while breathing smoothly with their eyes closed. The data were collected by using a three-dimensional spoiled gradient recalled echo sequence. Relevant details about the apparatus are as follows: 176 structural images (gap: 0.5 mm; repetition time (TR): 1900 ms; thickness: 1.0 mm; echo time (TE): 2.26 ms; flip angle: 9°; field of view: 250 × 250 mm; acquisition matrix: 256 × 256). In addition, 240 functional images (TE: 30 ms; TR: 2,000 ms; field of view: 220 × 220 mm; thickness: 4.0 mm; flip angle: 90°; acquisition matrix: 64 × 64; gap: 1.2 mm; and 29 axial) were likewise acquired. The entire scanning process lasted 15 min.

fMRI data processing

Firstly, we used the MRIcro software (http://www.MRIcro.com) to analyze the acquired information. The Data Processing Assistant for rs-fMRI software (http://rfMRI.org/, DPARSF) and the Statistical Parametric Mapping 8 (SPM8) was used to preprocess the acquired data. We rejected the data of the first 10 time points to eliminate any interference of an unsteady magnetic field. Subjects with more than 1.5° of angular displacement, and an offset > 1.5 mm in three dimensions during the whole scanning process were excluded from further consideration. Furthermore, the collected data were subjected to time correction, to eliminate the effects of different acquisition times.

Owing to the differences in brain volume and structure between subjects, spatial standardization was used to process the functional images. During this process, the functional images were unified according to the Montreal Neuroscience Institute standard, and the voxels were immediately re-sampled with a resolution of 3 mm × 3 mm × 3 mm. To dislodge the linear chemotactic effect produced while the subject adapts to the scanning environment, the linear drift was eliminated. Eventually, to reduce physiological high-frequency noise, such as the heartbeat or respiration, only data between 0.01 and 0.08 Hz were collected.

STATISTICAL ANALYSIS

The SPSS 22.0 software (IBM Corporation, Armonk, NY, USA) was used to compare the mean DC value of the SA and HC groups. For voxel-wise DC, the one sample t-test was applied in each group, to identify the spatial centrality distribution hubs of the whole brain functional network. Distinctions between the two groups were analyzed using the two-sample t-test and the representational state transfer (REST) software. When P-values were < 0.05, the differences between two groups were deemed statistically significant. The data were compared and analyzed using the gaussian random field theory, the AlphaSim corrected thresholds were set at $P < 0.01$, and the cluster size at > 40 voxels. In addition, we used Pearson's correlation to make a distinction between the mean DC values and clinical features in children with SA.

Demographics and visual measurements

No significant differences in age were noted between the SA and HC groups (P = 0.914). However, significant differences were noted in the best-corrected VA of both left and right eyes (P = 0.016, P = 0.019, respectively) (more details are presented in Table 2).

DC differences

Compared with HCs, the mean DC values of the left cerebellum and left precuneus of the SA group were significantly lower. The mean DC values in the SA group were significantly increased in other areas of the brain, including the left middle temporal gyrus, left superior parietal gyrus, right superior parietal gyrus, right orbital superior frontal gyrus, right superior frontal gyrus, and right medial superior frontal gyrus (Table 3). A comparison of the DC mean values between the two groups is shown in Figure 2.

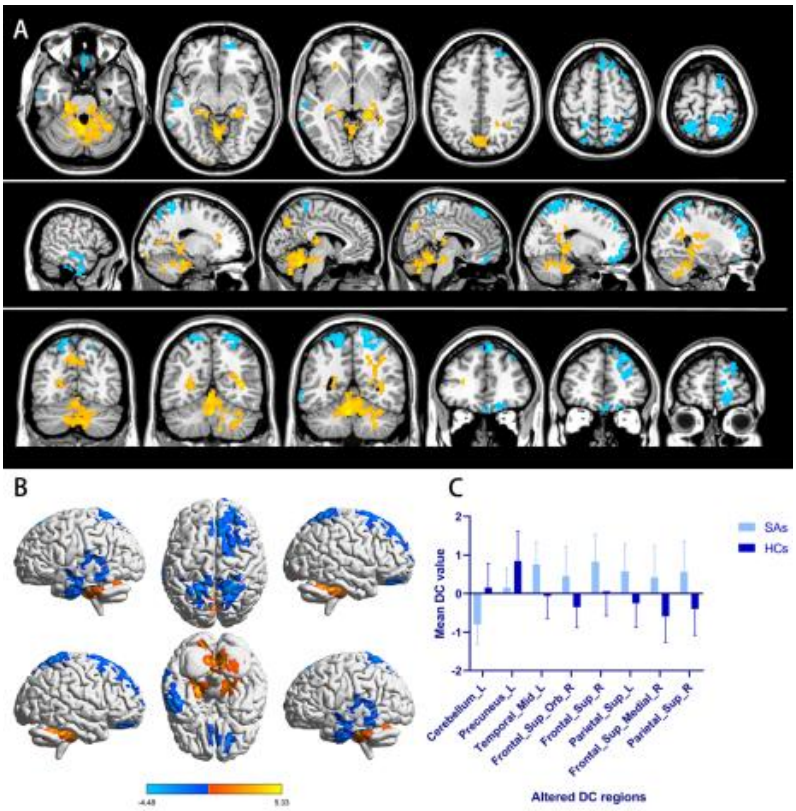

Figure 2. Voxel-wise comparison of DC in the SA and healthy control group.

Notes:(A and B) Significant differences in DC were observed. The yellow regions indicate higher DC values. AphaSim corrected at a cluster size>40 voxels and a level of P<0.05 for multiple comparisons using Gaussian random field theory. (C) The mean DC values between the SA and HC groups.Abbreviations: DC, degree centrality; SA, strabismus with amblyopia; HC, healthy control; Cerebellum_L, left cerebellum; Precuneus_L, left precuneus; Temporal_Mid_L, left middle temporal gyrus; Frontal_Sup_Orb_R, right orbital superior frontal gyrus; Frontal_Sup_R, right superior frontal gyrus;Parietal_Sup_L, left superior parietal gyrus; Frontal_Sup_Medial_R, right medial superior frontal gyrus; Parietal_Sup_R, right superior parietal gyrus.

RESULTS

ROC curve analysis

We assumed that the difference in DC values between the two groups was a potential diagnostic marker to distinguish the SA group from the HC group. Therefore, in order to verify our hypothesis, we performed data analysis on the mean DC values of specific brain regions of all

patients with SA, and presented the final results on a ROC curve. If the area under the curve (AUC) was 0.5–0.7, the accuracy was lower; if the AUC was 0.7–0.9, the accuracy was higher. The results of the final ROC curve showed that the left cerebellum (0.864, P < 0.001); left precuneus (0.777, P < 0.001) (Figure 3A, HCs > SAs); left middle temporal gyrus (0.822, P < 0.001); right orbital superior frontal gyrus (0.787, P < 0.001); right superior frontal gyrus (0.806, P < 0.001); left superior parietal gyrus (0.808, P < 0.001); right medial superior frontal gyrus (0.830, P < 0.001); right superior parietal gyrus (0.798, P < 0.001) (Figure 3B, SAs > HCs).

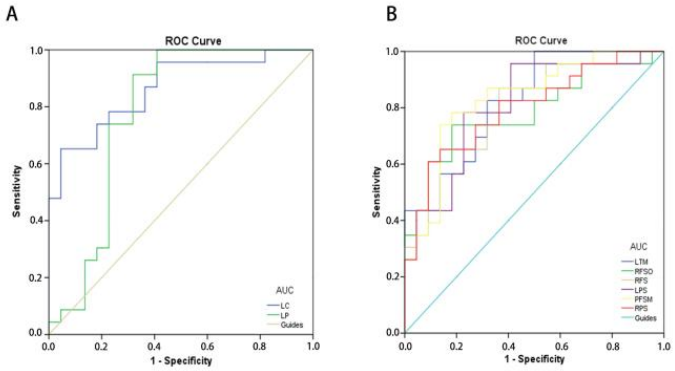

Figure 3. ROC curve analysis of the mean DC difference for altered brain regions. (A) The area under the ROC curve were 0.864, (p ＜ 0.0001; 95% CI: 0.758-0.969) for LC, LP 0.777, (p ＜ 0.001; 95% CI: 0.625-0.929). (B) The area under the ROC curve were 0.822, (p＜0.0001; 95% CI: 0.703-0.941) for LTM, RFSO 0.787, (p＜0.001; 95% CI: 0.651-0.922), RFS 0.806, (p＜ 0.0001; 95% CI: 0.679-0.934), LPS 0.808, (p ＜ 0.0001; 95% CI: 0.680-0.937), RFSM 0.830, (p＜0.0001; 95% CI: 0.709-0.952), RPS 0.798, (p ＜ 0.001; 95% CI: 0.669-0.928).Abbreviations: AUC, area under the curve; ROC, receiver operating characteristic. LC, left cerebellum; LP, left precuneus; LTM, left temporal mid; RFSO, right frontal sup orb; RFS, right frontal sup; LPS, left parietal sup; RFSM, right frontal sup medial; RPS, right parietal sup.

Correlation analysis

The results of linear analysis showed that DC values of the left cerebellum were positively correlated with the values of esotropic deviation (r = 0.9158, P < 0.0001) [Figure 4A]. The DC values of the right medial superior frontal gyrus were positively correlated with the AS (r = 0.7889, P < 0.0001) [Figure 4B], and DC values of the right orbital superior frontal gyrus were positively correlated with the DS (r = 0.8001, P < 0.0001) [Figure 4C].

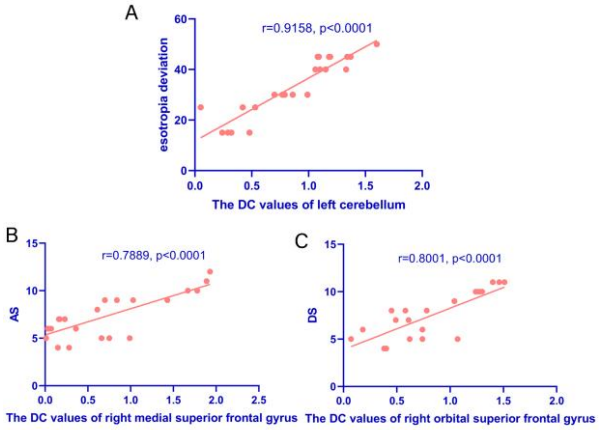

Figure 4. Correlations between the DC values of different regions and the clinical behaviors in SA group. The DC values of left cerebellum were positively correlated with the values of esotropia deviation (r= 0.9158, p<0.0001); the DC values of right medial superior frontal gyrus were positively correlated with the AS (r=0.7889, p<0.0001); and the DC values of right orbital superior frontal gyrus were positively correlated with the DS (r=0.8001, p<0.0001).Abbreviations: DC, degree centrality; SA, strabismus with amblyopia; AS, anxiety scores; DS, depression scores.

Table 2 The Conditions of participants included in the study

Condition	SA	HC	t	P-value*
Male/female	15/8	15/8	N/A	>0.99
Age (years)	9.32±3.57	9.96±2.98	0.289	0.914
Weight (kg)	24.87±5.15	23.35±4.67	0.237	0.926
Handedness	23R	23R	N/A	>0.99
VA-R	0.06±0.02	1.05±0.25	-5.769	0.001
VA-L	0.12±0.04	1.00±0.15	-6.754	0.003
Best-corrected VA-R	0.45±0.16	1.05±0.25	-3.146	0.019
Best-corrected VA-L	0.39±0.18	1.00±0.15	-3.327	0.016
IOL-L	14.38±3.43	15.74±3.31	0.675	0.774
IOL-R	13.27±3.52	15.85±3.24	0.709	0.813
Family history	5	N/A	N/A	N/A

Notes: * P<0.05, independent *t*-tests comparing the two groups; the data are shown as the mean ± standard deviation.
Abbreviations: SA, strabismus with amblyopia; HC, healthy controls; N/A, not applicable; VA, visual acuity.

Table 3 Brain regions with significant difference in DC between SA patients and HCs.

Conditions	**L/R**	**Brain regions**	**BA**	**MNI coordinates**			**Peak voxels**	**t-value**
				X	***Y***	***Z***		
SAs<HCs								
1	L	Cerebellum		-6	-51	-27	2869	5.33
2	L	Precuneus	7	-3	-69	42	124	3.45
SAs>HCs								
1	L	Middle temporal gyrus	21	-54	-21	-9	344	-4.48
2	R	Orbital superior frontal gyrus	11	18	57	-3	197	-3.79
3	R	Superior frontal gyrus	10	27	45	42	199	-4.07
4	L	Superior parietal gyrus	7	-18	-51	60	239	-3.94
5	R	Medial superior frontal gyrus	6	6	39	54	209	-4.24
6	R	Superior parietal gyrus	7	24	-57	69	364	-4.04

Notes: The statistical threshold was set at voxel with P<0.01 for multiple comparisons using false discovery rate.

Abbreviations: DC, degree centrality; BA, Brodmann area; SA, strabismus with amblyopia; HC, healthy control; MNI, Montreal Neurological Institute; R, right; L, left.

DISCUSSION

As far as we know, this study is the first to use the DC method to explore brain functional connectivity of pediatric patients with SA. We found that the functional connectivity of different brain regions in the SA group changed significantly, compared with the HC group. The mean DC values of the left cerebellum and left precuneus of patients with SA were significantly reduced, while the mean DC values of the left middle temporal gyrus, right orbital superior frontal gyrus, right superior frontal gyrus, left superior parietal gyrus, right medial superior frontal gyrus, and right superior parietal gyrus were significantly increased (Figure 5). The children with SA also had impaired visual function. However, the mean DC values of various brain regions in patients with SA showed no significant correlation with the corresponding clinical manifestations.

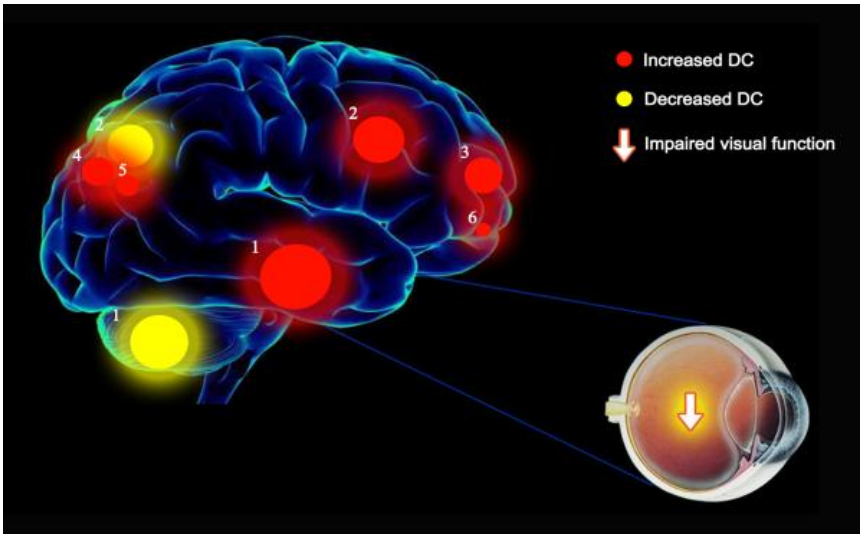

Figure 5. The mean DC values of altered brain regions. Compared with the HCs, the DC values of the following regions were decreased to various extents: 1- Left cerebellum; (BA 11, t = 5.33), 2- Left precuneus (BA 7, t = 3.45). Compared with the HCs, the DC values of the following regions were increased to various extents: 1- Left middle temporal gyrus (BA 21, t = -4.48), 2- Right medial superior frontal gyrus (BA 6, t = -4.24), 3- Right superior frontal gyrus (BA 10, t = -4.27), 4- Right superior parietal gyrus (BA 7, t = -4.04), 5-Left superior parietal gyrus (BA 7, t = -3.94), 6- Right orbital superior frontal gyrus (BA 11, t = -3.79).Abbreviations: DC, degree centrality; HCs, healthy controls; BA, Brodmann's area.

Analysis of lower DC values in the SA group

The cerebellum is located in the posterior and inferior part of the brain, in the posterior cranial fossa, behind the medulla oblongata and pons. The cerebellum can be divided into the middle vermis and the enlarged cerebellar hemispheres on both sides. The main function of the cerebellum is to coordinate movement of the limbs. A previous study has confirmed that the cerebellum coordinates eye and hand tracking movements[26]. Related studies have shown that injury to the cerebellar hemisphere will lead to corresponding ataxia of the limb on the same side, nystagmus, poor discrimination, and rotation disorders[27].

The functional state of the cerebellum is closely related to eye movements[28-30]. During the process of eye movement and formation of specific vision, the cerebellum and brain stem are usually well-coordinated and controlled[31]. An fMRI study showed that the functional status of the left cerebellum differs significantly between patients with epilepsy and a control group, and may further affect a patient's cognitive function[32].

Further experimental studies have showed that the cerebellum not only plays an important role in athletic ability, but is also closely linked with other brain regions in non-exercise-related ability to coordinate cognitive and social abilities[33-35]. For example, Gordon et al.[36] found that the cerebellum plays a central role in the process

of passively listening to music.

In the present study, we found that the average DC value of the left cerebellum of patients with SA was significantly lower than that of the HC group. Therefore, we inferred that the function of the left cerebellum of the SA group was impaired. We further deduced that patients with SA have impaired motor control as it relates to eye movement. According to the latest research, the corresponding cognitive function and social ability of patients with SA will also be greatly affected. After reviewing the literature, we found that the centrality of the brain network in the left cerebellum of adults with common strabismus is also altered significantly[21], which further verifies the accuracy and effectiveness of the present study.

The precuneus is located on the inner wall of Brodmann's area (BA) 7. This area is the somatosensory associative cortex, which plays an important role in visualization and visual motor coordination. Related research shows that the precuneus and thalamus have a broad and close relationship in the default mode network (DMN)[37, 38]. In addition, a study on social anxiety disorder confirmed that depression and anxiety are mainly related to functional defects of the precuneus related network[39]. Other related clinical experiments have confirmed that the ReHo of cingulate-precuneus regions is considered to be a biomarker of depression and anxiety[40]. Furthermore, Schott et al.[41] demonstrated that the functional state of the dorsal precuneus affects the representation of visual spatial associative memory.

Table 4 Changes in specific brain regions and their potential functional effects.
Abbreviation: SA, strabismus with amblyopia; HC, healthy control.

Brain regions	Experimental result	Brain function
Left cerebellum	SAs<HCs	Motor control, eye movements, cognitive function and social ability.
Left precuneus	SAs<HCs	Visual dysfunction, emotion and intelligence, memory function.
Left middle temporal gyrus	SAs>HCs	Auditory function, memory impairment and compound hallucinations.
Right orbital superior frontal gyrus	SAs>HCs	Social behavior, emotion control, and depression.
Right superior frontal gyrus	SAs>HCs	Anxiety and depression, memory and cognitive functions.
Right medial superior frontal gyrus	SAs>HCs	Social behavior, anxiety, fear circuit.
Bilateral superior parietal gyrus	SAs>HCs	Operation, reading memory and writing ability.

A recent magnetic resonance study showed that the ReHo values of the precuneus in patients with SA are significantly lower than those in a control group, and such ReHo values of the precuneus are negatively correlated with age[17]. These data are consistent with the findings of the present study. We found that the DC values of the left precuneus of the SA group were significantly lower than those of the HC group. The reduction observed in the signal imply that the functional state of the precuneus was altered. We contacted the above to discuss the specific functions of the precuneus. We believe that the DMN of the SA group will be significantly affected, as it is responsive to adverse emotional reactions such as anxiety and depression. These effects may directly affect the patient's social function status and indirectly affect the patient's memory function.

Analysis of higher DC values in the SA group

The temporal lobe is located below the lateral fissure of the brain, above the middle cranial fossa and the cerebellum. The temporal lobe is mainly responsible for auditory function in humans. Lesions of the middle temporal gyrus mainly manifest as contralateral trunkataxia[42]. If the temporal lobe is extensively damaged, this may also manifest as changes in personality, behavior, mood, and consciousness[43]. In severe cases, memory impairment and compound hallucinations may occur[44, 45].

One study on structural features of the main whitematter bundles in patients with SA showed that strabismus has an adverse effect on the visually connected cortex of the frontal and temporal lobes[46]. These findings further confirm that the temporal lobe also plays a role in the visual pathway. In addition, studies have shown that early visual experience disorders may cause structural changes in the cerebral cortex. These changes include audiovisual integration, visual processing, and hand-eye coordination[47]. These findings suggest that when visual motor processing ability is reduced in patients with SA, neural activity of the cerebral cortex may increase plasticity to compensate, and alter the structure of the cerebral cortex. Another magnetic resonance study on SA confirmed these findings, as the ReHo values of the left temporal lobe were increased[48].

On the other hand, a previous magnetic resonance study on adult exotropia showed that DC values of the superior temporal gyrus are significantly increased, implying that exotropia could lead to abnormal functional status of that gyrus[21]. However, the specific effects were not explained in detail. The present results show that the DC values of the left middle temporal gyrus in the SA group were significantly higher than those of the HC group. We inferred that middle temporal lobe function in patients with SA shows a compensatory increase in childhood. Auditory function compensates for the effects of SA on visual pathways. In addition, we believe that audiovisual integrative ability of patients with SA may have also been significantly affected.

The frontal lobe of the cerebral hemisphere is located in front of the central sulcus and above the lateral sulcus. The frontal lobe can be divided into the dorsal lateral surface, medial lateral surface, and ventral surface. The main function of the frontal lobe is to control voluntary movement, language, emotion, and intelligence[49]. In humans, some studies have subdivided the frontal lobe into the orbital and medial anterior frontal lobe. Thus, we divided our study of the frontal lobe into the orbital gyrus, dorsolateral gyrus, and medial gyrus rectus[50].

It is interesting that some studies have confirmed that the functional status of the orbital gyrus is related to behavioral inhibition associated with internet gaming disorders[51, 52]. Related research has shown that the functional status of an abnormal dorsolateral frontal gyrus can be used as a diagnostic marker for schizophrenia[53]. These findings also confirm that emotional function is associated with the frontal gyrus. In addition, many studies have confirmed that transcranial electrical stimulation of the frontal lobe has a significant effect on cognitive function[54]. Therefore, we infer that the frontal lobe may also participate in cognitive and memory functions.

Furthermore, some researchers have identified the role of the medial frontal lobe in controlling social behavior[55]. Other researchers have shown that the functional connectivity of the medial frontal lobe is related to emotions such as anxiety and depression[56]. Similarly, the amygdala and medial prefrontal cortex are important brain regions that control the fear circuit[57-59].

In our experimental data, DC values of the right orbital superior frontal gyrus, right superior frontal gyrus, and right medial superior frontal gyrus of the SA group were significantly higher than those of the HC group. Therefore, we infer that patients with SA are more prone to negative emotions such as anxiety and depression, and their social behavior may also be affected to a certain extent. The most recent research reports indicate that the superior frontal gyrus is associated with memory and cognitive function in humans. Thus, we also infer that memory and cognitive function in patients with SA will be affected compared with the HC group [Figure 6].

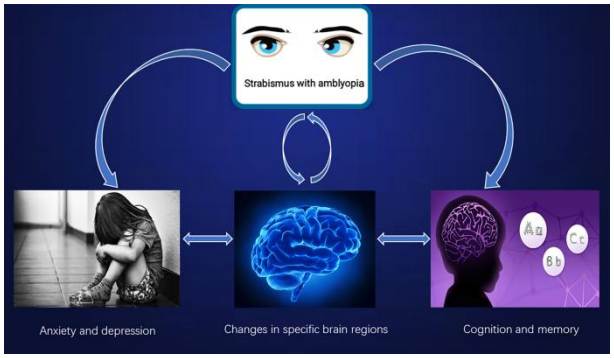

Figure 6. Strabismus with amblyopia in relation to changes in brain function and clinical manifestations.

The parietal lobe is located between the frontal lobe and the occipital lobe, and is divided into the central posterior gyrus, marginal gyrus, angular gyrus, and apical lobule. A magnetic resonance study of patients with amblyopia showed that the activation level of the superior parietal lobule is increased with as the attention load is increased. This reflects, to a certain extent, the low-level passive motion system and advanced active motion system in the multitarget tracking defect of amblyopia[60].

Other studies have used positron emission tomography

to determine that the rate of glucose metabolism is significantly reduced in the superior parietal lobule of patients with strabismus. This finding suggests that neurotrophic factors are involved in the pathogenesis of strabismus[61]. Related brain function research shows that the superior parietal lobule plays an important role in operating memory[62]. Another study on brain function in children with visual attention span disorder also suggested impaired function of the superior parietal lobule[63]. Therefore, we preliminarily concluded that the superior parietal lobule is related to reading and memory functions in humans.

In addition, studies have shown that the superior parietal lobule has a wide range of connections and coordination with language and motor areas of the brain during writing tasks[64]. We found that the DC values of the right superior parietal lobule in the SA group were significantly increased. These results indicate that the SA has an effect on the functional state of the patient's parietal lobule. We preliminarily speculate that these effects include impaired functional ability, reading, memory, and writing ability of patients with SA. Based on our findings above, we constructed a table of the functions corresponding with various brain regions, and the effects of alterations associated with SA on functional activities (Table 4).

CONCLUSIONS

In summary, our results indicate that patients with SA have abnormal spontaneous neural activity in specific brain regions. These abnormal neural activities may represent the potential neurological pathogenesis of SA.

Nevertheless, there are some limitations in our research. For example, the sample size was relatively small. Future research can provide higher accuracy if the sample size is increased. In addition, during the study, we did not classify pediatric strabismus in detail. In the future, we could study different types of strabismus, such as exotropia and medial strabismus, to more accurately evaluate the changes in brain functional activity. Despite the limitations of our study, our findings show that the neuropathology of specific brain regions is involved in the underlying pathogenesis of SA. This provides the basis for neuroimaging, to facilitate the early diagnosis and timely treatment of patients with strabismus.

AUTHOR CONTRIBUTIONS

YW analyzed the data and draft the manuscript, WS assisted with data interpretation and figure composing, PZ and YC collected the data, Guggenheim JA conceived, designed and directed the study, and final revised and approved the manuscript.

CONFLICTS OF INTEREST

The authors declare that they have no conflicts of interest.

FUNDING

Supported by National Natural Science Foundation of China (No.82160195); Jiangxi Double-Thousand Plan High-Level Talent Project of Science and Technology Innovation（No.jxsq2023201036）.

REFERENCES

1. Saxena R, Phuljhele S, Sharma P, et al. Periosteal fixation procedures in the management of incomitant strabismus.Middle East Afr J Ophthalmol.2015;22(3):320-326. doi:10.4103/0974-9233.159736
2. Park SJ, Yang HK, Byun SJ, et al. Ocular motor cranial nerve palsy and increased risk of stroke in the general population. PLoS One.2018; 13(10):e0205428.doi:10.1371/journal.pone.0205428 3. Herruzo, C., et al., Suicidal Behavior and Problematic Internet Use in College Students. Psicothema, 2023. 35(1): p. 77-86.
3. Ehrt O. [Possibilities and limitations of amblyopia screening with auto-refractometers]. Ophthalmologe .2016; 113(4): 289-295.doi:10.1007/s00347-016-0248-2
4. Polat U, Sagi D, Norcia A M. Abnormal long-range spatial interactions in amblyopia. Vision Res.1997; 37(6): 737-744.doi, https://pubmed.ncbi.nlm.nih.gov/9156218
5. Dorr M, Kwon M, Lesmes L A, et al. Binocular Summation and Suppression of Contrast Sensitivity in Strabismus, Fusion and Amblyopia. Front Hum

Neurosci 2019; 13: 234.doi:10.3389/fnhum.2019.00234
6. Zipori AB, Colpa L, Wong AMF, et al. Postural stability and visual impairment: Assessing balance in children with strabismus and amblyopia.PLoS One.2018;13(10): e0205857.doi:10.1371/journal.pone.0205857
7. Jeon H, Jung J, Kim H, et al. Strabismus in children with white matter damage of immaturity: MRI correlation. Br J Ophthalmol.2017; 101(4): 467-471.doi:10.1136/bjophthalmol-2016-308769
8. McGraw PV, Barrett T, Ledgeway T. Optical treatment of strabismic amblyopia. Ophthalmic Physiol Opt.2019; 39(5): 309-312.doi:10.1111/opo.12637
9. Kraus CL, Culican SM. New advances in amblyopia therapy I: binocular therapies and pharmacologic augmentation.Br J Ophthalmol.2018;102(11): 1492-1496.doi:10.1136/bjophthalmol-2018-312172
10. Manh VM, Holmes JM, Lazar EL, et al. A Randomized Trial of a Binocular iPad Game Versus Part-Time Patching in Children Aged 13 to 16 Years With Amblyopia. Am J Ophthalmol.2018; 186: 104-115.doi:10.1016/j.ajo.2017.11.017
11. Kelly KR, Jost RM, Dao L, et al. Binocular iPad Game vs Patching for Treatment of Amblyopia in Children: A Randomized Clinical Trial. JAMA Ophthalmol 2016; 134(12): 1402-1408.doi:10.1001/jamaophthalmol.2016.4224
12. Holmes JM, Manh VM, Lazar EL, et al. Effect of a Binocular iPad Game vs Part-time Patching in Children Aged 5 to 12 Years With Amblyopia: A Randomized Clinical Trial. JAMA.Ophthalmol 2016; 134(12): 1391-1400.doi:10.1001/jamaophthalmol.2016.4262
13. Smitha KA, Akhil Raja K, Arun KM, et al. Resting state fMRI: A review on methods in resting state connectivity analysis and resting state networks. Neuroradiol J.2017; 30(4): 305-317.doi:10.1177/1971400917697342
14. Liang M, Xie B, Yang H, et al. Altered interhemispheric functional connectivity in patients with anisometropic and strabismic amblyopia: a resting-state fMRI study. Neuroradiology.2017; 59 (5): 517-524.doi:10.1007/s00234-017-1824-0
15. Choi MY, Lee KM, Hwang JM, et al. Comparison between anisometropic and strabismic amblyopia using functional magnetic resonance imaging. Br J Ophthalmol.2001; 85(9): 1052-1056.doi, https://pubmed.ncbi.nlm.nih.gov/11520755
16. Thompson B, Maehara G, Goddard E, et al. Long-Range Interocular Suppression in Adults with Strabismic Amblyopia: A Pilot fMRI Study. Vision (Basel).2019;3(1): doi:10.3390/vision3010002
17. Yang X, Lu L, Li Q, et al. Altered spontaneous brain activity in patients with strabismic amblyopia: A resting-state fMRI study using regional homogeneity analysis. Exp Ther Med.2019; 18(5): 3877-3884.doi:10.3892/etm.2019.8038
18. Zuo X-N, Xing X-X. Test-retest reliabilities of resting-state FMRI measurements in human brain functional connectomics: a systems neuroscience perspective. Neurosci Biobehav Rev.2014; 45: 100-118.doi:10.1016/j.neubiorev.2014.05.009
19. Wang H, Chen T, Ye L, et al. Network centrality in patients with acute unilateral open globe injury: A voxel‐wise degree centrality study. Mol Med Rep.2017;16(6): 8295-8300.doi:10.3892/mmr.2017.7635
20. Hu Y-X, He J-R, Yang B, et al. Abnormal resting-state functional network centrality in patients with high myopia: evidence from a voxel-wise degree centrality analysis. Int J Ophthalmol.2018; 11(11): 1814-1820.doi:10.18240/ijo.2018.11.13
21. Tan G, Dan Z-R, Zhang Y, et al. Altered brain network centrality in patients with adult comitant exotropia strabismus: A resting-state fMRI study. J Int Med Res.2018; 46(1): 392-402.doi:10.1177/0300060517715340
22. Zhang B, Li B, Liu R-Q, et al. Altered spontaneous brain activity pattern in patients with ophthalmectomy: an resting-state fMRI study. Int J Ophthalmol.2020; 13(2): 263-270.doi:10.18240/ijo.2020.02.10
23. Cai F, Gao L, Gong H, et al. Network Centrality of Resting-State fMRI in Primary Angle-Closure Glaucoma Before and After Surgery. PLoS One.2015;10(10): e0141389.doi:10.1371/journal.pone.0141389
24. Zhang Q, Shu Y, Li X, et al. Resting-state functional magnetic resonance study of primary open-angle glaucoma based on voxelwise brain network degree

centrality. Neurosci Lett.2019; 712: 134500.doi:10.1016/j.neulet.2019.134500
25. Wang Y, Jiang L, Wang X-Y, et al. Evidence of altered brain network centrality in patients with diabetic nephropathy and retinopathy: an fMRI study using a voxel-wise degree centrality approach. Ther Adv Endocrinol Metab.2019;10: 2042018819865723.doi:10.1177/2042018819865723
26. Miall RC, Reckess GZ, Imamizu H. The cerebellum coordinates eye and hand tracking movements. Nat Neurosci.2001; 4(6):638-644.doi, https://pubmed.ncbi.nlm.nih.gov/11369946
27. Lee S-H, Park S-H, Kim J-S, et al. Isolated unilateral infarction of the cerebellar tonsil: ocular motor findings.Ann Neurol.2014;75(3):429-434.doi, https://pubmed.ncbi.nlm.nih.gov/24812698
28. Dell'Osso LF. Ocular Motor System Control Models and the Cerebellum: Hypothetical Mechanisms. Cerebellum.2019; 18 (3): 605-614.doi:10.1007/s12311-018-1001-y
29. Lee S-U, Kim H-J, Choi J-H, et al. Comparison of Ocular Motor Findings Between Neuromyelitis Optica Spectrum Disorder and Multiple Sclerosis Involving the Brainstem and Cerebellum. Cerebellum 2019; 18(3): 511-518.doi:10.1007/s12311-019-01018-4
30. Ohki M, Kitazawa H, Hiramatsu T, et al. Role of primate cerebellar hemisphere in voluntary eye movement control revealed by lesion effects. J Neurophysiol.2009; 101(2): 934-947.doi:10.1152/jn.90440.2008
31. Ruehl RM, Hinkel C, Bauermann T, et al. Delineating function and connectivity of optokinetic hubs in the cerebellum and the brainstem. Brain Struct Funct 2017; 222(9): 4163-4185.doi:10.1007/s00429-017-1461-8
32. Guo L, Bai G, Zhang H, et al. Cognitive Functioning in Temporal Lobe Epilepsy: A BOLD-fMRI Study. Mol Neurobiol.2017; 54(10): 8361-8369.doi:10.1007/s12035-016-0298-0
33. Badura A, Verpeut JL, Metzger JW, et al. Normal cognitive and social development require posterior cerebellar activity. Elife.2018; 7: doi:10.7554/eLife.36401
34. Schmahmann JD. The cerebellum and cognition. Neurosci Lett.2019;688: 62-75.doi:10.1016/j.neulet.2018.07.005
35. Hoche F, Guell X, Sherman J C, et al. Cerebellar Contribution to Social Cognition. Cerebellum.2016; 15(6): 732-743.doi, https://pubmed.ncbi.nlm.nih.gov/26585120
36. Gordon L, Cobb PR, Balasubramaniam R. Recruitment of the motor system during music listening: An ALE meta-analysis of fMRI data. PLoS One.2018; 13(11): e0207213.doi:10.1371/journal.pone.0207213
37. Cunningham SI, Tomasi D, Volkow ND. Structural and functional connectivity of the precuneus and thalamus to the default mode network. Hum Brain Mapp.2017; 38(2): 938-956.doi:10.1002/hbm.23429
38. Deng Z, Wu J, Gao J, et al. Segregated precuneus network and default mode network in naturalistic imaging. Brain Struct Funct.2019;224(9): 3133-3144.doi:10.1007/s00429-019-01953-2
39. Yuan C, Zhu H, Ren Z, et al. Precuneus-related regional and network functional deficits in social anxiety disorder: A resting-state functional MRI study. Compr Psychiatry.2018; 82: 22-29.doi:10.1016/j.comppsych.2017.12.002
40. Lai C-H. The regional homogeneity of cingulate-precuneus regions: The putative biomarker for depression and anxiety. J Affect Disord. 2018; 229: 171-176.doi:10.1016/j.jad.2017.12.086
41. Schott BH, Wüstenberg T, Lücke E, et al. Gradual acquisition of visuospatial associative memory representations via the dorsal precuneus. Hum Brain Mapp.2019; 40(5): 1554-1570.doi:10.1002/hbm.24467
42. Ghika J, Bogousslavsky J, Uske A, et al. Parietal kinetic ataxia without proprioceptive deficit. J Neurol Neurosurg Psychiatry.1995;59(5):531-533.doi, https://pubmed.ncbi.nlm.nih.gov/8530941
43. Reber TP, Faber J, Niediek J, et al. Single-Neuron Correlates of Conscious Perception in the Human Medial Temporal Lobe. Curr Biol.2017; 27(19):2991-2998.e2. doi:10.1016/j.cub.2017.08.025
44. Spray A, Beer AL, Bentall RP, et al. Microstructure of the superior temporal gyrus and hallucination

proneness - a multi-compartment diffusion imaging study. Neuroimage Clin.2018; 20: 1-6.doi:10.1016/j.nicl.2018.06.027

45. Martin CB, Mirsattari SM, Pruessner JC, et al. Relationship between déjà vu experiences and recognition-memory impairments in temporal-lobe epilepsy. Memory.2019:24;1-11. doi:10.1080/09658211.2019.1643891
46. Duan Y, Norcia AM, Yeatman JD, et al. The Structural Properties of Major White Matter Tracts in Strabismic Amblyopia. Invest Ophthalmol Vis Sci.2015;56(9): 5152-5160.doi:10.1167/iovs.15-17097
47. Tsai T-H, Su H-T, Hsu Y-C,et al. White matter microstructural alterations in amblyopic adults revealed by diffusion spectrum imaging with systematic tract-based automatic analysis. Br J Ophthalmol.2019; 103(4): 511-516.doi:10.1136/bjophthalmol-2017-311733
48. Lin X, Ding K, Liu Y, et al. Altered spontaneous activity in anisometropic amblyopia subjects: revealed by resting-state FMRI. PLoS One.2012; 7(8): e43373.doi:10.1371/journal.pone.0043373
49. Hiser J, Koenigs M. The Multifaceted Role of the Ventromedial Prefrontal Cortex in Emotion, Decision Making, Social Cognition, and Psychopathology. Biol Psychiatry.2018; 83(8): 638-647.doi:10.1016/j.biopsych.2017.10.030
50. Ongür D, Ferry AT, Price JL. Architectonic subdivision of the human orbital and medial prefrontal cortex. J Comp Neurol.2003; 460(3): 425-449.doi, https://pubmed.ncbi.nlm.nih.gov/12692859
51. Sun Y, Wang Y, Han X, et al. Sex differences in resting-state cerebral activity alterations in internet gaming disorder. Brain Imaging Behav.2019;13(5): 1406-1417.doi:10.1007/s11682-018-9955-4
52. Wang Y, Yin Y, Sun Y-w, et al. Decreased prefrontal lobe interhemispheric functional connectivity in adolescents with internet gaming disorder: a primary study using resting-state FMRI. PLoS One.2015; 10(3): e0118733.doi:10.1371/journal.pone.0118733
53. Glausier JR, Lewis DA. Mapping pathologic circuitry in schizophrenia. Handb Clin Neurol.2018;150: 389-417.doi:10.1016/B978-0-444-63639-3.00025-6
54. Dedoncker J, Brunoni AR, Baeken C, et al. A Systematic Review and Meta-Analysis of the Effects of Transcranial Direct Current Stimulation (tDCS) Over the Dorsolateral Prefrontal Cortex in Healthy and Neuropsychiatric Samples: Influence of Stimulation Parameters. Brain Stimul 2016; 9(4): 501-517.doi:10.1016/j.brs.2016.04.006
55. Ko J. Neuroanatomical Substrates of Rodent Social Behavior: The Medial Prefrontal Cortex and Its Projection Patterns. Front Neural Circuits.2017;11: 41.doi:10.3389/fncir.2017.00041
56. Bae S, Kang KD, Kim SW, et al. Investigation of an emotion perception test using functional magnetic resonance imaging. Comput Methods Programs Biomed.2019; 179: 104994.doi:10.1016/j.cmpb.2019.104994
57. Marek R, Strobel C, Bredy TW, et al. The amygdala and medial prefrontal cortex: partners in the fear circuit. J Physiol (Lond).2013;591(10): 2381-2391.doi:10.1113/jphysiol.2012.248575
58. Milad MR, Quirk GJ. Neurons in medial prefrontal cortex signal memory for fear extinction. Nature.2002; 420(6911): 70-74.doi, https://pubmed.ncbi.nlm.nih.gov/12422216
59. Marek R, Xu L, Sullivan RKP, et al. Excitatory connections between the prelimbic and infralimbic medial prefrontal cortex show a role for the prelimbic cortex in fear extinction. Nat Neurosci.2018;21(5): 654-658.doi:10.1038/s41593-018-0137-x
60. Secen J, Culham J, Ho C, et al. Neural correlates of the multiple-object tracking deficit in amblyopia. Vision Res.2011; 51(23-24): 2517-2527.doi:10.1016/j.visres.2011.10.011
61. Choi MY, Lee DS, Hwang J-M, et al. Characteristics of glucose metabolism in the visual cortex of amblyopes using positron-emission tomography and statistical parametric mapping. J Pediatr Ophthalmol Strabismus.2002;39(1):11-19.doi, https://pubmed.ncbi.nlm.nih.gov/11859911
62. Koenigs M, Barbey AK, Postle BR, et al. Superior parietal cortex is critical for the manipulation of information in working memory. JNeurosci.2009;29(47):14980-14986.doi:10.1523/JNEUROSCI.3706-09.2009
63. Peyrin C, Démonet JF, N'Guyen-Morel MA, et al. Superior parietal lobule dysfunction in a homogeneous group of dyslexic children with a

visual attention span disorder. Brain Lang.2011; 118(3):128-138.doi:10.1016/j.bandl.2010.06.005

64. Segal E, Petrides M. The anterior superior parietal lobule and its interactions with language and motor areas during writing. Eur J Neurosci.2012;35(2):309-322.doi:10.1111/j.1460-9568.2011.07937.x