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ORIGINAL RESEARCH

A functional MRI study of altered spontaneous brain activity pattern in patients with congenital comitant strabismus using amplitude of low-frequency fluctuation

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Objective: The aim of this study was to use amplitude of low-frequency fluctuation (ALFF) to investigate local features of spontaneous brain activity in patients with congenital comitant strabismus and clarify their relationship with emotional and psychosocial problems.

Methods: A total of 20 patients with congenital comitant strabismus (ten males and ten females), and 20 healthy controls (ten males and ten females) closely matched in age, sex, and education underwent resting-state functional magnetic resonance imaging scans. The ALFF method was used to assess local features of spontaneous brain activity. Congenital comitant strabismus patients were distinguished from healthy controls by receiver operating characteristic curve. Correlation analysis was performed to explore the relationships between the observed mean ALFF signal values of the different areas and the Chinese version of the Hospital Anxiety and Depression Scale.

Results: Compared with healthy controls, patients with congenital comitant strabismus had significantly lower ALFF in the bilateral medialfrontal gyrus and higher values in the bilateral cerebellum posterior lobe and left angular gyrus. In the congenital comitant strabismus group, the Hospital Anxiety and Depression Scale-depression score showed a negative correlation with the ALFF signal values of the bilateral medial frontal gyrus (r=–0.550, P=0.012) and a negative correlation was noted between the mean ALFF signal values of the left angular gyrus and strabismus duration (r=–0.515, P=0.020).

Conclusion: Congenital comitant strabismus mainly involves dysfunction in the bilateral medial frontal gyrus, bilateral cerebellum posterior lobe, and left angular gyrus, which may reflect the underlying pathologic mechanism of congenital strabismus.

Keywords: ALFF, congenital comitant strabismus, resting state, spontaneous activity, anxiety and depression

Introduction

Strabismus is a common eye disease with monocular or binocular abnormal position. The incidence rate of adult-onset strabismus in Olmsted County, MN, USA, was 54.1 cases per 100,000 individuals.[1] Strabismus often leads to compromised binocular vision and amblyopia. Clinically, strabismus also presents with stereopsis impairment. In addition to functional limitations (restriction in visual field and stereopsis), strabismic patients may suffer from significant psychosocial problems.[2] It was worthy of attention that the strabismus had posed great pressures on patients in all age groups.[3]

Neuronal activity within the oculomotor nucleus could drive abnormal cross-axis eye movements. The frontal eye field (FEF) is an area of the frontal cortex that can trigger eye movements.[4] In humans, gaze control systems also include the supplementary eye field, presupplementary eye field, dorsolateral prefrontal cortex, cingulate eye field within the anterior cingulate cortex, and dorsomedial frontal cortex. The FEF is involved in executing saccadic and smooth pursuit eye movements.[5]

Previous studies demonstrated that there were many psychiatric problems in patients with strabismus.[6,7] The frontal gyrus played an important role in emotion.[8] A previous study proved severely depressed patients with cortical thickening in left frontal brain regions compared favourably with healthy control (HCs).[9] Moreover, the patients with depression showed enhanced default mode network connectivity with ventral striatum.[10] The anxiety disorder also leads to the dysfunction of brain function. The patients with social anxiety disorder might have an insular volume reduction.[11]

Magnetic resonance imaging (MRI) has been used to study strabismus. A previous report described reduced gray matter volume in the occipital eye field and parietal eye field and increased gray matter volume in FEF of adults with strabismus.[12] Another group demonstrated reduced functional connections in the V1 and V2 areas of macaque monkeys with strabismic amblyopia.[13] Another study showed increased mean diffusivity in the occipital tracts of patients with strabismic amblyopia.[14] Although these findings have revealed morphological changes in the neurons of subjects with strabismus, there is far less evidence for neuromechanical changes.

Resting state functional MRI (fMRI) is a functional brain imaging technique that is increasingly used to evaluate spontaneous brain activity in subjects at rest.[15] Amplitude of low-frequency fluctuation (ALFF) is a resting state-fMRI analysis technique used to measure spontaneous fluctuations in blood-oxygen level-dependent signal, which reflects regional spontaneous brain activity at rest. ALFF has been used to investigate neurological conditions, including optic neuritis,[16] glaucoma,[17] and Parkinson's disease.[18] The current study is the first, to our knowledge, to evaluate spontaneous brain activity in subjects with congenital comitant strabismus and its relationship with behavioral measures.

Materials and methods

Subjects

A total of 20 patients with congenital comitant strabismus (ten males and ten females, five esotropia and 15 exotropia) were recruited from the First Affiliated Hospital of South China University and the Ophthalmology Department of the First Affiliated Hospital of Nanchang University Hospital. The diagnostic criteria of congenital comitant strabismus were: 1) strabismus from birth; 2) stereo vision defects (no visual fusion); 3) binocular corrected visual acuity (VA) is equal; and 4) with alternated cover, the experimental and strabismus angle were equal, and the large squint angle range was 34±9.12 triple prism degree. Subjects were excluded if they met any one of the following criteria: 1) acquired strabismus, incomitant strabismus, and concealed oblique; 2) condition due to eye disease (infection, inflammation, and ischemic disease); 3) patients with eye surgery (outside the eye surgery and intraocular surgery); 4) psychiatric disorders (obsessive compulsive disorder, anxiety disorder, schizophrenia, depression, etc), diabetes, cardiovascular disease, and cerebral infarction disease; and 5) addiction (eg, drugs or alcohol).

Twenty HCs (ten males and ten females) who were age-, sex-, and education status-matched to subjects in the strabismus group were also recruited for this study. The HCs were recruited from healthy volunteers of Nanchang in Jiangxi province. All HCs met the following criteria: 1) no abnormalities in the brain parenchyma on cranial MRI; 2) no ocular disease with uncorrected or corrected VA $>$1.0; 3) no psychiatric disease (obsessive compulsive disorder, anxiety disorder, schizophrenia, depression, etc); and 4) able to undergo MRI (eg, no cardiac pacemaker or implanted metal devices). This study was authorized by the First Affiliated Hospital of Nanchang hospital's ethics committee. All research methods followed the Declaration of Helsinki and conformed to the principles of medical ethics. All volunteers participated voluntarily and were informed of the purposes, methods, and potential risks before signing an informed consent.

MRI parameters

MRI scanning was performed on a 3-Tesla MR scanner (Trio, Siemens, Munich, Germany). All the participants were required to keep awake and maintain quiet breathing until the end of the scan. Structural data and functional data were acquired with a 3D spoiled gradient-recalled echo sequence with the following parameters: 176 structural images (repetition time =1,900 ms, echo time =2.26 ms, thickness =1.0 mm, gap =0.5 mm, acquisition matrix =256×256, field of view =250×250 mm, flip angle =9°). We also obtained 240 functional images (repetition time =2,000 ms, echo time =30 ms, thickness =4.0 mm, gap =1.2 mm, acquisition matrix =64×64, flip angle =90°, field of view =220×220 mm, 29 axial). The duration of scan time was 15 minutes.

fMRI data analysis

Functional data were classified by MRIcro software (www.MRIcro.com) to eliminate incomplete data. The first ten volumes were discarded due to magnetization equilibration. The rest of the data preprocessing was performed by DPARSFA (http://rfmri.org/DPARSF) software, including Digital Imaging Communications in Medicine form transformation, slice timing, head-motion correction, spatial normalization, and smooth with a Gaussian kernel of 6×6×6 mm^3 full-width at half-maximum. The subjects who had more than 1.5 mm maximum shift in x, y, or z and 1.5 of angular motion would be dismissed. The Friston six head-motion parameters were used to regress out head-motion effects based on recent work showing that higher-order models were more effective in removing head-motion effects.[19,20] Linear regression was also applied to remove other sources of false variables, which contain the signal from the ventricular system and a region centered in the brain white matter.[21] After head-motion correction, the functional images were spatially normalized to the Montreal Neurological Institute space using the standard echoplanar image template. The details of ALFF calculation can be referred to a previous study.[22] To reduce the global effects of variability across the participants, the ALFF of each voxel was divided by the global mean ALFF value for each participant.

A general linear model analysis

A general linear model analysis was performed with the SPM8 toolkit to investigate the ALFF signal group differences in resting state between patients with strabismus and HCs, after controlling for the effects of age and sex. The significance level was set at $P<0.05$, Gaussian random field theory corrected, minimum $z>2.3$.

Brain-behavior linear correlation analyses

Brain areas with different ALFF findings between groups were classified as regions of interest with REST software. For each region of interest, the mean ALFF value was extracted by averaging the ALFF value over all voxels. Linear correlation analysis was performed to investigate the relationship between the mean ALFF value in each area in the strabismus group and behavioral performances. $P<0.05$ was considered statistically significant.

Independent *t*-tests on clinical data analysis

Our previous study reported that the Chinese version of the Hospital Anxiety and Depression Scale (HADS) scores were higher in child strabismus patients compared with HCs.[23] The HADS has been widely used to evaluate patients' mental state in many diseases.[24,25] It includes seven anxiety and seven depressive symptom items and has demonstrated good reliability. Our patient questionnaire scores were obtained. The maximum anxiety and depression scores are both 21. A subject is with significant depression if his or her score is ≥8, and significant anxiety if his or her score is ≥11. The clinical data of the comitant strabismus patients were collected, including the course of the disease and best-corrected VA. Two-sample Student's *t*-test was used for clinical measures between strabismus group and HCs. All the statistical analysis was done with the IBM SPSS version 20.0 statistical software (IBM Corporation, Armonk, NY, USA).

Results

Demographics and visual measurements

The mean ± standard deviation of age for strabismus group and HCs were 26.95±9.05 (years) and 27.45±8.99 years. The scores of HADS-anxiety and HADS-depression were 7.55±1.54 and 9.20±1.36 for strabismus group. The average weight for strabismus group and HCs was 59.00±8.28 (kg) and 58.75±6.37 (kg). There were no obvious differences in weight (P=0.915), age (P=0.862), best-corrected VA-Right (P=0.351) and best-corrected VA-Left (P=0.540) between the two groups (Table 1).

ALFF differences

Compared with HCs, strabismus patients had significantly decreased ALFF values in the bilateral medial frontal gyrus (Figure 1 [blue] and Table 2). The brain areas with significantly increased ALFF values in the strabismus group were the bilateral cerebellum posterior lobe and left angular gyrus (Figure 1 [red] and Table 2). The mean values of altered

Table 1 Demographics and clinical measures by group

	Strabismus	HC	*t*	*P*-value*
Male/female	10/10	10/10	N/A	>0.99
Age (years)	26.95±9.05	27.45±8.99	–0.175	0.862
Weight (kg)	59.00±8.28	58.75±6.37	0.107	0.915
Handedness	20R	20R	N/A	>0.99
Esotropia or exotropia	5/15	N/A	N/A	N/A
Duration of strabismus (years)	26.95±9.05	N/A	N/A	N/A
Best-corrected VA-Right	1.06±0.22	1.12±0.18	–0.944	0.351
Best-corrected VA-Left	1.09±0.22	1.05±0.15	0.675	0.540
HADS-A	7.55±1.54	N/A	N/A	N/A
HADS-D	9.20±1.36	N/A	N/A	N/A

Note: *Independent *t*-tests comparing the two groups. Data presented as mean ± standard deviation.

Abbreviations: HADS-A, hospital anxiety and depression scale-anxiety; HADS-D, hospital anxiety and depression scale-depression; HC, healthy control; N/A, not applicable; VA, visual acuity.

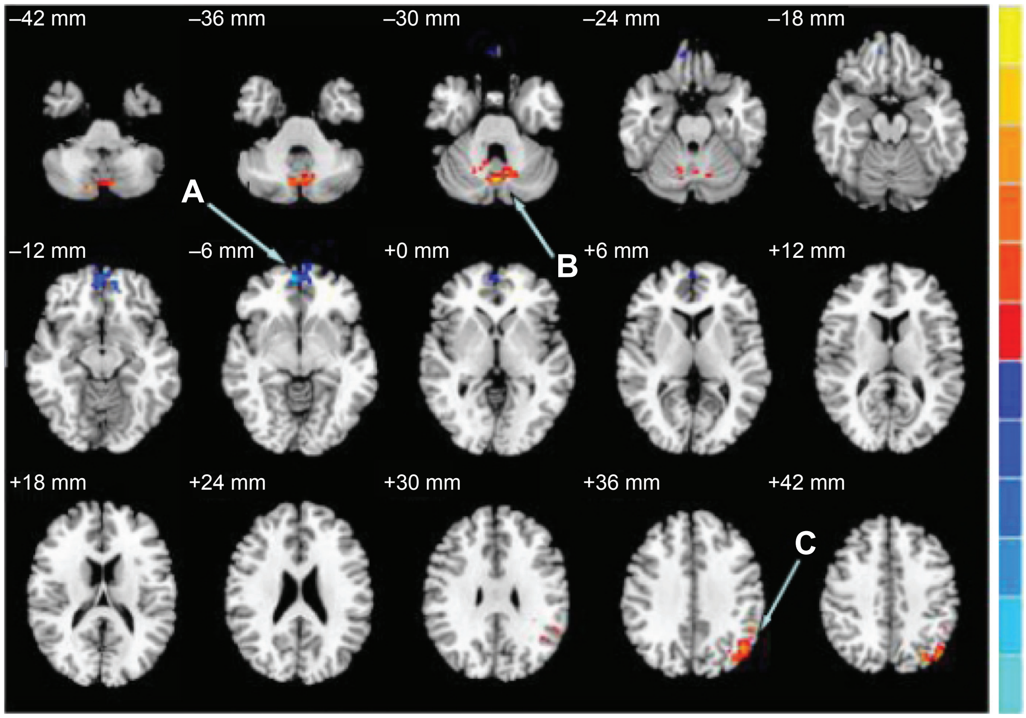

Figure 1 Spontaneous brain activity in the strabismus group.
Notes: Significant differences in activity were observed for the bilateral medial frontal gyrus (**A**), bilateral cerebellum posterior lobe (**B**), and left angular gyrus (**C**). The red and blue areas denote higher and lower amplitude of low-frequency fluctuation values, respectively ($P<0.05$ for multiple comparisons using Gaussian Random Field theory) ($z>2.3$, cluster-wise $P<0.05$ corrected).

ALFF between the strabismus and HC groups are shown in Figure 2.

Correlation analyses

In the strabismus group, the mean HADS-depression score was negatively correlated with the ALFF signal values of the bilateral medial frontal gyrus ($r=-0.550$, $P=0.012$; Figure 3A). Duration of strabismus was negatively correlated with the ALFF signal values of the left angular gyrus ($r=-0.515$, $P=0.020$; Figure 3B).

Receiver operating characteristic curve

We considered that ALFF differences between the strabismus and HC groups might be useful diagnostic markers. To test this possibility, the mean ALFF values of the different brain regions were extracted and used to analyze receiver operating characteristic curves. The values for the areas under the curves of the bilateral medial frontal gyrus were 0.915 (Figure 4).

Discussion

To our knowledge, this is the first study to evaluate the effect of strabismus on resting-state brain activity using the ALFF technique. Compared with HCs, subjects with strabismus had significant ALFF value changes in many brain regions. Furthermore, the HADS-depression score in strabismus patients was negatively correlated with the ALFF signal values of the bilateral medial frontal gyrus ($r=-0.550$, $P=0.012$)

Table 2 Brain regions with significant ALFF differences between groups

ALFF	Brain area	BA	Peak *T* values	Voxels	MNI coordinates		
					x	y	z
Stra <HC							
1	Bilateral medial frontal gyrus	10, 11	–4.887	118	6	57	–6
Stra >HC							
1	Bilateral cerebellum posterior lobe	–	4.768	152	0	–69	–30
2	Left angular gyrus	19, 39	4.247	146	–30	–75	42

Notes: The statistical threshold was set at voxel with $P<0.05$ for multiple comparisons using Gaussian random field theory ($z>2.3$, cluster-wise $P<0.05$ corrected).
Abbreviations: ALFF, amplitude of low-frequency fluctuation; BA, Brodmann area; HC, healthy control; MNI, Montreal Neurological Institute; Stra, strabismus.

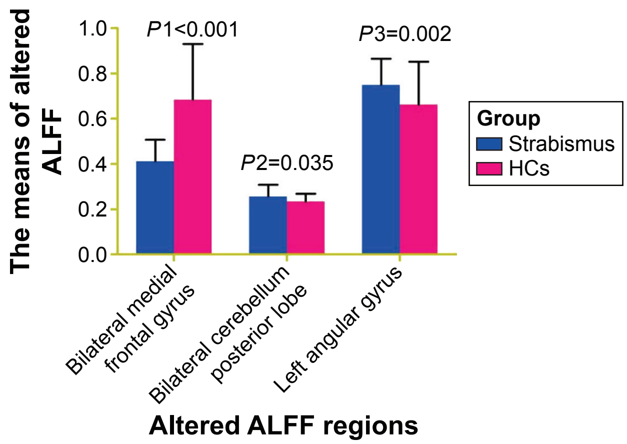

Figure 2 The mean of altered ALFF values between the strabismus and HC groups.
Note: P1, P2, P3 represent the *P*-values in independent *t*-tests comparing the two groups in ALFF values of bilateral medial frontal gyrus, bilateral cerebellum posterior lobe, and left angular gyrus, respectively.
Abbreviations: ALFF, amplitude of low-frequency fluctuation; HCs, healthy controls.

and there was a negative correlation between the mean ALFF signal values of the left angular gyrus and strabismus duration (r=–0.515, P=0.020).

Both the FEF in the prefrontal cortex and the superior colliculus are implicated in strabismus.[26] The location of the FEF is proposed to be within a larger oculomotor region in the posterior part of the middle frontal gyrus.[27] A previous study demonstrated that FEF played an important role in saccade selection and execution.[28] It was also involved in sustained attention.[29] Yan et al[30] reported reduced white matter volumes in the right frontal lobe/subgyral areas of patients with comitant exotropia. In support of these findings, we also found that patients with strabismus had lower ALFF values in the bilateral medial frontal gyrus. The decreased ALFF values in these regions may reflect FEF functional damage in patients with strabismus. Furthermore, the ALFF signal values of the bilateral medial frontal gyrus were negatively correlated with the HADS-depression score in the strabismus group. Previous studies had demonstrated that frontal gyrus dysfunction was related to depression.[31,32] A previous study found that there were lesions in the medial orbital frontal region in depressed patients.[33] Meanwhile, many studies have demonstrated that the patients with strabismus often accompanied with psychological abnormality of depressive symptoms.[34,35] We therefore hypothesized that strabismus may be related to medial frontal gyrus dysfunction, which may give an explanation to depression in patients with strabismus. The mean and standard deviation HADS-anxiety in strabismus patient was 7.55±1.54, which reflected strabismus patients accompanied by feelings of anxiety. However, we did not find a relationship between the HADS-anxiety scores and ALFF signal values of different regions.

The cerebellum is involved in balance and motor control as well as the execution of accurate eye movements.[36] One group reported that the cerebellum is involved in the execution of eye and hand movements.[37] A previous study showed that cerebellar vermis activation is related to visually guided saccades.[38] Joshi and Das[39] found that the function of posterior interposed nucleus in the cerebellum played an important role in conjugate eye movements in strabismic monkeys. In support of these findings, we also observed higher ALFF values in the bilateral cerebellum posterior lobe in strabismus, which may reflect functional reorganization to compensate for conjugate eye movement abnormalities.

The angular gyrus occupies a posterior part of the inferior parietal lobule corresponding to Brodmann area 39,[40] which is one of the major connecting hubs of the brain.[41] The parietal and occipital lobes were involved in gaze, movement, and body

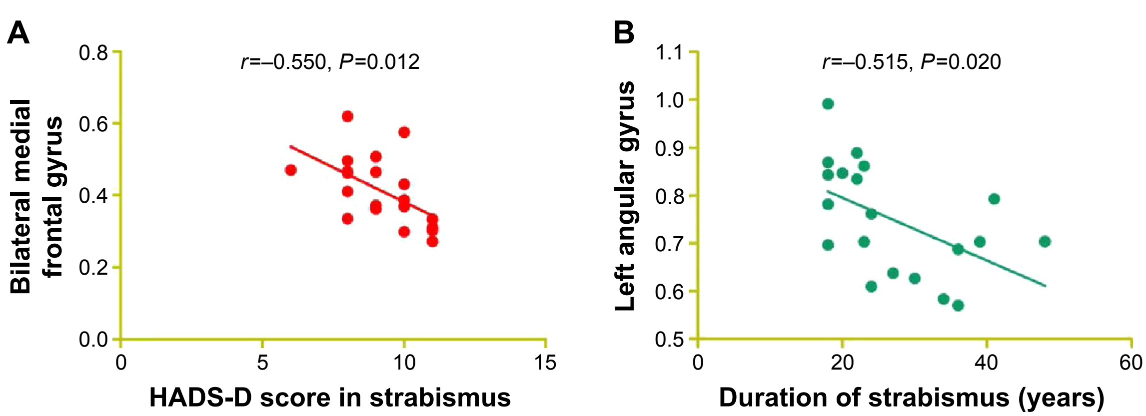

Figure 3 Correlations between mean ALFF signal values and behavioral performance.
Notes: (**A**) The HADS-D score in the strabismus group was negatively correlated with the ALFF signal values of the bilateral medial frontal gyrus (r=–0.550, P=0.012). (**B**) Strabismus duration was negatively correlated with the ALFF signal values of the left angular gyrus (r=–0.515, P=0.020).
Abbreviations: ALFF, amplitude of low-frequency fluctuation; HADS-D, hospital anxiety and depression scale-depression.

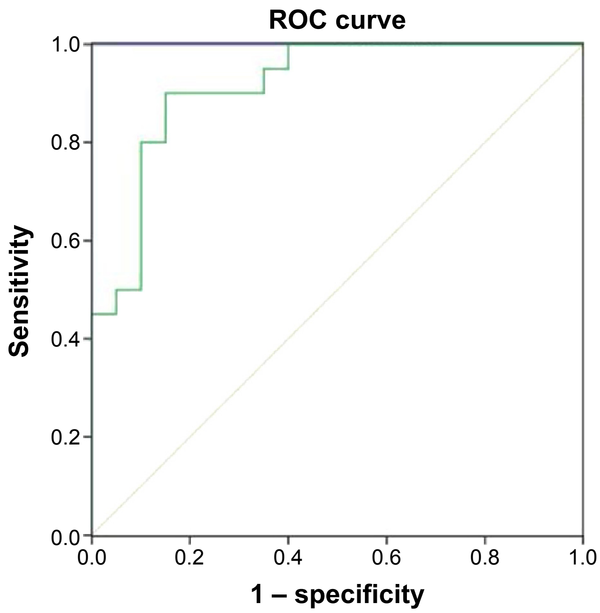

Figure 4 ROC curve analysis of mean ALFF signal values for altered brain regions.
Notes: The area under the ROC curve for ALFF values of the bilateral medial frontal gyrus was 0.915 (P=0.001; 95% confidence interval: 0.829–1). The area in the 0.5–0.7 is low sensitivity; 0.7–0.9 is middle sensitivity; and $>$0.9 is high sensitivity.
Abbreviations: ALFF, amplitude of low-frequency fluctuation; ROC, receiver operating characteristic.

guidance.[42] Yang et al[43] showed that the left cingulate gyrus, bilateral precuneus, and left angular gyrus visual cortex may compensate for fusion dysfunction in infantile esotropia. In our study, we found higher ALFF values in the left angular gyrus, which may reflect a compensation for visual fusion dysfunction in patients with strabismus. The higher ALFF values indicated the compensatory function of the region. Furthermore, we found a negative correlation between the mean ALFF value of the left angular gyrus and strabismus duration. That is to say, the shorter the duration of strabismus, the higher the ALFF values in the left angular gyrus. We therefore concluded that the compensation of function in the left angular gyrus may relate to the duration of strabismus.

Conclusion

In summary, our results showed that strabismus was characterized by abnormal spontaneous activities in various brain regions. These findings provided important information that clarifies the underlying neural mechanisms of strabismus. The correlation analyses suggested that changes in these areas could be related to the incidence of depression in the strabismus group.

Prospects and problems

The rapid development of fMRI technology has facilitated its wide use in many fields of neurologic diseases, including strabismus. ALFF is a useful measurement because it can accurately reflect whole-brain activity. Future research should be performed to clarify the brain regions involved in strabismus and possibly develop new treatments. The present study also had several limitations. Firstly, the sample size was small; future research should expand the size for more accurate results. Second, the clinical characteristics were not strict; we included both exo- and esotropic patients. Future research should distinguish between different types of strabismus to more accurately assess brain function activity changes. It would also be important to streamline the scanning protocol. For some subjects, the scan time was too long, and body movement can affect ALFF findings. Despite these shortcomings, the present study of congenital comitant strabismus revealed that dysfunction in specific brain areas underlies the pathogenesis of congenital comitant strabismus.

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Disclosure

The authors report no conflicts of interest in this work.

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