

Original Article

Alternations of interhemispheric functional connectivity in patients with comitant exotropia: a resting state fMRI study

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Abstract: Objective: Previous neuroimaging studies demonstrated that comitant exotropia (CE) showed significant brain functional and anatomical changes, whereas alterations of interhemispheric functional connectivity (FC) in CE patients at rest are not well studied. This study investigated the interhemispheric FC of the whole brain in CE patients using voxel-mirrored homotopic connectivity (VMHC) and their relationship with clinical features. Methods: Thirty-two comitant strabismus patients (25 males and 7 females) were enrolled in the study and 32 (25 males and 7 females) education- and age-matched healthy controls (HCs) were evaluated by functional magnetic resonance imaging (fMRI) examinations. The VMHC method was used to evaluate directly the functional interactions between the hemispheres. The receiver operating characteristic curve (ROC) analyses had been used to identify the VMHC in these brain areas, which could be used as biomarkers to distinguish CEs and from HC. The relationship between the mean VMHC signal values in many brain regions and clinical features in these patients was evaluated by Pearson correlation analysis. Results: Compared with HCs, CE patients showed significantly lower VMHC values in the bilateral precentral gyrus, inferior parietal lobule and superior parietal lobule. Higher VMHC values occurred in the bilateral superior temporal gyrus, medial frontal gyrus in CE patients. However, there was no relationship between the mean VMHC signal values of the different areas and clinical manifestations in CE patients. Conclusion: CE patients have abnormal interhemispheric functional connectivity in many regions, which may indicate the dysfunction of eye movements and visual fusion function in the CE patients.

Keywords: Comitant exotropia, voxel-mirrored homotopic connectivity, resting state, functional magnetic resonance imaging

Introduction

Strabismus is a common eye disease characterized by abnormal eye position and motion. According to a study conducted in Eastern China, the prevalence of strabismus in pre-school children was 5.65% [1]. The incidence of the strabismus was associated with a variety of factors, such as heredity [2], genetics [3], and refractive errors [4]. Strabismus was divided into comitant strabismus and incomitant strabismus [5]. Strabismus is a disorder of eye movement that impairs stereo vision [6]. At present, surgery is the main treatment for strabismus [7].

Resting-state fMRI (rs-fMRI) is a useful functional brain-imaging technique that reveals brain activity and has been used to study strabismus. Chen et al. [8] demonstrated that strabismus patients showed suppression of the primary visual cortex [8]. A previous study of comitant exotropia patients showed impaired dorsal visual pathways [9]. Other studies reported that the infantile exotropia was associated with a higher BOLD (blood oxygen level-dependent fMRI) signal in the left cingulate gyrus, bilateral precuneus, and left angular gyrus using fMRI [10]. In our previous study, the comitant strabismus showed higher regional homogeneity (ReHo) values in vision-related brain

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Table 1. Demographics and clinical measurements by two groups

Condition	CE	HC	t	P-value*
Male/female	25/7	25/7	N/A	> 0.99
Age (years)	22.91 ± 2.70	23.00 ± 2.77	-0.137	0.891
Weight (kg)	57.56 ± 5.93	57.65 ± 5.57	-0.064	0.949
Handedness	32R	32R	N/A	> 0.99
Duration of CE (years)	22.25 ± 2.51	N/A	N/A	N/A
Best-corrected VA-right eye	1.20 ± 0.17	1.20 ± 0.17	0.076	0.940
Best-corrected VA-left eye	1.21 ± 0.17	1.21 ± 0.13	0.241	0.810

Note: *P < 0.05 Independent t-tests comparing two groups. Abbreviations: CE, comitant exotropia; HC, healthy control; N/A, not applicable; VA, visual acuity.

regions [11]. Prior investigations have shown cortical dysfunction in strabismus. However, little is known about the interhemispheric functional synchronization changes in CEs.

Resting-state fMRI (rs-fMRI) can be used to assess the patterns of coherent spontaneous fluctuations of blood oxygen level dependent (BOLD) signals during rest. The BOLD signals can be used to measure the inter-hemispheric coordination [12]. Functional homotopy, the high degree of correlated activity between homotopic interhemispheric counterparts, is one of the most salient aspects of the brain's intrinsic functional architecture [13]. Previous studies have shown that interhemispheric synchrony is closely related to the visual experience [14, 15]. In addition, the homotopic resting-state function connectivity (RSFC) has been shown to be available in the auditory, sensorimotor systems [16]. Voxel-mirrored homotopic connectivity (VMHC) was used to quantify the interhemispheric functional connectivity (FC) between the time series for a given voxel and its mirrored counterpart in the opposite hemisphere [17]. The VMHC method has been successfully applied in many diseases such as primary open-angle glaucoma [18], postherpetic neuralgia [19], irritable bowel syndrome [20] and schizophrenia [21]. Liang et al. [22] reported that anisometropic and strabismic amblyopia patients had altered VMHC in the lingual gyrus and fusiform gyrus. These findings suggested that specific patterns of inter-hemispheric disconnection could reflect the functional consequences of pathologic damages in the abovementioned diseases. However, the interhemispheric functional connectivity changes in comitant exotropia (CE) patients remains unknown. Here, our study was the first to assess the alternations of the interhemispheric functional connectivity in CE patients

using the VMHC method. We hypothesized that an impairment of inter-hemispheric functional coordination might be involved in the neural mechanism of CE, which would reflect impaired homotopic RSFC in CE patients.

Materials and methods

Subjects

In total, 32 CE patients (25 male and 7 female) were enrolled as subjects in the study. All subjects were recruited at the Ophthalmology Department of the First Affiliated Hospital of Nanchang University in Jiangxi province of China. The criteria of comitant exotropia subjects in the study were ; strabismus with stereopsis defects; and visual acuity (VA) > 1.0. The exclusion criteria were acquired or incomitant strabismus; other eye diseases, trauma, or eye surgery; psychiatric disorders (e.g., depressive disorder or delusional disorder); diabetes; cardiovascular disease; or cerebral disease.

Thirty-two healthy controls (HCs; 25 male and 7 female) with similar age range, sex ratio, and educational status were enrolled in the study. All HCs met the following requirements: 1) normal brain parenchyma on cranial MRI; 2) no ocular disease with visual acuity (VA) > 1.0; 3) no psychiatric disease (depressive disorder, delusional disorder); and 4) no contraindications for MRI scanning (e.g. no cardiac pacemaker or implanted metal devices).

This research was approved by the committee on medical ethics of the Ophthalmology Department of the First Affiliated Hospital of Nanchang University, in accordance with the Declaration of Helsinki. All of the participants were informed the content of the study and signed informed consent.

MRI data acquisition

Imaging was performed by a 3T MRI system (Siemens, Munich, Germany). The MRI scanning parameters were: repetition time (TR) = 2,000 ms, echo time (TE) = 40 ms, flip angle = 90°, slice thickness/gap = 4.0/1 mm, field of view (FOV) = 240 mm × 240 mm, in-plane resolution = 64 × 64, 30 axial slices and 240 volumes acquired in 8 min [23].

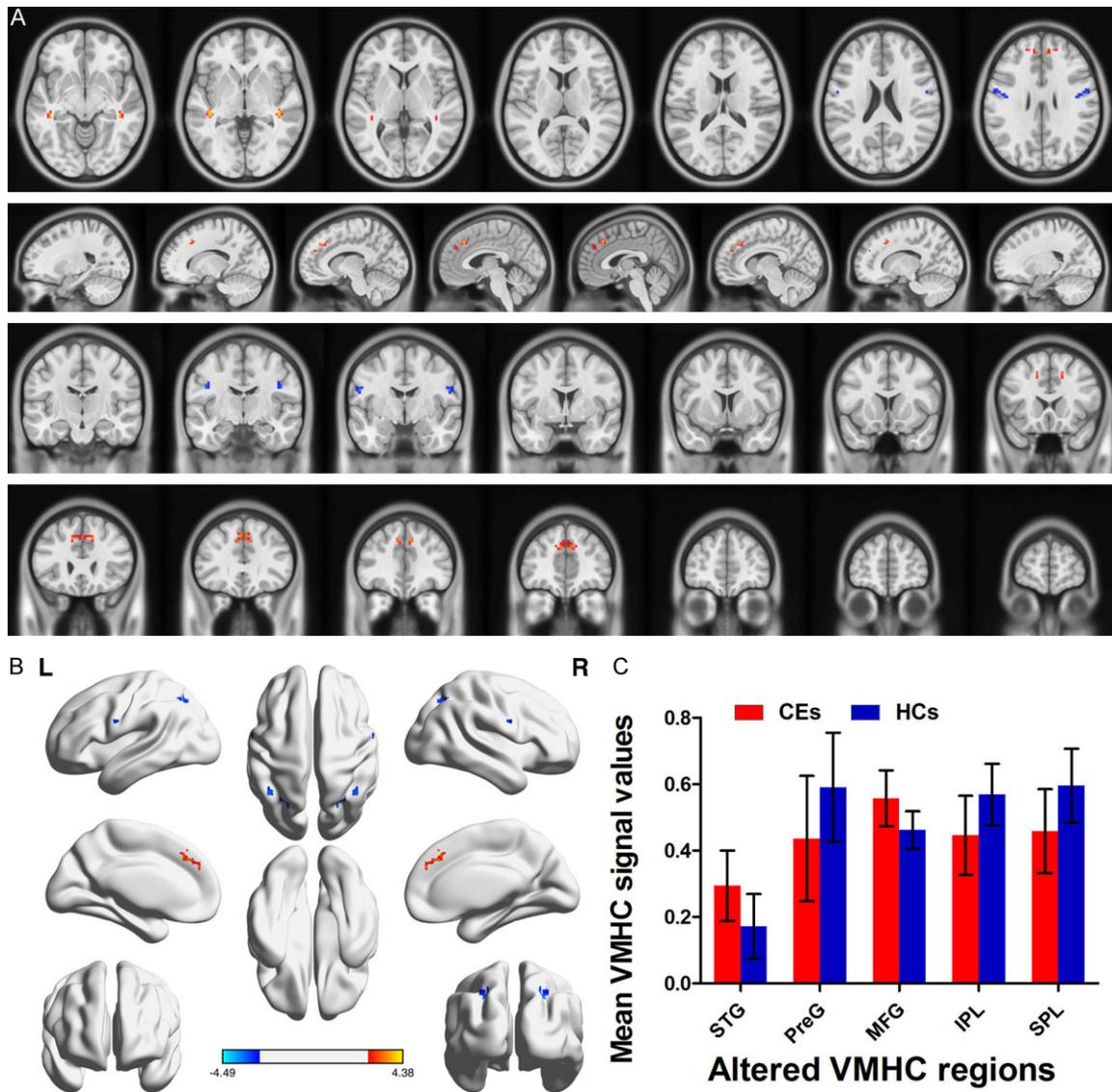


Figure 1. Group comparison of interhemispheric functional connectivity between CE patients and HCs. Significant FC differences were observed in the bilateral precentral gyrus, inferior parietal lobule, superior parietal lobule, bilateral superior temporal gyrus and medial frontal gyrus. The red or yellow denotes higher VMHC values, and the blue areas indicate lower VMHC values, respectively. $p < 0.01$ for multiple comparisons using Gaussian Random Field (GRF) theory ($z > 2.3$, $p < 0.01$, cluster > 20 voxels, FDR corrected). (A) and (B) The mean values of altered ReHo values were shown with a histogram between two groups (C). Abbreviations: VMHC, voxel-mirrored homotopic connectivity; BA, Brodmann area; CE, comitant exotropia; HCs, healthy controls; STG, superior temporal gyrus; PreG, precentral gyrus; MFG, medial frontal gyrus; IPL, inferior parietal lobule; SPL, superior parietal lobule.

fMRI data preprocessing

In order to exclude defective data, MRIcro software was used to check Functional data (www.MRIcro.com). Data Processing Assistant was utilized to analyze the rs-fMRI data for Resting-State fMRI Advanced Edition (DPARSFA; <http://rfmri.org/DPARSFA>) with MATLAB2010a (Mathworks, Natick, MA, USA). The following steps

were performed: 1) The first ten volumes of each subject were discarded due to the signal reaching equilibrium and the participants adapting to the scanning noise. 2) After the head motion correction, the Motion time courses were obtained by estimating the values for translation (mm) and rotation (degrees) for each subject. Participants who had more than 1.5 mm maximum displacement in x, y, or z and

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

Brain areas	BA	MNI			Cluster size	t-values
		x	y	z		
CEs > HCs						
Superior Temporal Gyrus	13	± 42	-30	-3	27	4.383
Medial Frontal Gyrus	6,9	± 3	30	42	51	4.307
CEs < HCs						
Precentral Gyrus	6	± 54	-3	24	21	-3.458
Inferior Parietal Lobule	40	± 42	-57	42	26	-4.492
Superior Parietal Lobule	7	± 27	-63	42	30	-3.669

Notes: The statistical threshold was set at the voxel level with $P < 0.05$ for multiple comparisons using Gaussian Random Field (GRF) theory ($z > 2.3$, $P < 0.01$, cluster > 20 voxels, FDR corrected). Abbreviations: VMHC, voxel-mirrored homotopic connectivity; BA, Brodmann area; CE, comitant exotropia; HCs, healthy controls; MNI, Montreal Neurological Institute.

1.5° of angular motion during the entire fMRI scan would be rejected. 3) The nuisance covariate effects of non-neuronal BOLD fluctuations including white matter signal and CSF signal were also removed by a linear regression process. 4) A temporal filter (0.01-0.08 Hz) was applied to reduce the effect of low-frequency drift and high-frequency noise. Subsequently, the fMRI images were spatially normalized to the Montreal Neurological Institute space criteria using the standard echo-planar imaging template and resampling the images at a resolution of 3 mm × 3 mm × 3 mm to compute the VMHC.

VMHC statistical analysis

The VMHC mapping was converted to z-value by the Fisher z-transformation, and the REST software (<http://resting-fmri.sourceforge.net>) was applied to improve normality. Global VMHC was used as covariate to separate z-image input random effects by voxel-wise two sample's t test to identify VMHC differences between two groups (false discovery rate (FDR) correction, $P < 0.05$ and cluster > 20 , as shown in a previous study [17]).

Brain-behavior correlation analysis

Brain areas with different VMHC findings between the two groups were classified as regions of interest (ROIs) with the REST software. The relationship between the mean VMHC values in different brain regions in the CEs group and behavioral performances were

calculated with correlation analysis ($P < 0.05$ denotes a significant difference).

Statistical analysis

SPSS 16.0 (SPSS Inc, Chicago, IL, USA) was used to process the data. The duration of CE and other cumulative clinical measurements were evaluated using independent sample t tests ($P < 0.05$ was considered statistically significant).

The differences in the z-maps between the CE groups and the healthy controls were analyzed by Two-sample t-tests, using Gaussian Random Field (GRF) theory with $P < 0.01$ for multiple comparisons ($z > 2.3$, $P < 0.01$, cluster > 20 voxels, FDR corrected).

The average differences of VMHC values between the two groups in different brain regions were analyzed by ROC curve method. Pearson correlation analysis was used to evaluate the relationship between the average VMHC values in the many brain regions and clinical manifestations ($P < 0.05$ was considered statistically significant).

Results

Demographics and visual measurements

There were no marked differences in weight ($P = 0.949$), age ($P = 0.841$), best-corrected VA-Right ($P = 0.940$), and best-corrected VA-Left ($P = 0.810$) between the two groups (Table 1).

VMHC differences

Compared with HCs, CEs had significantly lower VMHC values in the bilateral precentral gyrus, inferior parietal lobule and superior parietal lobule (Figure 1A, 1B [blue] and Table 2). In contrast, higher VMHC values were found in the bilateral superior temporal gyrus and medial frontal gyrus. (Figure 1A, 1B [red] and Table 2). The mean values of altered VMHC between the two groups are shown in (Figure 1C). ($z > 2.3$, $P < 0.01$, cluster > 20 voxels, FDR corrected). In the CEs group, there was no significant correlation between the mean VMHC values in differ-

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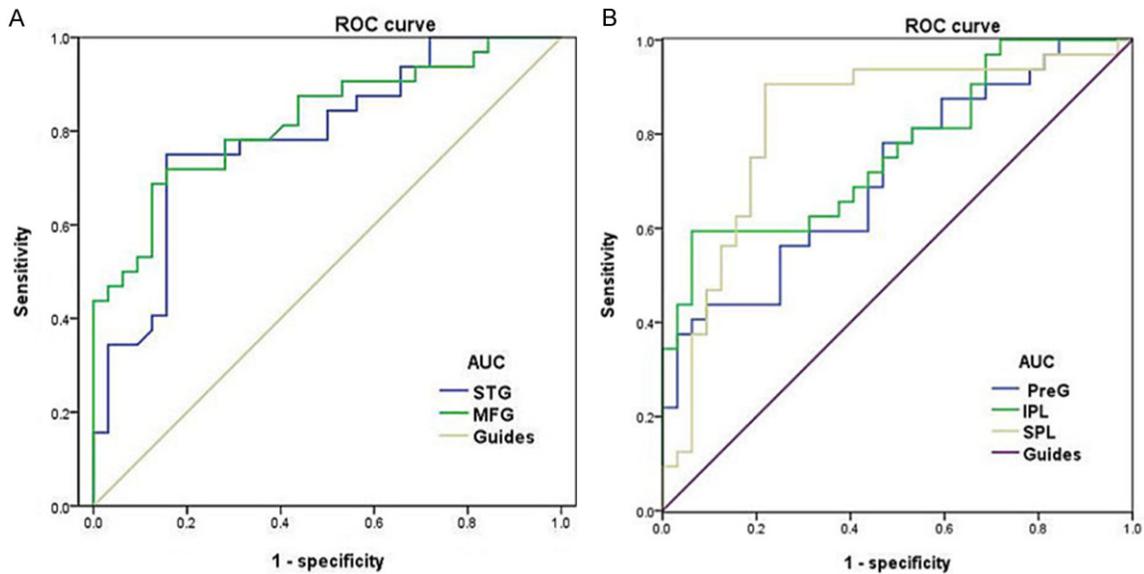


Figure 2. ROC curve analysis of the mean VMHC values for altered brain regions. Notes: The areas under the ROC curve were 0.789 ($p < 0.001$; 95% CI: 0.676-0.901) for the STG; 0.823 ($p < 0.001$; 95% CI: 0.720-0.925) for the MFG; (CEs > HCs) (A). The areas under the ROC curve were: 0.731 ($p = 0.003$; 95% CI: 0.588-0.838) for the PreG; 0.766 ($p < 0.001$; 95% CI: 0.650-0.882) for the IPL; 0.827 ($p < 0.001$; 95% CI: 0.718-0.937) for the SPL. (CEs < HCs) (B). Abbreviations: ROC, receiver operating characteristic; VMHC, voxel-mirrored homotopic connectivity; CI, confidence interval; CE, comitant exotropia; HCs, healthy controls; STG, superior temporal gyrus; PreG, precentral gyrus; MFG, medial frontal gyrus; IPL, inferior parietal lobule; SPL, superior parietal lobule.

ent brain regions and the clinical manifestations ($P > 0.05$).

Receiver operating characteristic curve

We hypothesized that the VMHC differences between the CE and HC groups might be useful diagnostic markers. The mean VMHC values in the different brain regions were analyzed by the receiver operating characteristic (ROC) curve method. The areas under the ROC curve (AUCs) for VMHC values with CEs > HCs were: the superior temporal gyrus (0.789) and medial frontal gyrus (0.823) (**Figure 2A**). The areas under the ROC curves with CEs < HCs were: the precentral gyrus (0.731); inferior parietal lobule (0.766); and superior parietal lobule (0.827) (**Figure 2B**).

Discussion

The VMHC method is a reliable and non-invasive rs-fMRI that can reveal interhemispheric functional connectivity. The present study is, to the best of our knowledge, the first to assess interhemispheric functional connectivity changes in CE patients. Compared with the HC, the CE subjects had decreased VMHC values bilat-

erally in the precentral gyri, inferior parietal lobules, and superior parietal lobules. In contrast, the CE subjects had increased VMHC values bilaterally in the superior temporal gyrus and medial frontal gyrus.

Analysis of the decreased VMHC values in the CEs

The precentral gyrus (PreG), the locus of the primary motor cortex, is located in the posterior frontal lobe. The PreG is involved in the encoding of sequential movement [24] and coordinated movement [25]. In addition, the PreG plays a critical role in oculomotor and somatomotor special coding [26]. Meanwhile, previous studies demonstrated that strabismus individuals were associated with the impaired motor behaviour function [27, 28]. Previous studies found that the frontal eye field (FEF) was located in the precentral sulcus [29], which was related to saccade initiation and control [30, 31]. Strabismic adults had greater gray matter volume in the frontal eye field (FEF) compared with healthy controls [32]. Given these findings, we demonstrated that CE subjects had decreased VMHC values bilaterally in the precentral gyri, which reflected impaired inter-

hemispheric FC in these structures. We speculated that CE individuals were associated with impaired eye motor and motor behaviour function. The abnormal interhemispheric FC of the precentral gyrus in CE might be used to as a clinical maker to assess the motor function. The inferior parietal lobule (IPL) is a part of the parietal lobule that plays an important role in spatial selectivity, visual word recognition [33], and language learning [34]. The IPL is involved in selection of saccade targets [35]. Furthermore, comitant exotropia patients show decreased white matter volumes in the left inferior parietal lobule [9]. In our study, we also found that CE patients showed the decreased VMHC values in the bilateral IPL, which indicated the dysfunction of the interhemispheric FC in the IPL. Therefore, our results suggested that CE might lead to impairment of spatial encoding. Superior parietal lobules (SPL), known as BA 7, play an critical role in visuospatial attention [36] and spatial selection [37] in the SPL connect language and motor areas [34]. The SPL performs stereopsis-processing [38, 39]. The exotropia patients were associated with the dysfunction of stereopsis [40]. Li et al. [41] demonstrated that intermittent exotropia involved increased activation in the bilateral SPL, and exotropia patients have impaired stereopsis [42]. In our study, CE patients showed decreased VMHC values in the bilateral SPL, which reflected dysfunction of interhemispheric FC in the IPL. Thus, we speculated that the abnormal interhemispheric FC in the IPL indicated the impaired stereopsis function in CE.

Analysis of the increased VMHC values in the CEs

The medial frontal gyri, including the frontal eye fields (FEF), plays a critical role in the control of the eye movement [43]. A previous study demonstrated that the FEF was involved in the visuomotor aspects of anti-saccade encoding [44]. The FEF was responsible for the selection and maintenance of saccade goals and FEF lesions can lead to eye movement disorders [45]. Previously, we found that congenital comitant strabismus showed significantly lower amplitude of low-frequency fluctuations in the bilateral medial-frontal gyrus [46]. Chan et al. found that strabismic adults had greater gray matter volume in the FEF [32]. Consistent with this finding, we found that CE subjects had

increased VMHC values in the medial frontal gyrus, which reflected increased interhemispheric FC. The increased interhemispheric FC in MFG might reflect the function of compensatory in impaired eye movement.

Conclusion

In summary, we demonstrate abnormal interhemispheric FC exists in many brain regions involving in eye movement control and visual fusion regions, which might provide some useful insights to explain the neural mechanisms of comitant exotropia patients. The VMHC results can be used to as biomarkers for the impairment of the interhemispheric connectivity in CEs.

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Disclosure of conflict of interest

None.

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