Glaucoma

Reduced Functional and Anatomic Interhemispheric Homotopic Connectivity in Primary Open-Angle Glaucoma: A Combined Resting State-fMRI and DTI Study

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PURPOSE. To investigate if abnormal interhemispheric homotopic functional connectivity were accompanied by corresponding anatomic connectivity changes in primary open-angle glaucoma (POAG) patients, and to relate connectivity changes with retinal nerve fiber layer (RNFL) thickness and ganglion cell complex (GCC) thickness.

METHODS. Resting-state functional magnetic resonance imaging (rs-fMRI) and diffusion tensor imaging (DTI) were performed in 16 POAG patients and 19 healthy controls. Indices of interhemispheric homotopic functional connectivity and the underlying anatomic connectivity changes were derived with voxel-base whole-brain voxel-mirrored homotopic connectivity (VMHC) analyses and VMHC-guided probabilistic tractography. Pearson correlation analyses were used to explore the correlations between interhemispheric homotopic functional connectivity changes and anatomic connectivity alterations, and RNFL and GCC thickness.

RESULTS. Reduced VMHC values between bilateral homotopic cortical areas located in Brodmann area (BA)17, BA18, and BA19. Decreased anatomic connectivity between bilateral visual cortical areas in BA17 and BA18 were observed in POAG patients. Furthermore, positive correlations between average RNFL thickness and reduced VMHC values of BA17 (r = 0.572, P = 0.021)/BA18 (r = 0.600, P = 0.014)/BA19 (r = 0.550, P = 0.027) are found using Pearson correlation analyses.

CONCLUSIONS. Combinations of interhemispheric homotopic functional connectivity and anatomic connectivity changes may help to elucidate the mechanism of interhemispheric synchronization injury in POAG patients. Reduced VMHC values positively correlate with glaucomatous changes of RNFL thickness, which strengthens the hypothesis that POAG affects the visual cortex using a novel functional MRI characteristic.

Keywords: functional magnetic resonance imaging, resting state, diffusion tensor imaging, voxel mirrored homotopic connectivity, primary open angle glaucoma

Primary open-angle glaucoma (POAG) is one of the major causes of irreversible blindness worldwide.1 The number of open-angle glaucoma (OAG) patients worldwide is estimated to be 45 million.1 POAG usually initiates and progresses silently.2 When the first sign of visual field (VF) impairment appears, a significant amount (between 40% and 50%) of retinal ganglion cells (RGCs) have been irreversibly lost,2,3 which is one of the main reasons why POAG causes a high rate of blindness.4,5 Unfortunately, the pathogenesis of POAG remains elusive, and early diagnosis of glaucoma is still a great challenge.

Recent studies of experimental glaucoma models, human autopsy cases and neuroimaging studies indicated glaucomatous damage affects multiple visual stations in the brain in POAG patients from the eye to brain.6–12 The morphologic, functional, and metabolic damages of nervous system sites have been detected in POAG,9,11–13 including the optic nerve; optic chiasm; optic tract; lateral geniculate nucleus (LGN); optic radiation; and visual cortex; and these changes are associated with long-standing VF loss. Furthermore, widespread damage of anatomic connectivity and functional connectivity within and beyond the visual system has been demonstrated in the early disease stage of POAG, and is correlated with the VF defect.12 Robust homotopic resting-state functional connectivity is a key characteristic of the brain’s intrinsic functional architecture.14,15 Functional homotopy is the high degree of synchrony in spontaneous activity between geometrically corresponding interhemispheric (i.e., homotopic) regions,16 and likely plays an important role in interhemispheric communication to integrated brain function.15 Here, we directly evaluated homotopic resting-state functional connectivity in POAG patients using a novel voxel-wise image analysis method of resting-state functional magnetic resonance imaging (rs-fMRI), called voxel-mirrored homotopic connectivity (VMHC), which was developed by Zuo et al.17 VMHC quantifies the resting state functional connectivity between each voxel in one hemisphere and its mirrored counterpart in the other.17 Alterations in VMHC have recently
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been detected in normal aging,17 different psychiatric and neurologic disorders (e.g., schizophrenia,18 Parkinson’s disease,19 Alzheimer’s disease,20 and somatization disorder21), and yielded a number of new disease-related findings. These findings indicated that VMHC might be a promising tool to detect the alterations of interhemispheric functional coordination in both normal aging and disease states.

Our previous study showed that reduced VMHC in precuneus correlated with larger cup-to-disk ratio (CDR).22 However, the possibly concomitant anatomic connectivity changes underlying abnormal interhemispheric synchrony remain unclear. Considering that our previous study did not acquire the diffusion tensor imaging (DTI) data, we didn’t use the previous data and recruited subjects for this study, and supplemented the clinical data and DTI scans. Based on the previous studies, we hypothesized that abnormal interhemispheric homotopic functional connectivity is one of the main reasons for interhemispheric synchronization injury in POAG patients, and may be accompanied by corresponding anatomic connectivity changes.

With rs-fMRI, we examined whole-brain interhemispheric functional connectivity in POAG patients using the method of VMHC, and then we explored the alterations of interhemispheric anatomic connectivity in brain regions with abnormal VMHC and explored the correlations between the abnormal VMHC and anatomic connectivity changes; glaucomatous changes of retinal nerve fiber layer (RNFL); and ganglion cell complex (GCC) thickness. This study can provide a more complete understanding of the abnormal interhemispheric synchronization in POAG patients.

MATERIALS AND METHODS

Subjects

The present study was approved by the medical ethics committee of our hospital. A total of 17 POAG patients (15 males and 4 females, age = 41 ± 13 years) and 21 healthy controls (14 males and 7 females, age = 38 ± 12 years) were enrolled in this study. The relatively young age was chosen to reduce the risk of a confounding effect of aging on the resting-state cerebral function. The range and mean deviation (MD) of visual field defects in the right and left eye was −10.57 ± 10.82 dB and −9.80 ± 9.06 dB, respectively. There were six early, four intermediate, and seven advanced-stage glaucoma patients in the present study, and the mean and range of duration of diagnosed glaucoma is (8.57 ± 5.98 months). The patients were recruited from the inpatient and outpatient clinics of our hospital, while the age- and sex-matched healthy controls were enrolled from local community via advertisement. All participants are right-handed. Written informed consents in accordance with the Declaration of Helsinki were obtained from all participants.

A total of 16 POAG patients and 19 controls were included according to the inclusion/exclusion criteria. The data sets of one patient and two controls are excluded due to the unqualified head movement that affects the image quality. The glaucoma diagnosis was made based on the diagnostic criteria of the Primary Open-Angle Glaucoma Preferred Practice Pattern Guidelines of the American Academy of Ophthalmology.23 Participants were enrolled in the study only when all three specialists agreed with the diagnosis. Inclusion criteria for POAG patients were: (1) aged between 30 and 60 years; (2) a clinical examination confirming POAG; (3) the presence of a glaucomatous damage to the optic nerve and glaucomatous visual field defect; and (4) includes individuals with bilateral glaucoma. Three glaucoma specialists evaluated examination results in a masked manner. Exclusion criteria included: (1) clinical evidence or history of other ocularpathy; (2) abnormality detected in the optic pathway or brain such as cerebral infarction, intracranial tumors, previous cranial surgery, and traumatic brain injury; (3) evidence of hypertension, diabetes, or other systemic diseases; (4) use of alcohol, caffeine, nicotine, or drugs such as oral or intravenous carbonic anhydrase inhibitors within the last 5 months; (5) contraindications to MRI scanning; and (6) any participant with a head motion more than 1.5 mm translation or 1.5° rotation on any axis was excluded.

Ophthalmic Examination

The ophthalmic examination included visual acuity; refraction; slit-lamp biomicroscopy; applanation tonometry; gonioscopy; dilated fundus examination; optical coherence tomography (OCT); and visual field assessment. Among these ophthalmic examinations, this study focuses on the RNFL and GCC thickness of the OCT and visual field measurements, while the rest of the ophthalmic examinations were used to diagnose POAG. All POAG subjects underwent a minimum of two standard automated perimetry examinations (central 50-2 full threshold program, Humphrey Field Analyzer, Zeiss Meditec AG, Jena, Germany) within a 6-month period. A reliable visual field had to meet the criteria of < 20% fixation errors, < 15% false-positive results, and < 35% false-negative results. Advanced stage VF loss is defined as MD worse than −12 dB, intermediate stage VF loss is defined as having a MD between −12 and −6 dB, early VF loss is defined as having MD larger than −6 dB. Fundus photographs (fundus camera EOS D60; Canon Co., Utsunomiya-shi, Tochigi, Japan) and RNFL and GCC thickness by spectral domain optical coherence tomography (RTVue-100, software version 4.0; Optovue, Inc., Fremont, CA, USA) were obtained.

MRI Acquisition

MRI data were obtained using a 3.0-Tesla MR scanner (Discovery MR750; GE Healthcare, Milwaukee, WI, USA), with an 8-channel head coil. Foam padding and headphones were used to limit head motion and reduce scanner noise. For structural MRI, three-dimensional brain volume imaging sequences were obtained (repetition time [TR] = 8.16 ms, echo time [TE] = 3.18 ms, inversion time [TI] = 450 ms, flip angle = 12°, matrix = 256 × 256, thickness = 1.0 mm, gap = 0 mm, 188 slices and voxel size = 1 × 1 × 1 mm). Subsequently, DTI data were acquired using a spin-echo single-shot diffusion tensor echo planar imaging (TR = 6000 ms, TE = 61 ms, 64 diffusion gradient directions [b = 0 and 1000 s/mm²]; matrix = 128 × 128, field of view [FOV] = 256 × 256 mm; and 50 axial slices [thickness = 3 mm, gap = 0 mm]). Finally, rs-fMRI data were acquired using a gradient-echo single-shot echo planar imaging (36 axial slices, slice thickness = 3 mm, gap = 1 mm, TR = 2000 ms, TE = 30 ms, flip angle = 90°, FOV = 220 × 220 mm, matrix = 64 × 64, and 180 time points).

During the rs-fMRI scans, all subjects were instructed to keep their eyes closed, remain as still as possible, not to think of anything in particular and not to fall asleep. Considering that we need to monitor the patients’ situation at any time and keep them relaxed, the light is on in the scanning room in this study.

MRI Data Analysis

Functional Images Analysis. The rs-fMRI data were processed using a toolbox for Data Processing and Analysis of Brain Imaging (DPABI, Yan et al.,24 provided in the public domain, http://rfmri.org/DPABI) running on a matrix laboratory platform named as (https://www.mathworks.com/products/matlab.html, MATLAB R2012a; The MathWorks Inc., Natick, MA, USA).
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The procedures were as follows: (1) converting DICOM files to NIFTI images; (2) discarding the first 10 volumes to allow for scanner calibration, and for the subjects to adapt to the scanner noise; (3) performing slice timing and realignment for head motion correction for the remainder volumes (any participant with a head motion more than 1.5 mm translation or 1.5° rotation on any axis was excluded); (4) nuisance covariates regression (including signals of linear drift, six head movement parameters and their first time derivations, and the signals of white matter, cerebrospinal fluid, and the whole brain); (5) spatial normalization; (6) applying temporal band-pass filter (frequency range of 0.01–0.08 Hz); and (7) spatial smoothing (full width at half maximum [FWHM] = 4 mm). Finally, the functional images of each subject were registered to a study-specific and symmetric Montreal Neurological Institute (MNI) space template for computing the VMHC.\(^{17}\) VMHC was calculated also using the DPABI software.\(^{24}\) For each subject, the homotopic functional connectivity was computed as the Pearson correlation coefficient between each voxel’s preprocessed signal time series and that of its symmetrical interhemispheric counterpart. To improve the normality of the distribution, correlation coefficients were then standardized using Fisher’s \(z\)-transformed.\(^{21}\) The resultant \(z\)-values, constituting the VMHC, were used for subsequent voxel-wise group comparison.

A gray matter mask for the analysis of homotopic connectivity was obtained through averaging all smoothed gray matter volumes (\(3 \times 3 \times 3\) mm) of all subjects. The smoothed gray matter volumes were averaged with a left-right flipped images and then with an intensity threshold of 0.2 to produce a symmetrical gray matter mask for VMHC analysis. Homotopic regions showing changed VMHC in POAG were adopted as regions of interest (ROIs) for an analysis of DTI. The ROIs were located using the Brodmann atlases.

**DTI Data Analysis.** Diffusion tensor images (DTI) were preprocessed with steps including the correction of eddy current distortion, brain extraction, reconstruction of diffusion tensors using DTIFIT (provided in the public domain, https://fsl.fmrib.ox.ac.uk/fsl/fslwiki/DTIFIT) and smooth (FWHM = 6 mm). Then the bedpost tool\(^{25}\) of FMRI’s Diffusion Toolbox is applied to estimate the local modeling of diffusion parameters, which is an essential step for the further probabilistic fiber tracking.

To test whether the interhemispheric desynchronization was associated with corresponding alterations of anatomic connectivity, the regions of interest (ROIs) for analyzing DTI probabilistic tractography were generated from the resultant images of VMHC in POAG. The T1 template from VMHC was registered to the B0 image using the FMRIB Linear Image Registration Tool (FLIRT) and the FMRIB Non-linear Image Registration Tool (FNIRT) (provided in the public domain, https://fsl.fmrib.ox.ac.uk/fsl/fslwiki/FNIRT). The resultant matrices were used to transform the ROIs from functional space to diffusion space. Probabilistic fiber tracking\(^{26}\) was then performed using the average of left-to-right and right-to-left tracking results in individual space. The resulted probabilistic track images were registered to the standard MN152 space for further group analysis. The resulting probability track images were averaged for all subjects and then binarized at the threshold of 15%, yielding ROIs of the probability track image. The mean fractional anisotropy (FA) for each subject was generated through FA value extraction using the ROIs of probability track image.

**Statistical Analysis**

**Demographic and Clinical Data.** All non-voxel-wise demographic and clinical data were analyzed with statistical software (SPSS 20 version 20.0.; SPSS, Inc., Chicago, IL, USA). For demographic variables, group differences in age and sex were compared using independent-samples \(t\)-tests and \(\chi^2\) test, respectively. To test whether there was significantly statistical difference in the severity of the binocular disease, we applied a paired \(t\)-test on the MD and pattern standard deviation (PSD) of visual field defects: RNFL thickness; and GCC thickness between left and right eyes.

To investigate the possible correlations between reduced \(z\)-VMHC values and RNFL and GCC thickness, Pearson correlation analyses were performed. RNFL and GCC thickness data involved in the analyses were averaged from left and right retina. The average thickness of RNFL denoted by RNFL\(_{\text{mean}}\) for each subject is computed as:

\[
RNFL_{\text{mean}} = \frac{\text{RNFL}_{\text{left}} + \text{RNFL}_{\text{right}}}{2} \quad (1)
\]

where the RNFL\(_{\text{left}}\) and RNFL\(_{\text{right}}\) are the RNFL thickness of left and right retina from the same patient. The average thickness of GCC denoted by GCC\(_{\text{mean}}\) for each subject is computed as:

\[
GCC_{\text{mean}} = \frac{\text{GCC}_{\text{left}} + \text{GCC}_{\text{right}}}{2} \quad (2)
\]

where the GCC\(_{\text{left}}\) and GCC\(_{\text{right}}\) are the GCC thickness of left and right retina from the same patient.

**Rs-fMRI Data.** Group comparisons of VMHC analysis were conducted by DPABI software (Yan et al.,\(^{24}\) provided in the public domain, http://rfmri.org/DPABI),\(^{24}\) using a voxel-based whole-brain, two-sample \(t\)-test analysis of covariance with age, sex, and total gray matter volume as the nuisance covariates (masked by a gray matter segmentation of the symmetrical MNI template). Significant differences of VMHC between POAG patients and healthy controls were set at a cluster level of \(P < 0.01\) and cluster size \(> 249 \text{ mm}^3\), and the threshold of voxel-wise was \(P < 0.05\) by Alphasim correction.

The clusters with significant differences in the results of the VMHC analysis are taken as the regions having a significant difference in POAG. Regions exhibiting significantly different \(z\)-VMHC in POAG patients compared to controls were defined as ROIs, and for a more accurate localization, we used Brodmann Atlas to obtain the accurate symmetric ROI. The mean \(z\)-VMHC values within these regions were extracted for subsequent Pearson correlation analyses.

**DTI Data.** The FA values of fibers connecting the homotopic ROIs were extracted. An independent sample \(t\)-test was used for group differences between POAG patients and controls, and Pearson correlation analyses were used to explore the possible correlation between interhemispheric functional connectivity and corresponding anatomic connectivity.

**RESULTS**

**Demographic Characteristics**

There was no significant difference in age (\(t = 0.439, P = 0.663\)) and sex (\(\chi^2 = 1.128, P = 0.288\)) between the POAG group and the control group. No significant difference was found between eyes in MD, PSD, RNFL, and GCC thickness (Table 1).

**Group Differences in VMHC**

The \(z\)-VMHC in POAG patients was reduced compared to healthy controls after Alphasim correction. As shown in Figure 1, statistically significant \(z\)-VMHC reductions were observed in visual cortex (Peak MNI coordinates \((x, y, z)\): ±14, -88, 21;
cluster size, 251 mm$^3$), including Brodmann area 17 (BA17), BA18, and BA19.

**Group Differences on Interhemispheric Anatomic Connectivity**

Probabilistic tractography results of the homotopic ROIs inside BA17/18/19 from all participants are shown in Figure 2. FA values extracted from the fiber bundles connecting the bilateral ROIs in POAG patients and healthy controls are noted in Table 2. FA values of the fiber bundles connecting bilateral ROIs inside BA17 and BA18 was significantly decreased in POAG patients compared with healthy controls.

**Correlations With FA, RNFL and GCC Thickness**

Correlations between z-VMHC and RNFL thickness were shown in Figure 3. Positive correlations between the RNFL$\text{mean}$ thickness and z-VMHC of BA17 ($r = 0.572, P = 0.021$); BA18 ($r = 0.600, P = 0.014$); and BA19 ($r = 0.550, P = 0.027$) are found using the Pearson correlation analyses. There was no correlation between z-VMHC and FA of the fiber bundles inside homotopic ROIs and GCC$\text{mean}$ thickness (Fig. 4).

**DISCUSSION**

Compared with healthy controls, POAG patients showed decreased interhemispheric homotopic functional connectivity between the bilateral visual cortical areas inside areas BA17, BA18, and BA19, respectively. Alterations of interhemispheric anatomic connectivity were in accordance with interhemispheric homotopic functional connectivity changes in areas BA17 and BA18. Furthermore, the decreased interhemispheric homotopic functional connectivity inside areas BA17, BA18, and BA19 positively correlated with RNFL thickness.

The results of this study is slightly different from the previous study$^{22}$ for several reasons: (1) we didn’t use the previous data and recruited subjects in our hospital for this study, and supplemented the clinical data and DTI scans; (2) compared with the subjects in previous study, younger POAG

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**Table 1.** Comparison of Glaucomatous Damage Between Left and Right Eye in POAG Patients

<table>
<thead>
<tr>
<th>Parameters, Units</th>
<th>Right Eye</th>
<th>Left Eye</th>
<th>$t$</th>
<th>$P$</th>
</tr>
</thead>
<tbody>
<tr>
<td>MD, dB</td>
<td>$-10.57 \pm 10.82$</td>
<td>$-9.79 \pm 9.05$</td>
<td>$-2.710$</td>
<td>0.790</td>
</tr>
<tr>
<td>PSD, dB</td>
<td>$6.04 \pm 4.30$</td>
<td>$6.10 \pm 4.21$</td>
<td>$-0.047$</td>
<td>0.963</td>
</tr>
<tr>
<td>Average RNFLT, $\mu m$</td>
<td>$77.58 \pm 17.10$</td>
<td>$77.77 \pm 14.40$</td>
<td>$-0.065$</td>
<td>0.949</td>
</tr>
<tr>
<td>Superior RNFLT, $\mu m$</td>
<td>$93.97 \pm 17.10$</td>
<td>$100.50 \pm 20.47$</td>
<td>$-1.159$</td>
<td>0.265</td>
</tr>
<tr>
<td>Inferior RNFLT, $\mu m$</td>
<td>$90.13 \pm 18.40$</td>
<td>$92.25 \pm 23.32$</td>
<td>$-0.291$</td>
<td>0.775</td>
</tr>
<tr>
<td>Nasal RNFLT, $\mu m$</td>
<td>$66.56 \pm 14.99$</td>
<td>$62.56 \pm 10.82$</td>
<td>$0.969$</td>
<td>0.348</td>
</tr>
<tr>
<td>Temporal RNFLT, $\mu m$</td>
<td>$59.00 \pm 18.33$</td>
<td>$66.00 \pm 19.50$</td>
<td>$1.677$</td>
<td>0.114</td>
</tr>
<tr>
<td>Total GCCT, $\mu m$</td>
<td>$75.62 \pm 10.24$</td>
<td>$76.90 \pm 13.93$</td>
<td>$-0.396$</td>
<td>0.698</td>
</tr>
<tr>
<td>Superior GCCT, $\mu m$</td>
<td>$78.34 \pm 13.43$</td>
<td>$80.46 \pm 16.87$</td>
<td>$-0.578$</td>
<td>0.572</td>
</tr>
<tr>
<td>Inferior GCCT, $\mu m$</td>
<td>$72.16 \pm 11.05$</td>
<td>$72.46 \pm 13.51$</td>
<td>$-0.100$</td>
<td>0.922</td>
</tr>
</tbody>
</table>

$P < 0.05$ indicating statistical significances.
patients in the present study are enrolled to reduce the risk of a confounding effect of aging on rs-fMRI; (3) we have adjusted the sequence parameters of rs-fMRI to increase the resolution of the images on a new 3.0-Tesla MR scanner (GE Healthcare); (4) the GM volume has been taken as a covariate of no interest in analyses of voxel-wise group comparisons to eliminate the potential structural differences in VMHC analysis; and (5) small sample and severity of POAG of the two studies may also contribute to the slightly different results.

POAG has been described as a progressive neurodegenerative disease along the visual pathway.26,27 The human visual pathway is composed of the retina; optic nerve; chiasm; lateral geniculate nucleus (LGN); the optic radiations; and visual cortex. These structures anatomically link the brain regions to the eye. RGC axonal injury in the optic nerve head (comprised of RGC axons) is an important early event in glaucomatous neurodegeneration.28 Optic nerve head damage can lead to the degeneration of RGC along its axons. The prevailing view suggests that the majority of glaucomatous degeneration of the posterior visual pathway is preceded by the degeneration of RGC axonopathy, implying that anterograde degeneration is responsible for glaucomatous brain changes.29 There is only one synapse between the optic nerve head and the visual cortex, where BA17 is part of the primary visual cortex, which is the predominant brain area receiving direct input relating to visual stimuli. BA17 also forms connections with areas of secondary visual cortex, including BA18 and BA19.30 Trans-synaptic anterograde degeneration will lead to changes of the posterior visual pathway.31

The neuropathologic and neuroimaging studies showed decreased neuronal density in LGN31,32; reduced volume in visual cortex31,33; reduced visual-evoked metabolic activation and functional activity in ventral and dorsal visual pathways6,7,9,34; alterations of functional connectivity30 and network integrity in the visual system.12,35 Different from the existing studies, our study evaluated brain changes in the viewpoint of interhemispheric functional homotopy. Previous studies have demonstrated that among the patterns of the brain’s intrinsic functional architecture, homotopic functional connectivity was one of the most salient characteristics.14,15

Our results demonstrated reduced VMHC located in visual cortical areas BA17, BA18, and BA19. Reduced VMHC values provide evidence that homotopic functional synchronization is reduced in POAG patients.

**TABLE 2.** Group Comparisons of FA Values of the Fiber Bundles Connecting Bilateral ROIs Within Bilateral BA17/18/19

<table>
<thead>
<tr>
<th>ROIs</th>
<th>POAG, mm²/s</th>
<th>HC, mm²/s</th>
<th>t</th>
<th>P</th>
</tr>
</thead>
<tbody>
<tr>
<td>BA17</td>
<td>0.272 ± 0.010</td>
<td>0.279 ± 0.009</td>
<td>-2.319</td>
<td>0.027</td>
</tr>
<tr>
<td>BA18</td>
<td>0.298 ± 0.009</td>
<td>0.305 ± 0.009</td>
<td>-2.320</td>
<td>0.027</td>
</tr>
<tr>
<td>BA19</td>
<td>0.336 ± 0.010</td>
<td>0.343 ± 0.012</td>
<td>-1.962</td>
<td>0.058</td>
</tr>
</tbody>
</table>

P < 0.05 indicating statistical significances.
Reduced VMHC and Corresponding AC Changes in POAG

FIGURE 3. Significantly positive correlation between RNFL thickness and z-VMHC values within BA17/18/19 in POAG patients. (A1–3) scatterplots show significantly positive correlations between RNFL thickness and z-VMHC values within BA17/18/19, respectively. The results suggest interhemispheric synchronization of BA17/18/19 decreased with reduced RNFL thickness in POAG patients. RNFLT, retinal nerve fiber layer thickness.

FIGURE 4. Correlations between z-VMHC of BA17/18/19 and GCC thickness in POAG patients. The scatterplots (A1, A2, A3) show correlations between z-VMHC for BA17/18/19 and GCC thickness, respectively. The findings suggest there is no significant correlation between interhemispheric synchronization and GCC thickness. GCCT, ganglion cell complex thickness.

disturbed. Similarly, findings of Sponsel et al.36 and Reilly et al.37 indicate that chronic glaucomatous neurodegeneration is mediated by an integrated process. The two studies provide strong clinical evidence that the brain exerts bilaterally coordinated direct influences on ganglion cell function, and implicate a symmetry-breaking process of POAG.

Visual information from each hemi-field is transmitted to the contralateral side of the primary visual cortex simultaneously, and this information needs to be integrated in bilateral cortical hemispheres. Normal vision condition is essential for maintaining both the amplitude and phase of neuronal activity in the visual cortex.38 Visual input is permanently reduced in POAG patients, leading to a constricted visual field and impaired color perception due to RGC loss.39,40 Both hemispheres contribute to the processing of visual input, and the activation of interhemispheric connection of visual cortex is important for the early stage of the visual information processing.41 The signal reaching the corresponding visual cortex with reduced contrast sensitivity might have a poor signal-to-noise ratio due to the irreversible loss of RGCs and impairment of the visual field in POAG patients, which could lead to heterogeneity in oscillations of neuronal elements. The heterogeneity in oscillations of neuronal elements could result in reduction of interhemispheric synchronization as well as disturb the exchanging and processing of visual information between the bilateral hemispheres in POAG patients.42 Furthermore, the present study discovered positive correlations between VMHC in visual cortical areas (BA17, BA18, and BA19) and RNFL thickness. All the optic nerve fibers ultimately converge toward the optic nerve head. Thinning of RNFL thickness on OCT is direct clinical evidence of retrograde degeneration of the RGC in POAG.43 These findings provide further evidence that posterior visual system is affected in POAG in a novel rs-fMRI characteristic. In addition, BA17, BA18, and BA19 are recognized as crucial nodes of the visual network,44 where the visual network state might be disturbed by reduced interhemispheric synchronization, which could aggravate the functional consequences of reduced visual input.

The pathophysiology underlying the abnormal VMHC is unclear. Our study reveals that decreased FA of the fiber bundles that connected the bilateral brain regions inside areas BA17/18/19 with reduced z-VMHC in POAG patients. However, there was no correlation between FA and z-VMHC. These results supported that the injury of homotopic anatomic connectivity might disrupt interhemispheric functional coordination because neural signals cannot be transmitted from one hemisphere to another. However, direct homotopic anatomic connectivity does not appear to be a strict determinant of the homotopic functional connectivity, and there may be other pathways contributing to the reduced VMHC in POAG patients. They could be related to subcortical pathways, in support of this notion, robust homotopic functional connectivity with sparse callosal connectivity in primary visual cortex has been found,47 suggesting contribu-
ions beyond direct callosal connections. An rs-fMRI study found that a normal complement of resting state networks and intact functional coupling between bilateral hemispheres were essentially unaffected by the absence of the corpus callosum in split-brain patients. In another, widespread white matter integrity abnormalities observed in POAG using DTI, including decreased FA in optic nerve, optic chiasm, and inferior fronto-occipital fasciculus, and the longitudinal and inferior frontal fasciculi. In addition, not mutually exclusive, a possible explanation is that dysfunctions in visual cortical gray matter structure could account for the reduced VMHC. Reductions in GMV and cortical thickness have been observed in visual cortical areas; but in our study, the GMV has been taken as a covariate of no interest in analyses of voxel-wise group comparisons to eliminate the potential structural differences in VMHC analysis. Finally, reduced neuropil or aberrant local oscillatory firing within these regions may disrupt coherent low frequency oscillatory activity and/or its generation in one region, and thereby, impair its functional connectivity with other regions.

These findings suggested that direct homotopic anatomic connectivity only partially shapes functional organization, while subcortical and polysynaptic feedback and feedforward mechanisms play a role in reducing interhemispheric synchronization; a local neuroplasticity may also contribute. Further studies on combining homotopic and nonhomotopic (heterotopic and intrahemispheric) functional connectivity to facilitate synchronization in POAG patients are needed in the future.

There are a few limitations in the present study. First, the sample size was relatively small. A larger sample size is required to explore the more extensive functional and anatomic interhemispheric desynchronization of POAG with different stages. Second, the imaging analysis method applied in our study had its own limitations. The analysis of VMHC assumes and enforces a symmetrical standard template although the human brain is not completely symmetrical. Thus, the method is insensitive to potential asymmetric group differences. Third, this study was a cross-sectional study, and further longitudinal studies on interhemispheric changes would help to explore the mechanisms of brain functional and structural damage in POAG patients. Fourth, not all patients in the study had the same disease severity. In our future study, “same disease severity of glaucoma in both eyes of each patient” should be regarded as an inclusion criteria. Finally, we did not investigate nonhomotopic (heterotopic and intrahemispheric) communication. Since homotopic and nonhomotopic communications are correlated, future investigations are warranted.

CONCLUSIONS

Our study demonstrates that reduced VMHC in visual cortex is one of the main reasons of interhemispheric synchronization injury in POAG patients. Combination of the interhemispheric functional and anatomic connectivity changes would help to elucidate the mechanism of interhemispheric synchronization injury in visual cortex in POAG patients. Reduced VMHC positively correlate with glaucomatous changes of RNFL. These findings may provide a novel functional characteristic for the involvement of the visual cortex in POAG patients.

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