Original Article

An fMRI study of altered spontaneous brain activity patterns in patients after ophthalmectomy procedures using regional homogeneity

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Abstract: Objective: The aim of the current study was to use regional homogeneity (ReHo) to explore local features of spontaneous brain activity in patients after ophthalmectomy procedures, examining their relationship with emotional and psychosocial problems. Methods: Eighteen (6 women and 12 men) patients undergoing ophthalmectomy procedures and 18 (6 women and 12 men) age, sex, and education-matched healthy controls (HCs) underwent MRI scans. Local features of spontaneous brain activity were assessed using the ReHo method. Relationships between observed mean ReHo signal values of the different areas and the Chinese version of Hospital Anxiety and Depression Scale (HADS) scores were calculated via correlation analysis. Receiver operating characteristic curve analysis was performed, evaluating mean ReHo values in different brain regions, aiming to verify whether ReHo values can distinguish patients from HCs. Results: Compared with healthy subjects, patients undergoing ophthalmectomy procedures had significantly reduced ReHo values in the left inferior occipital gyrus/middle occipital gyrus, left limbic lobe/anterior cingulate, right limbic lobe/anterior cingulate, and right lateral occipital cortex. ReHo signal values of the right lateral occipital cortex showed a negative correlation with HADS-depression scores (r = -0.4806, p = 0.0435) and a positive correlation with duration of the ophthalmectomy procedure (r = 0.4958, p = 0.0364). Receiver operating characteristic curve analysis showed that ReHo might be a valuable biomarker in differentiating ophthalmectomy patients from HCs. Conclusion: Patients undergoing ophthalmectomy procedures showed dysfunction in many brain regions. These may reflect the underlying pathologic mechanisms of ophthalmectomy procedures. Thus, they are beneficial for clinical treatment.

Keywords: Regional homogeneity, ophthalmectomy, resting state, spontaneous activity, depression

Introduction

An ophthalmectomy (enucleation and evisceration of the orbit) is a surgical procedure in which the partial or total loss of function of the eyeball is removed. This procedure is a kind of destructive disfiguring surgery, causing serious psychological burden and mental pressure for patients. Patients often show severe anxiety, depression, and fear after surgery [1]. Therefore, postoperative patients should be given necessary psychological support, promoting rehabilitation.

Ocular trauma is the main cause of monocular blindness. This can result in serious damage to the structure and function of the eyeball, leading to loss of vision or ophthalmectomies [2]. Common ocular trauma includes eyeball rupture injuries, prolapse of the intraocular contents, traumatic cornea-scleral staphyloma, traumatic eyeball atrophy, and traumatic endophthalmitis. There are many factors that cause eye injuries, such as direct contact with sharp/hot objects, chemicals, and different types of radiation (ultraviolet rays, x-rays, or microwaves). Eye injuries are responsible for a large fraction of disabling ocular morbidities in children [3, 4]. The public health importance of such eye injuries is significant [5]. Worldwide, approximately 1.6 million people are totally blind as a result of ocular trauma, 2.3 million
have bilateral low vision, and 19 million have unilateral visual loss (defined as visual acuity in that eye of less than 6/60) [6]. Eye trauma appears to have a bimodal distribution with age, with peak incidence rates occurring in people aged 15 to 29 years and those over 70 years [4]. Peak incidence rates appear to coincide with the age of maximal youthful activity and the age of debility, respectively.

There are few studies concerning brain activity in patients after ophthalmectomy procedures. Few studies have utilized functional magnetic resonance imaging (fMRI) to assess brain activity. Previous studies of patients with acute impairment of vision using objective examination methods employed electroretinograms (ERGs), orbital CT scans, and visual evoked potentials. However, these techniques have limitations. Thus, in most cases, these methods were not the sole basis for making a diagnosis. As a result, there is a need for comprehensive analysis of patients, including symptoms, signs, laboratory studies, and auxiliary examinations. Magnetic resonance imaging (MRI) allows for a noninvasive, longitudinal, and multiparametric assessment of the visual system without depth restrictions.

Resting-state fMRI (rs-fMRI) is a functional brain imaging technique. It was developed recently, for clinical neuroimaging. During the resting state, correlated spontaneous fluctuations occur within spatially distinct and functionally related groups of cortical and subcortical brain regions, representing the intrinsic functional networks of the central nervous system [7]. Altered features detected during the resting state can serve as markers of the pathogenesis of various conditions, such as primary insomnia [8], obstructive sleep apnea [9, 10], and sleep deprivation [11]. Moreover, rs-fMRI can be used to evaluate spontaneous brain activity that occurs when a subject is at rest, not performing any appointed tasks [12]. Regional homogeneity (ReHo) has been used to calculate the Kendall harmonious coefficient, measuring each voxel at a given point and its surrounding voxel point time series similarity [13]. Compared with other methods, this technique does not need to delimit the specific area of seeds. It can analyze the function of the whole brain [14]. The ReHo method has been successfully used to investigate the mechanisms of various diseases, including epilepsy [15], primary insomnia [16], Parkinson’s disease [17], and depression [18]. However, it has not yet been used to explore pathophysiological changes after ophthalmectomy procedures. The current study is the first to evaluate changes of spontaneous brain activity after ophthalmectomy procedures, examining its relationship with clinical features.

Materials and methods

Subjects

A total of 18 patients undergoing ophthalmectomy procedures (six women and 12 men) were recruited from the First Affiliated Hospital of South China University and the Ophthalmology Department of the First Affiliated Hospital of Nanchang University Hospital. Diagnostic criteria: 1) History of eye disease, monocular vision loss to light, or no light perception not ruling out congenital eye lesions; 2) Compliance with the indications of eyeball enucleation patients; and 3) Elimination of other anophthalmos.

Eighteen healthy controls (HCs) (six women and 12 men), closely matched in age, sex, and demographic parameters to the post-operative enucleation group, were also recruited for this study. All HCs met the following criteria: 1) No abnormalities in the brain parenchyma found on MRIs; 2) No ocular disease, severe eye injuries, or corrected visual acuity (VA) > 1.0; 3) Normal mental health and no abnormalities during neural system examinations; and 4) No contraindications for undergoing magnetic resonance imaging (such as having a cardiac pacemaker or other implanted metallic devices). The current study was authorized by the Ethics Committee. All research methods complied with the provisions of the Declaration of Helsinki and conformed to the principles of medical ethics. All volunteers participated voluntarily and were informed of the purpose, methods, and potential risks inherent in the study protocol. All participants signed an informed consent form.

MRI parameters

All subjects were scanned with a 3-Tesla magnetic resonance scanner (Trio, Siemens, Munich, Germany). They were instructed to keep their eyes closed, but to remain awake and relaxed until the end of the scan. Using a three-dimensional spoiled gradient-recalled echo
sequence in the MRI, relevant data was then obtained. Imaging parameters of the T1 and T2 sequences for 176 traverse images were as follows: TR = 1900 ms, TE = 2.26 ms, thickness = 1.0 mm, gap = 0.5 mm, acquisition matrix = 256 × 56, field of view = 250 × 250 mm, and flip angle = 9°. Imaging parameters for 240 functional images were as follows: TR = 2000 ms, TE = 30 ms, thickness = 4.0 mm, gap = 1.2 mm, acquisition matrix = 64 × 64, flip angle = 90°, field of view = 220 × 220 mm, and 29 axial. Scanning times were 5 minutes and 10 minutes, respectively.

fMRI data processing

From September 2017 to March 2018, MRI data of eligible patients was collected during hospitalization. MRIcro software was used to classify and filter the acquired brain data. It was necessary to balance the scanning signal. Thus, the first 15 scanned images were deleted. Data Processing Assistant for Resting-State fMRI (DPARSFA 4.0, http://rfmri.org/DPARSF) software and Statistical Parametric Mapping software (SPM, http://www.fil.ion.ucl.ac.uk/spm) were used for data preprocessing. The main steps of preprocessing included slice timing, head motion correction, using Friston six-head motion parameters to regress out head motion effects, spatial normalization with standard echo planar image templates to achieve Neurology Montreal Institute (MNI) standards, and smoothening with a Gaussian kernel of 6 × 6 × 6 mm³ full-width at half-maximum (FWHM). REST software (State Key Laboratory of Cognitive Neuroscience and Learning, Beijing Normal University, Beijing, China) was used to calculate ReHo. The basic method of evaluation was to analyze Kendall consistency coefficients (KCC) of a given voxel and the adjacent voxel time series.

Clinical data analysis

From September 2017 to March 2018, eligible clinical data was collected during hospitalization. Hospital Anxiety and Depression Scale (HADS) scores were designed to screen for clinically significant anxiety and depression in patients [19]. HADS includes questions for identification of anxiety (7 items) and depressive (7 items) symptoms. It has demonstrated good reliability and has been widely used in the evaluation of patient mental states in many diseases [20, 21]. HADS gives maximum scores of 21 for anxiety and depression. All ophthalmectomy patient HADS scores were counted.

Statistical analysis

For demographic and clinical measurements, differences in clinical features between patients and normal controls were examined using independent sample t-tests via SPSS 20.0 software (SPSS, Chicago, IL, USA). Statistical significance is set at P < 0.05.

Two-tailed-tests were performed to examine ReHo differences between patients and HCs using REST software. P < 0.05 indicates statistically significant differences, corrected with random field (Gaussian random field) theory with cluster size > 40 voxels.

It was speculated that ReHo value differences could be potentially used as biomarkers for diagnosis and prediction of treatment outcomes. The ROC curve method was used to test this hypothesis. Average ReHo values of abnormal brain regions were collected and ana-
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Accuracy was considered low or high if the area under the curve (AUC) was 0.5-0.7 or 0.7-0.9, respectively.

Brain-behavior correlation analysis

REST software divides the brain into different regions of interest (ROIs) based on different ReHo values. The average ReHo value for each ROI is the average of all voxels ReHo for that region. Correlation between ReHo values in ROIs and clinical features in ophthalmectomy patients were evaluated in terms of Pearson’s correlation analysis. $P < 0.05$ indicates statistical significance.

Results

Demographics and visual measurements

Ages of the ophthalmectomy patients and HCs were 47.78 ± 12.73 and 47.22 ± 11.36 years, respectively. Average HADS-A (Hospital Anxiety and Depression Scale-Anxiety) and HADS-D (Hospital Anxiety and Depression Scale-Depression) scores of the ophthalmectomy patients were 7.67 ± 1.20 and 9.22 ± 1.31, respectively. The average duration of the ophthalmectomy procedures was 46.39 ± 8.76 hours. There were no obvious differences in sex or age ($P = 0.8940$) between ophthalmectomy patients and HCs. A detailed summary of the data is presented in Table 1.

ReHo differences

Compared with HCs, the ophthalmectomy patients had significantly reduced ReHo values in the left inferior occipital

Figure 1. Significant differences of spontaneous brain activity between the ophthalmectomy group and healthy controls. Notes: Blue areas denote significantly reduced ReHo values in the left inferior occipital gyrus, middle occipital gyrus, right lateral occipital cortex, bilateral limbic lobe, and anterior cingulate ($p < 0.05$ for multiple comparisons using Gaussian Random Field (GRF) theory ($[z > 2.3$, cluster-wise $P < 0.05$ corrected]). Abbreviations: ReHo, regional homogeneity; L, left; R, right.
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Table 2. Brain areas with significantly different ReHo between ophthalmectomy and HCs

<table>
<thead>
<tr>
<th>Condition</th>
<th>L/R</th>
<th>Brain regions</th>
<th>BA</th>
<th>MNI coordinates</th>
<th>Cluster size</th>
<th>t-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Ophthalmectomy &lt; HCs</td>
<td>L</td>
<td>Inferior Occipital Gyrus, Middle Occipital Gyrus</td>
<td>18</td>
<td>-24 -105 -9</td>
<td>115</td>
<td>-4.54</td>
</tr>
<tr>
<td>Ophthalmectomy &lt; HCs</td>
<td>L</td>
<td>Limbic Lobe, Anterior Cingulate</td>
<td>24/32</td>
<td>-15 -27 33</td>
<td>143</td>
<td>-4.59</td>
</tr>
<tr>
<td>Ophthalmectomy &lt; HCs</td>
<td>R</td>
<td>Limbic Lobe, Anterior Cingulate</td>
<td>24/32</td>
<td>6 30 21</td>
<td>155</td>
<td>-4.28</td>
</tr>
<tr>
<td>Ophthalmectomy &lt; HCs</td>
<td>R</td>
<td>Lateral Occipital Cortex</td>
<td>19</td>
<td>15 87 45</td>
<td>99</td>
<td>-4.52</td>
</tr>
</tbody>
</table>

Notes: The statistical threshold was set at voxel with p < 0.05 for multiple comparisons using Gaussian Random Field (GRF) theory (z > 2.3, cluster-wise P < 0.05 corrected). Abbreviations: ReHo, regional homogeneity; HCs, health controls; BA, Brodmann area; MNI, Montreal Neurological Institute.

Figure 2. (A) Mean of altered ReHo values between patients with ophthalmectomy and HCs. (B) and (C) Correlation between mean ReHo signal values and behavioral performance. Notes: The ReHo signal value of the right lateral occipital cortex showed a negative correlation with HADS-depression scores (r = -0.4806, p = 0.0435; B) and a positive correlation with duration of the ophthalmectomy (r = 0.4958, p = 0.0364; C). (D) ROC curve analysis of the mean ReHo values for altered brain regions. Note: Areas under the ROC curve (AUCs) for ReHo values: Left IOG/MOG (0.951), Left LL/AC (0.941), Right LL/AC (0.966), and Right LOC (0.920). Abbreviations: ReHo, regional homogeneity; HCs, healthy controls; IOG, left inferior occipital gyrus; MOG, middle occipital gyrus; LLL, left limbic lobe; RLL, right limbic lobe; AC, anterior cingulate; RLOC, right lateral occipital cortex; ROC, receiver-operating characteristic; Left IOG/MOG, left inferior occipital gyrus/middle occipital gyrus; Left LL/AC, left limbic lobe/anterior cingulate; Right LL/AC, right limbic lobe/anterior cingulate; Right LOC, right lateral occipital cortex.

Correlation analyses

In ophthalmectomy patients, ReHo signal values of the right lateral occipital cortex showed a negative correlation with HADS-depression scores (r = -0.4806, P = 0.0435, Figure 2B) and a positive correlation with duration of the ophthalmectomy (r = 0.4958, P = 0.0364, Figure 2C).

Receiver operating characteristic curve

Different ReHo values were obtained in ophthalmectomy patients and HCs. These could be utilized to separate the patients and HC groups. To test this possibility, mean ReHo values in different brain regions were used for analysis of the ROC curves. In this study, values of the area under the curve of the left inferior occipital gyrus/middle occipital gyrus, left limbic lobe/anterior cingulate, right limbic lobe/anterior cingulate, and right lateral occipital cortex were 0.951, 0.941, 0.966, and 0.920 (Figure 2D and Table 3). Cutoff-values of the left inferior occipital gyrus/middle occipital gyrus, left limbic lobe/anterior cingulate, right limbic lobe/anterior cingulate, and right lateral occipital cortex were 0.951, 0.941, 0.966, and 0.920 (Figure 2D and Table 3).
The occipital lobe is found in the back of the brain and is responsible for language, action, abstract concepts, and visual feelings. The occipital lobe is the visual cortical center. When the occipital lobe is damaged, visual disturbances, memory defects, and kinesthetic disturbances occur. However, visual symptoms are dominant [29]. Studies have shown that occipital lobe injuries are associated with occurrence of epilepsy and can lead to visual hallucinations in patients with epilepsy [30]. Another study found a significant decrease in γ-amino butyric acid (GABA) in the occipital lobe of Parkinson’s patients with pseudoscopic vision. This was presumed to be one of the causes of visual impairment and visual illusion in Parkinson’s patients [31]. A recent meta-analysis showed that more than half of patients with occipital lobe epilepsy had different degrees of postoperative visual acuity after surgery [32]. A case report reported a significant illusion in the early stages of a patient with occipital cerebral infarction. The illusion was thought to be due to integration failure of visual information [33]. The current study found that, after ophthalmectomy procedures, the patients had significantly reduced ReHo values in the left inferior occipital gyrus, middle occipital gyrus, and right lateral occipital cortex. The possible mechanism is that during the enucleation surgery, the optic nerve was cut, leading to disruption of the visual pathway. Thus, coherent visual information from the fiber projections to the visual cortex was reduced or lost, resulting in neuronal activity in the cerebral cortex becoming significantly reduced.

The bilateral limbic lobe is the area around the corpus callosum lesions in the cortex and cingulate cortex, hippocampus, septal area, and pyriform lobe of the limbic system. Fiber linkages are complex and have various functions. It not only deals with the sense of smell, but also involves a series of internal activities, physical activity, endocrine functions, emotion, learning and memory, as well as other complex functions [34]. Many diseases have been found to have abnormal cingulate gyrus or hippocampal, such as schizophrenia, Alzheimer’s disease, autism, and depression [35-40]. The current study found that after enucleation of the eye, patients had significantly reduced ReHo values in the left limbic lobe/anterior cingulate and right limbic lobe/anterior cingulate. A possible reason for this is that postoperative visual information transmissions are reduced and the lateral geniculate body develops contraction dysfunction.

**Table 3. Cutoff values, sensitivity, specificity, and AUCs for altered ReHo values in distinguishing between patients with ophthalmectomy and HCs**

<table>
<thead>
<tr>
<th>Cutoff value</th>
<th>Sensitivity (%)</th>
<th>Specificity (%)</th>
<th>AUC</th>
<th>P</th>
</tr>
</thead>
<tbody>
<tr>
<td>Left IOG/MOG</td>
<td>0.983</td>
<td>100.00</td>
<td>83.33</td>
<td>0.951</td>
</tr>
<tr>
<td>Left LL/AC</td>
<td>0.718</td>
<td>83.33</td>
<td>94.4</td>
<td>0.941</td>
</tr>
<tr>
<td>Right LL/AC</td>
<td>0.891</td>
<td>100.00</td>
<td>83.33</td>
<td>0.966</td>
</tr>
<tr>
<td>Right LOG</td>
<td>1.014</td>
<td>88.89</td>
<td>88.89</td>
<td>0.920</td>
</tr>
</tbody>
</table>

Note: Sensitivity and specificity were obtained at the point of cutoff value. P < 0.05 represented statistically significant. Abbreviations: Left IOG/MOG, left inferior occipital gyrus/middle occipital gyrus; Left LL/AC, left limbic lobe/anterior cingulate; Right LL/AC, right limbic lobe/anterior cingulate; Right LOC, right lateral occipital cortex; AUC, area under the curve; ReHo, regional homogeneity; HCs, healthy controls.

**Discussion**

Resting-state function ReHo has been successfully applied in several ophthalmological diseases (Table 4) [22-28]. This represents an important aspect of resting-state fMRI. It provides a further approach to understand the functional links between acute eye injuries and local spontaneous brain activity.

To the best of our knowledge, the current study is the first to evaluate the effects of ophthalmectomy procedures on resting-state brain activity using the ReHo technique. Compared with HCs, ophthalmectomy patients had significantly reduced ReHo values in the left inferior occipital gyrus/middle occipital gyrus, left limbic lobe/anterior cingulate, right limbic lobe/anterior cingulate, and right lateral occipital cortex (Figure 3). Furthermore, ReHo signal values of the right lateral occipital cortex showed a negative correlation with HADS-depression scores ($r = -0.4806, P = 0.0435$) and a positive correlation with duration of the ophthalmectomy ($r = 0.4958, P = 0.0364$).

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Table 4. ReHo method applied in ophthalmological diseases

<table>
<thead>
<tr>
<th>Author</th>
<th>Year</th>
<th>Disease</th>
<th>Brain areas</th>
</tr>
</thead>
<tbody>
<tr>
<td>SONG YW, et al. [22]</td>
<td>2014</td>
<td>Glaucoma</td>
<td>RDACC; BMFG; RCAL</td>
</tr>
<tr>
<td>CUI Y, et al. [23]</td>
<td>2014</td>
<td>Diabetic retinopathy</td>
<td>PLC; ACC; FL</td>
</tr>
<tr>
<td>SHAO Y, et al. [24]</td>
<td>2015</td>
<td>Optic neuritis</td>
<td>LFG; RIPL; BC; BP/PG; LIPL; LCPL</td>
</tr>
<tr>
<td>HUANG X, et al. [25]</td>
<td>2016</td>
<td>Comitant strabismus</td>
<td>RITC/FG/CAL; RLG; BCG</td>
</tr>
<tr>
<td>HUANG X, et al. [26]</td>
<td>2016</td>
<td>Open-globe injury</td>
<td>RCPL/LG; LSTG/IFG; LIFG; LPCC/PCUN; LP/CD</td>
</tr>
<tr>
<td>HUANG X, et al. [27]</td>
<td>2017</td>
<td>Retinal detachment</td>
<td>ROL; RSTG; BC; LMFG</td>
</tr>
<tr>
<td>TANG LY, et al. [28]</td>
<td>2018</td>
<td>Acute eye pain</td>
<td>LSFG; RIPL; LP; LP/PG; RP/PG; LMFG</td>
</tr>
</tbody>
</table>

Abbreviations: HCs, healthy controls; RDACC, right dorsal anterior cingulated cortex; BMFG, bilateral medial frontal gyrus; RCAL, right cerebellar anterior lobe; BC, bilateral calcarine; BP/PG, bilateral pre/postcentral gyrus; LIPL, left inferior parietal lobule; LCPL, left cerebellum posterior lobe; PLC, posterior lobe of cerebellum; ACC, anterior cingulate cortex; FL, frontal lobe; OL, occipital lobe; LFG, left fusiform gyrus; RIPL, right inferior parietal lobule; LCPL, left cerebellum posterior lobe; LMTG, left middle temporal gyrus; RI, right insula; RSTG, right superior temporal gyrus; LSMFG, left middle frontal gyrus; ROL, right occipital lobe; BACC, bilateral anterior cingulate cortex; BMFG, bilateral medial frontal gyrus; BC, bilateral calcarine; BP/PG, bilateral pre/postcentral gyrus; LIFG, left inferior frontal gyrus; LP, left precuneus; LP/PG, left precentral/postcentral gyrus; RP/PG, right precentral; LMFG, left middle frontal gyrus.

Figure 3. ReHo results of brain activity in the ophthalmectomy group. Compared with HCs, the ReHo of the following regions in the ophthalmectomy group were decreased to various degrees: 1-left inferior occipital gyrus/middle occipital gyrus (BA 18, t = -4.54); 2-right lateral occipital cortex (BA 19, t = -4.52); 3-right limbic lobe/anterior cingulate (BA 24/32, t = -4.28); 4-left limbic lobe/anterior cingulate (BA 24/32, t = -4.59). Notes: Sizes of the spots denote the degree of quantitative changes. Abbreviations: ReHo, regional homogeneity; HCs, healthy controls; BA, Brodmann area.

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Disclosure of conflict of interest
None.

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