

# Altered intrinsic functional connectivity of the primary visual cortex in youth patients with comitant exotropia: a resting state fMRI study

Pei-Wen Zhu<sup>1</sup>, Xin Huang<sup>1,2</sup>, Lei Ye<sup>1</sup>, Nan Jiang<sup>1</sup>, Yu-Lin Zhong<sup>1</sup>, Qing Yuan<sup>1</sup>, Fu-Qing Zhou<sup>3</sup>, Yi Shao<sup>1</sup>

<sup>1</sup>Department of Ophthalmology, the First Affiliated Hospital of Nanchang University, Nanchang 330006, Jiangxi Province, China

<sup>2</sup>Eye Center, Renmin Hospital of Wuhan University, Wuhan University, Wuhan 430060, Hubei Province, China

<sup>3</sup>Department of Radiology, the First Affiliated Hospital of Nanchang University, Nanchang 330006, Jiangxi Province, China

**Co-first authors:** Pei-Wen Zhu and Xin Huang

**Correspondence to:** Fu-Qing Zhou. Department of Radiology, the First Affiliated Hospital of Nanchang University, No.17, Yongwaizheng Street, Donghu District, Nanchang 330006, Jiangxi Province, China. fq.chou@yahoo.com; Yi Shao. Department of Ophthalmology, the First Affiliated Hospital of Nanchang University, No.17, Yongwaizheng Street, Donghu District, Nanchang 330006, Jiangxi Province, China. freebee99@163.com

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## Abstract

• **AIM:** To evaluate the differences in the functional connectivity (FC) of the primary visual cortex (V1) between the youth comitant exotropia (CE) patients and health subjects using resting functional magnetic resonance imaging (fMRI) data.

• **METHODS:** Totally, 32 CEs (25 males and 7 females) and 32 healthy control subjects (HCs) (25 males and 7 females) were enrolled in the study and underwent the MRI scanning. Two-sample *t*-test was used to examine differences in FC maps between the CE patients and HCs.

• **RESULTS:** The CE patients showed significantly less FC between the left Brodmann area (BA17) and left lingual gyrus/cerebellum posterior lobe, right middle occipital gyrus, left precentral gyrus/postcentral gyrus and right inferior parietal lobule/postcentral gyrus. Meanwhile, CE patients showed significantly less FC between right BA17 and right middle occipital gyrus (BA19, 37).

• **CONCLUSION:** Our findings show that CE involves abnormal FC in primary visual cortex in many regions, which may underlie the pathologic mechanism of impaired fusion and stereoscopic vision in CEs.

• **KEYWORDS:** comitant exotropia; functional connectivity; primary visual cortex; spontaneous activity

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## INTRODUCTION

The strabismus is a common eye disease characterized by the dysfunction of eye movement<sup>[1]</sup> and binocular vision<sup>[2]</sup>. The incidence rate of strabismus is 5.65% in Eastern China in preschool children<sup>[3]</sup>. There are a variety of factors contributing to the strabismus, including congenital and acquired factors, such as genetic mutations<sup>[4]</sup>, refractive errors<sup>[5]</sup>, amblyopia<sup>[6]</sup> and so on. Strabismus can be classified into exotropia and esotropia based on the oblique direction. According to the change of the squint angle direction, we can classify strabismus as comitant strabismus and incomitant strabismus. Clinically, the manifestation of exotropia patients is a noticeable outward deviation of the eyes, which will not only lead to appearance problem but also cause impairment of stereo vision<sup>[7]</sup>. At present, surgery is the main treatment for exotropia<sup>[8]</sup>. Meanwhile, the surgical correction for exotropia is beneficial for the recovery of binocular visual function<sup>[9]</sup>.

The esotropia patients are often associated with the impairment of stereo vision<sup>[10]</sup>. Because of the disruption in binocular visual signal correspondence in strabismus patients, the binocular activation of visual cortical neurons in the primary visual cortex [Visual area 1 (V1)] may change<sup>[2]</sup>. Receiving inputs from both eyes, the primary visual cortex is the first step of stereo vision processing<sup>[11]</sup>. A previous study demonstrated that all visual areas play important roles in disparity-defined depth<sup>[12]</sup>. Other research exhibited that neurons in the V5 have similar response to that of V1. And the V4 neurons reflect an experience of stereoscopic depth<sup>[13]</sup>. However, understanding of the abnormalities of V1 in the comitant exotropia (CE) remains unknown.

Resting-state functional magnetic resonance imaging (rs-fMRI) is an effective method to evaluate the changes of the brain neural anatomy and function in strabismus. Yan *et al*<sup>[14]</sup> demonstrated that the CE showed the impaired dorsal visual

pathway. Strabismic patients show suppression in the primary visual cortex<sup>[15]</sup>. Other study demonstrated that the monocular deprivation by strabismus leads to the dysfunction of the V1<sup>[16]</sup>. Additionally, the V1 neurons in the strabismic group showed reduction of interocular spatial phase disparities (disparity sensitivity) and a higher prevalence of binocular inhibitory interactions<sup>[17]</sup>. Many previous studies have demonstrated that the primary angle-closure glaucoma patients and amblyopia patients showed abnormal FC in primary visual cortex<sup>[18-19]</sup>. Although the above mentioned studies have demonstrated that strabismus could lead to the dysfunction of the V1, the abnormal intrinsic functional connectivity (FC) between the V1 and the other cortex has not been revealed yet.

Here, our study is the first to assess the alternations in FC of V1 in CE, which might help to reveal the pathogenesis of abnormal visual fusion function in youth patients with strabismus.

## SUBJECTS AND METHODS

**Subjects** In total, individuals with CEs (25 males and 7 females) were enrolled in this study from Department of the Ophthalmology, the First Affiliated Hospital of Nanchang University in Jiangxi Province of China. The criteria for the study include: 1) exotropia with stereopsis defects (no visual fusion); 2) visual acuity (VA) >1.0; 3) the deflection angle of strabismus group were equal. The exclusion criteria of the study were: 1) acquired strabismus, esotropia strabismus, incomitant strabismus; 2) ocular diseases or surgery history; 3) without psychiatric disorders, cardiovascular disease and cerebral disease.

We also recruited 32 healthy control subjects (HCs) including 25 males and 7 females with matched age and education in this study. HCs were recruited based on the following criteria: 1) normal brain parenchyma on cranial MRI; 2) VA>1.0 and free of any ocular diseases; 3) absence of psychiatric diseases including depressive disorder and delusional disorder; 4) accessible to the MRI scanning.

The study were approved by the committee of the medical ethics of the Department of Ophthalmology, the First Affiliated Hospital of Nanchang University. The participants provided an informed consent.

**Magnetic Resonance Imaging Parameters** MRI images were scanned on a 3-Tesla MR scanner (Trio, Siemens, Germany). rs-fMRI data acquisition was obtained in 8min. High-resolution T1-weighted images were acquired with a three-dimensional spoiled gradient-recalled sequence in an axial orientation and 240 functional images with each patient covering the whole brain were obtained<sup>[18,20]</sup>.

## Functional Magnetic Resonance Imaging Data Processing

The data were preprocessed with Data Processing Assistant for rs-fMRI (DPARSF 2.3, <http://rfmri.org/DPARSF>) run on MATLAB2014b (Mathworks, Natick, MA, USA) which was

**Table 1 MNI coordinates for selected seed regions**

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

ROI: Region of interest; MNI: Montreal Neurological Institute.

based on statistical parametric mapping (SPM; <http://www.fil.ion.ucl.ac.uk/spm>) and the rs-fMRI Data Analysis Toolkit (REST; <http://www.restfmri.net>)<sup>[21]</sup>. The preprocessing steps are illustrated as follows: 1) the first ten time points were trimmed off due to the signal reaching equilibrium<sup>[22]</sup>; 2) the remaining 230 volumes of functional BOLD images were corrected for slice timing effects, motion corrected and realigned. fMRI scans with more than 2 mm maximum displacement in any direction or more than 2° angular motion were discarded<sup>[23]</sup>; 3) spatial normalized with re-sampling to 3-mm isotropic voxels. After smoothing with a 6-mm full width half maximum (FWHM) Gaussian kernel, linear trend was removed, the band-pass temporal filtering (0.01-0.08 Hz), and the covariates were then removed, including head motion parameters, whole brain, white matter (WM), and cerebrospinal fluid (CSF) signal.

**Definition of the Region of Interest in BA17** We chose each side of the primary visual cortex, also known as brodmann area 17 (BA17), as region of interests (ROIs) using the software WFU Pick Atlas (<http://www.ansir.wfubmc.edu/>)<sup>[24]</sup>, which has been used in previous studies to define ROIs<sup>[19]</sup>. The steps of defining the seed ROI of the BA17 were as follows: 1) both sides of BA17 were selected from the TD (Talairach Daemon) BA atlas; 2) the location of the left BA17 was intersected to generate the left ROI of the primary visual cortex; 3) the right ROI was obtained similarly (Table 1).

**Functional Connectivity Analysis** FC analyses were performed for the left and right BA17 separately. The rs-fMRI data was analyzed by the statistical module of the dpabi (<http://rfmri.org/dpabi>). One-way analysis of covariance (ANCOVA) and generalized linear model (GLM) was applied to produce the FC maps, with age and gender used as covariates. Two-sample *t*-test was used to examine differences in FC between the CE patients and HCs [at voxel level  $P<0.01$  and cluster level  $P<0.05$ , Gaussian random field (GRF)-corrected].

## Correlation Analysis Between Brain Function and Clinical Behavior

All clinical data including the duration of CEs and VA of both eyes were collected. The correlation between the mean FC value in various brain regions and the behavioral performance in CEs groups was analyzed with correlation analysis.  $P<0.05$  was set as statistical threshold.

**Clinical Data Analysis** Two-sample Student's *t*-test was used for comparison between behavior data (IBM SPSS software version 20.0).  $P<0.05$  was set as statistical threshold.

**Table 2 Demographics and clinical measures by group**

Condition	CEs	HCs	<i>t</i>	<sup>a</sup> <i>P</i>
M/F	25/7	25/7	N/A	>0.99
Age (y)	24.56±1.96	25.16±2.68	-1.011	0.316
Weight (kg)	58.34±3.66	59.00±3.78	-0.705	0.483
Handedness	32R	32R	N/A	>0.99
Exotropia	32	N/A	N/A	N/A
Duration of strabismus (y)	22.25±2.21	N/A	N/A	N/A
VA-right	1.20±0.20	1.14±0.19	1.154	0.253
VA-left	1.18±0.18	1.12±0.16	1.408	0.164

CEs: Comitant exotropia strabismus; HCs: Healthy controls; N/A: Not applicable; VA: Visual acuity; <sup>a</sup>Independent *t*-tests comparing two groups.

**Table 3 Brain regions with significant differences in FC between CEs and HCs**

Brain regions	BA	Cluster size	Brain region of peak MNI coordinates			<i>t</i>
			X	Y	Z	
ROI in left BA 17						
Left lingual gyrus/cerebellum posterior lobe	17, 18	184	-24	-96	-15	-3.428
Right middle occipital gyrus	19, 37	341	45	-69	-12	-3.886
Left precentral gyrus/postcentral gyrus	6, 9	166	-45	0	30	-3.949
Right inferior parietal lobule/postcentral gyrus	40	168	39	-36	36	-4.959
ROI in right BA 17						
Right middle occipital gyrus	19, 37	487	45	-72	-9	-4.158

The significance level was set at voxel level  $P < 0.01$  and cluster level  $P < 0.05$ , cluster  $> 40$  voxels, Gaussian random field theory corrected. FC: Functional connectivity; CEs: Comitant exotropia strabismus; HCs: Healthy controls; BA: Brodmann area; MNI: Montreal Neurological Institute; ROI: Region of interest.

**RESULTS**

**Demographics and Clinical Behaviors** Thirty-two CE patients (25 males, 7 females; mean age: 24.56±1.96y) and 32 health subjects volunteer individuals (25 males, 7 females; mean age: 25.16±2.68y) were recruited in the study. We did not observe significant difference in weight ( $P=0.483$ ), age ( $P=0.316$ ), VA-right ( $P=0.253$ ) and VA-left ( $P=0.164$ ) between HCs and CEs patients. Details are presented in Table 2.

**Functional Connectivity Differences** A two-sample *t*-test was used to determine the different FC maps between two groups. Compared with HCs ( $n=32$ ), the CE patients ( $n=32$ ) showed significantly lower FC with the left BA17 in left lingual gyrus/cerebellum posterior lobe (BA17, 18), right middle occipital gyrus (BA19, 37), left precentral gyrus/postcentral gyrus (BA6, 9) and right inferior parietal lobule/postcentral gyrus (BA40) (Figure 1, Table 3). On the contrary, CE patients showed significantly lower FC with the right BA17 in the right middle occipital gyrus (BA19, 37) (Figure 1, Table 3). In the meanwhile, Figures 1 and 2 showed the mean values of altered FC in the CEs and HCs. We did not observe obvious correlation between the mean FC values in different brain areas and the behavioral performance in the CEs patients ( $P > 0.05$ ).

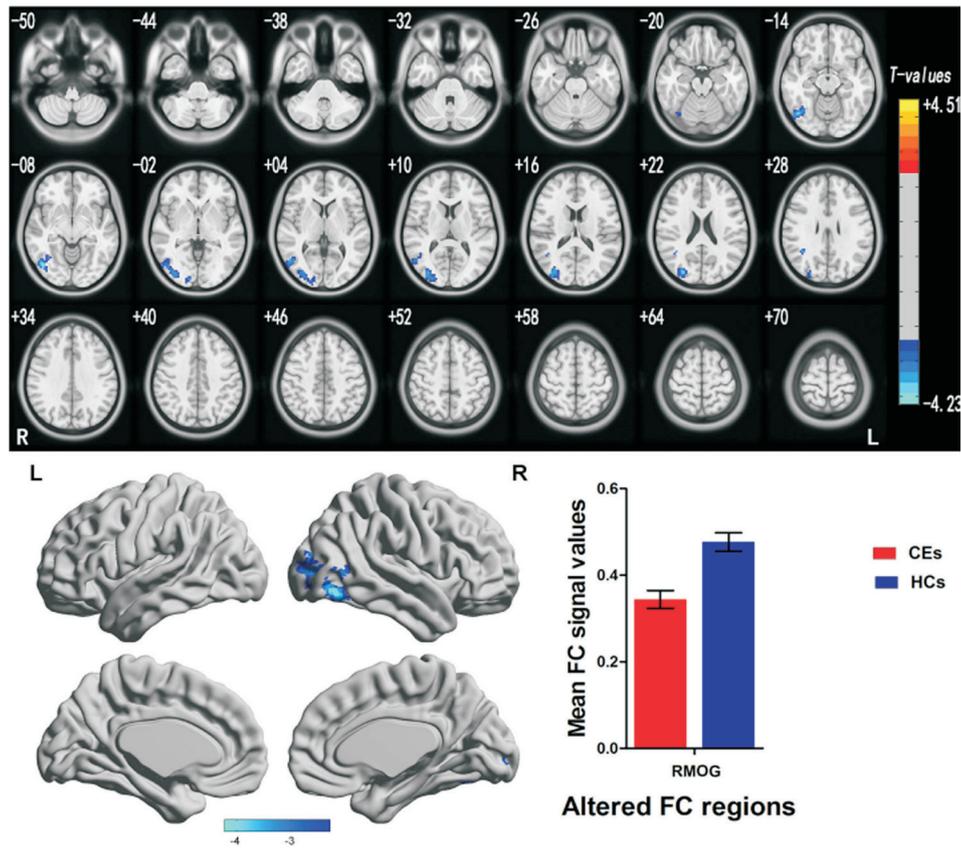
**Receiver Operating Characteristic Curve** We identified FC values in different brain regions with significant differences

between the CEs and HCs groups. In our study, the area under the curve (AUC) was as follows: left lingual gyrus/cerebellum posterior lob (0.821), right middle occipital gyrus (0.734), left precentral gyrus/postcentral gyrus (0.711), right inferior parietal lobule/postcentral gyrus (0.709) (CEs<HCs) (ROI in left BA17; HMs<HCs) (Figure 3A), and right middle occipital gyrus (0.786) (CEs<HCs) (ROI in right BA17; HMs<HCs) (Figure 3B), respectively.

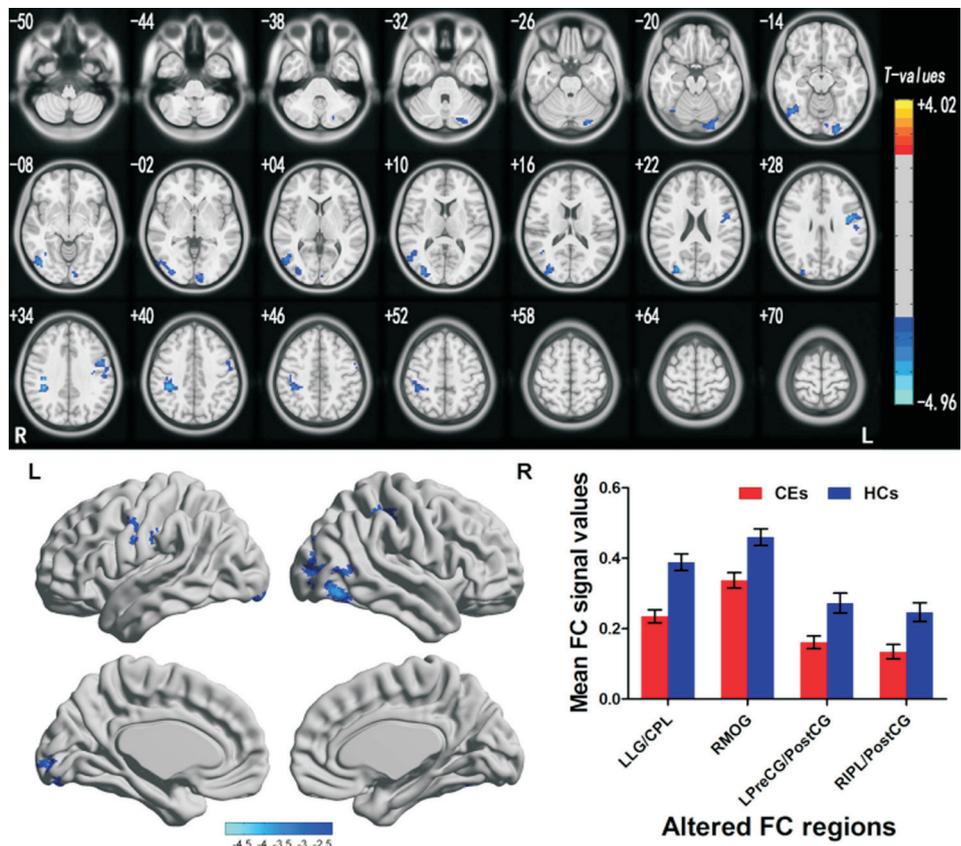
**DISCUSSION**

In this study, we discovered that young CEs patients had significantly decreased FC in the left BA17, left lingual gyrus/cerebellum posterior lobe, right middle occipital gyrus, left precentral gyrus/postcentral gyrus and right inferior parietal lobule/postcentral gyrus. Additionally, the youth CE patients showed significantly decreased FC in the right BA17 and right middle occipital gyrus.

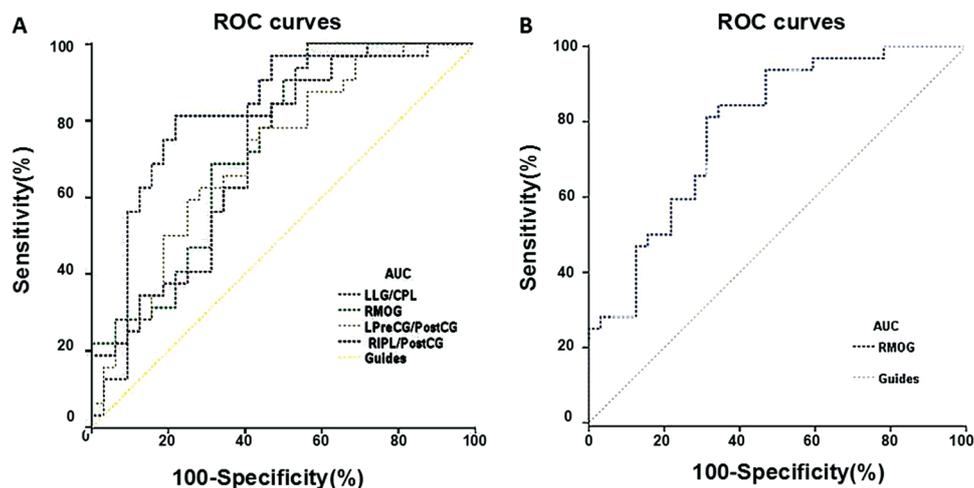
The lingual gyrus, as a part of the V1, resides in the occipital lobe. The lingual gyrus is functional in the apprehension of vision<sup>[25]</sup> and reading<sup>[26]</sup>. It has been shown that the lingual gyrus is less activated in the infantile esotropia, indicating the fusion defects<sup>[27]</sup>. Another research demonstrated that the strabismic amblyopia patients had reduced activities in the V1<sup>[28]</sup>. Consistent with that, we also showed that the CEs had decreased FC in the left V1 and left lingual gyrus, which might reflect the defects in the processing of vision in CEs.



**Figure 1** Brain regions demonstrating statistically significant differences between two groups in terms of FC in the left BA17. Significant FC differences were observed in the left lingual gyrus/cerebellum posterior lobe, right middle occipital gyrus (RMOG), left precentral gyrus/postcentral gyrus, right inferior parietal lobule/postcentral gyrus, and the blue areas denote lower FC values. CEs: Comitant exotropia strabismus; HCs: Healthy controls; BA: Brodmann area; FC: Functional connectivity.



**Figure 2** Brain regions demonstrating statistically significant differences between two groups in terms of FC in the right BA17. Significant FC differences were observed in the right middle occipital gyrus (RMOG); the blue areas denote lower FC values. CEs: Comitant exotropia strabismus; HCs: Healthy controls; BA: Brodmann area; FC: Functional connectivity.



**Figure 3** ROC curve analysis of the mean FC values for altered brain regions. ROC: Receiver operating characteristic; FC: Functional connectivity; CI: Confidence interval; HCs: Healthy controls; CEs: Comitant exotropia strabismus; LG: Lingual gyrus; CPL: Cerebellum posterior lobe; MOG: Middle occipital gyrus; PreCG: Precentral gyrus; PostCG: Postcentral gyrus; IPL: Inferior parietal lobule; R: Right; L: Left; B: Bilateral.

The middle occipital gyrus (BA19) is a visual association area involved in the stereovision function<sup>[29]</sup>. The middle occipital gyrus (MOG) also plays an important role in the category-selective attention-modulated unconscious face/tool processing<sup>[30]</sup> and spatial processing<sup>[31]</sup>. It has been shown that the intermittent exotropia showed lower activities in the MOG<sup>[32]</sup>. Consistently, we demonstrated that the CEs had significantly decreased FC in the left/right BA17 and right MOG (BA19), reflecting the defects in the right MOG in the CEs. The precentral gyrus is located in the frontal eye fields (FEF), which is responsible for the oculomotor<sup>[33]</sup>. A previous study demonstrated that the precentral gyrus is involved in the encoding of oculomotor<sup>[34]</sup>. Moreover, another research showed that the stimulating precentral gyrus controls eye movement<sup>[35]</sup>. A recent study demonstrated that the stimulation of early visual cortex is associated with feed forward in the FEF<sup>[36]</sup>. We found that functional connectivity between left primary visual cortex and left precentral gyrus was significantly decreased in CEs, indicating the impaired interaction of the V1 and precentral gyrus in CEs. Thus, we speculated that the decrease of the FC might indicate oculomotor disorder in CEs.

The dorsal stream begins with V1, goes through V2, then to the visual area MT (middle temporal/V5) and to the inferior parietal lobe<sup>[37]</sup>. Additionally, the inferior parietal lobule (IPL) is involved in the visual categorization<sup>[38]</sup> and visual word recognition<sup>[39]</sup>. Meanwhile, the IPL plays an important role in the stereopathway<sup>[40]</sup>. Ding *et al*<sup>[19]</sup> showed decreased FC in the BA17 and IPL of the amblyopia patients. In this study, we demonstrated that FC in the left BA17 and right IPL was significantly decreased, which might reflect the defects in stereo vision in CEs.

Our study showed that CEs had significantly decreased FC in the primary visual cortex and other brain regions, which might provide valuable information to explain the defects in stereo vision in the youth CE patients.

There are some limitations in the study. First, the CEs patients with long-term duration might be associated with depression, mental disorders and other mental symptoms. A neuropsychological assessment in CEs patients would be necessary to dissect out the relationship of CE and neural disorders. Second, the number of youth CE patients in the study was relatively small. Increasing the number of study subject will improve the accuracy of the results. Third, the different strabismus angle of the CEs might have some impacts on the accuracy of the result.

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