Reduction in interhemispheric functional connectivity in the dorsal visual pathway in unilateral acute open globe injury patients: a resting-state fMRI study

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Abstract

This study investigated the changes in interhemispheric functional connectivity (FC) of the whole brain in open globe injury (OGI) patients, using voxel-mirrored homotopic connectivity (VMHC), and their relationships with clinical features. Totally, 16 male and 2 female acute OGI patients and 18 sex, age, and education-matched healthy volunteers were enrolled in the study. All subjects were scanned through functional magnetic resonance imaging (fMRI). Receiver operating characteristic (ROC) curves analyses had been used to identify the VMHC in these brain areas could be used as biomarkers to distinguish OGI and from healthy control (HC). The mean VMHC values in multiple brain areas and clinical OGI manifestations were evaluated with a Pearson correlation analysis. OGI patients had significantly decreased VMHC in the bilateral calcarine/lingual/cuneus (BA18, 19, 30) and middle occipital gyrus (BA18, 19). The OGI patients had abnormal interhemispheric FC in the dorsal visual pathway, which may represent the pathophysiological mechanism that underlies acute vision loss after OGI.

KEYWORDS: unilateral acute open globe injury; voxel-mirrored homotopic connectivity; resting state; functional magnetic resonance imaging

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INTRODUCTION

Ocular trauma is responsible for a large proportion of vision loss, with a prevalence in the adult population in Beijing of 1.6%±0.2% according to one survey[1]. Ocular trauma caused open globe injury (OGI) is an important cause of the blindness[2]. These OGIs can lead to corneal rupture[3] or scleral rupture[4]. At present, surgery is the definitive treatment for OGI[5]. However, OGI can still result in various serious complications including retinal detachment[6], glaucoma[7], and endophthalmitis[8]. The successful application of functional magnetic resonance imaging (fMRI) in OGI patients to assess the neurophysiological changes has been reported previously. In our own study, acute OGI patients were found to present with abnormal amplitudes of the low-frequency fluctuation (ALFF) in the precuneus, left cuneus, and left middle cingulate cortex[9]. Moreover, the OGI patients were also characterize by altered regional homogeneity in many brain regions[10]. However, it remains to be investigated if these patients also have alterations of interhemispheric functional synchronization. However, it is known that visual experience is closely related to interhemispheric synchrony[11-12]. The resting state-fMRI technology termed voxel-mirrored homotopic connectivity (VMHC) was used to quantify the functional connectivity (FC) of the time series of mirrored pairs of corresponding voxels in opposite hemispheres[13]. Its main advantage lies in its ability to reflect interhemispheric disconnection,
Here, we assessed alternations of interhemispheric FC in OGI patients using the VMHC method.

**METHODS**

This research was conducted in accordance with the Declaration of Helsinki, with approval by the medical ethics committee of the Department of Ophthalmology, the First Affiliated Hospital of Nanchang University, and all participants signed informed consent forms. A total of 16 male and 2 female patients with acute OGI from the Department of Ophthalmology, the First Affiliated Hospital of Nanchang University in Jiangxi Province, China, were enrolled in this study. Patients were selected for unilateral acute OGI, with inclusion criteria as follows: 1) proven history of severe ocular trauma; 2) acute loss of vision following the trauma; 3) incomplete eyeball wall as shown by orbital computed tomography (CT) or MRI; 4) corneal or scleral rupture; 5) a value from 1.0 to 1.5 for best-corrected visual acuity (BCVA) in the contralateral eye. The exclusion criteria were eye disease (cataract, corneal ulcer, glaucoma, or optic nerve disease) affecting vision before the ocular trauma; other diseases, trauma or surgery of the eyes; psychiatric disorders (depressive disorder or delusions), cerebral disease (cerebral hemorrhage, vascular malformation or infarction), cardiovascular disease, or diabetes. The final cohort encompassed 16 male and 2 female healthy volunteers, matched for sex, age, and educational status. The requirements for healthy controls (HCs) were: normal brain parenchyma as shown by cranial MRI; no ocular or psychiatric disease as defined above; visual acuity (VA) from 1.0 to 1.5; and no contraindications for MRI (implanted metal devices, e.g. cardiac pacemaker).

A 3T MRI system (Siemens, Munich, Germany) was used for imaging, as described previously, and functional data were analyzed according to a published protocol. A study-specific symmetric Montreal Neurological Institute (MNI) template was used to register reprocessed images of each subject, which were used to calculate the VMHC. Fisher’s z-transformation in REST software (http://resting-fmri.sourceforge.net) was used to convert the individual VMHC maps to z values to improve the normality. A voxel-based random-effects two-sample t-test [false discovery rate (FDR) corrected, \(P<0.05\) and cluster \(>20\) voxels] was conducted using the individual z-maps in conjunction with the global VMHC as covariate to identify the differences of VMHC in the two groups. A detailed description is available in a previous paper.

Finally, independent-sample \(t\)-tests used to evaluate the onset, duration of OGI and other cumulative clinical measurements using SPSS version 16.0 (IBM Corp., USA). Differences with \(P<0.05\) were considered statistically significant. The differences in the z-maps between the OGI groups and the HCs were examined using two-sample \(t\)-tests using Gaussian Random Field (GRF) theory (cluster \(>20\) voxels, FDR corrected, \(z>2.3, P<0.01\)). The mean differences of VMHC values between pairs of groups in corresponding brain regions were analyzed using receiver operating characteristic (ROC) curves, and Pearson correlation analysis was used to analyze the relationships between the mean VMHC values. Differences with \(P<0.05\) were considered statistically significant.

**RESULTS AND DISCUSSION**

**Demographic Characteristics and Visual Acuity** There were no statistically significant differences between the study and control groups in age and weight (\(P=0.856\) and 0.908, respectively; Table 1). However, there were significantly lower VMHC values in the OGIIs of bilateral lingual/calcarine/cunei (BA18, 19, 30) and the cunei/middle occipital gyri [BA19; Figure 1A and 1B (blue); Table 2]. The mean values of the changed VMHC between the two groups are shown in Figure 1C (cluster \(>20\) voxels, FDR corrected; \(z>2.3, P<0.01\)). There was no significant correlation between the clinical manifestations and the mean VMHC values in the OGI group (\(P=0.05\)). We hypothesized that differences in the VMHC of different brain regions between the OGI and HC groups have diagnostic potential as markers. To test this, we used receiver
operating characteristic (ROC) curves to analyze the mean VMHC values of different brain regions. The VMHC values had areas under the ROC curve (AUC) of 0.861 for calcarine/lingual/cuneus and 0.870 for cuneus/middle occipital gyri (OGIs<HCs; Figure 2).

The VMHC method utilizes reliable and non-invasive resting state-fMRI to reveal interhemispheric FC. Compared with the HC, the OGI patients in our study had significantly lower VMHC values in the bilateral calcarine/lingual/cunei (BA18, 19, 30) and middle occipital gyri (BA18, 19), which are important parts of the dorsal visual pathways. The cuneus is a crucial part for visual processing in the occipital lobe. The anteromedial cuneus interacts with the primary visual cortex (V1) to encode visual information for the extrastriate cortex[17]. The cuneus is the part of the visual pathway involved in spatial location[18]. In patients with late

Figure 1 Group comparison of interhemispheric FC between OGI patients and HCs There were significant differences of FC in the bilateral calcarine/lingual/cunei (BA18, 19, 30) and cuneus/middle occipital gyri (BA19). Lower VMHC values are shown in blue. P<0.01; multiple comparisons via Gaussian Random Field (GRF) theory (cluster >20 voxels, FDR corrected; z>2.3, P<0.01; A and B, C: The mean values of the altered regional homogeneity were shown with a histogram between two groups. FC: functional connectivity; OGI: Open globe injury; HCs: Healthy controls; BA: Brodmann area; VMHC: Voxel-mirrored homotopic connectivity; FDR: False discovery rate.

Table 2 Brain areas with significant differences of VMHC between the patients and the control group

<table>
<thead>
<tr>
<th>Brain areas</th>
<th>BA</th>
<th>MNI</th>
<th>Cluster size</th>
<th>t</th>
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</thead>
<tbody>
<tr>
<td>OGI&lt;HCs</td>
<td></td>
<td></td>
<td></td>
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</tr>
<tr>
<td>Calcarine/Lingual/ Cuneus</td>
<td>18, 19, 30</td>
<td>±51</td>
<td>-57</td>
<td>-21</td>
</tr>
<tr>
<td>Cuneus/ Middle Occipital Gyrus</td>
<td>19</td>
<td>±18</td>
<td>-99</td>
<td>12</td>
</tr>
</tbody>
</table>

The voxel-level statistical threshold for multiple comparisons using Gaussian random field (GRF) theory was P<0.05 (cluster >20 voxels, FDR corrected; z>2.3, P<0.01). OGI: Open globe injury; HCs: Healthy controls; VMHC: Voxel-mirrored homotopic connectivity; BA: Brodmann area; MNI: Montreal Neurological Institute.
This provides new knowledge on the physiological mechanisms underlying sharp loss of visual acuity in unilateral acute OGI patients.

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VMHC study in unilateral acute OGI patients


