Amplitude of low frequency fluctuation in Primary open angle glaucoma: a resting state fMRI study

Zhenyu Liu and Jie Tian*, Fellow, IEEE

Abstract—**Primary open angle glaucoma (POAG) is a kind of progressive neuropathy with no clear cause. In the present fMRI study, a data-driven approach was employed to map the alteration of regional spontaneous activity in POAG patients by measuring the amplitude of low-frequency fluctuation (ALFF) of the blood oxygen level-dependent (BOLD) signal. Twenty one POAG patients and 22 age and gender matched healthy subjects participated in this study. We found that the abnormal ALFF values in the POAG patients compared with healthy controls were not only detected in the visual regions but also across the whole brain. We also found the correlations between ALFF values and the POAG stages for POAG patients. We concluded that the abnormality of spontaneous brain activity in patients with POAG existed in visual cortex as well as in distal brain regions associated with sensation, motion, emotion and psychology. And the abnormal spontaneous neural activity in different brain regions could be better detected by specific frequency bands. These findings might contribute to a better understanding of the pathophysiology of POAG.**

I. Introduction

Primary open angle glaucoma (POAG) is a kind of progressive neuropathy with no clear cause, which is characterized by the loss of retinal ganglion cells (RGC) [1]. It always turns up in a silent way and makes a slow progress [2]. If left untreated, the patient would be blind in the end [3]. It is predicted that glaucoma will affect 79.6 million people by 2020, and 74% of these patients will have open angle glaucoma [4].

Age and increased intraocular pressure are considered as the most important risk factors in POAG. However, some patients treated by IOP-lowering therapy still suffered from continuous vision loss [5]. Increasing evidences were accumulated to testify the Wallerian degeneration and dying back mechanisms in retinal ganglion cells and optic projection [6], indicating POAG was a kind of degeneration disease. Optic nerve is a part of central nervous system. And the pathologic mechanism in glaucomatous RGC was reported similar to that in Alzheimer disease [7]. Thus, POAG was supposed to be a neurodegenerative disease involving the brain [8]. It was found that the primary visual cortex was involved [9]. Moreover, structure abnormality extended into areas beyond the visual pathway, involving some areas in frontal lobe, temporal lobe, somatic cortex, and the limbic system [10]. And with VBM, atrophy of cortex was found in the middle temporal gyrus, inferior parietal gyrus, angular gyrus, precuneus, superior parietal gyrus [11], paracentral lobule, precentral gyrus, middle frontal gyrus, inferior temporal gyrus, and superior temporal gyrus [12]. These results lead to the hypothesis that POAG is not a neurodegeneration limited in visual system, but a neurodegeneration involves the whole brain.

Functional MRI, which is widely used in various neurodegenerative diseases, is also appropriate for exploring the mechanism of POAG. With monocular visual stimulation, the attenuation of BOLD signal in the primary visual cortex is consistent with the visual defect of POAG patients [13]. Furthermore, Guo et al. found that the cortical depression is negatively correlated with PSD of visual field analysis [14]. These task-related studies helped a lot to correlate the visual defect with the alteration of brain function. But these results could not interpret whether the abnormal activity in the brain is spontaneous or a response to the abnormal impulse introduced by the injured retinal ganglion cells. Regional spontaneous BOLD fluctuations of resting-state fMRI could reflect spontaneous neuronal activity [15]. Previous study found that nonrandom spontaneous activity exists in the primary visual cortex of waking adults, and it may be associated with memory-related mental imagery and visual memory consolidation processes [16]. And in a resting-state functional MRI study of POAG, Dai et al. pointed out the functional connectivity between the visual cortex and the components of some resting state networks were abnormal in patients with POAG [17]. However, the research of resting-state fMRI for POAG is rare, and the alteration of regional spontaneous activity still needs further exploration.

The amplitude of low-frequency fluctuations (ALFF) represents for the intensity of low frequency oscillations (LFOs) [18]. And it has been proven to be a valuable parameter to reflect the intensity of regional spontaneous neural activity [19].

In our present study, we explored the distribution of abnormal regional intrinsic activities in glaucomatous brain, and to find the correlation between the brain abnormality and the severity of the disease. We hypothesis that in patients with POAG the abnormal spontaneous activity not only located in visual cortex but also some distal brain areas associated with somatic sensation, motion and memory.

* This paper is supported by the knowledge innovation program of the Chinese academy of sciences under grant No.KGCX2-YW-129, the National Natural Science Foundation of China under Grant Nos. 81071137, 81071217, the Fundamental Research Funds for the Central University, the Beijing Nova program, the Project for the National Key Basic Research and Development Program (973) under Grant No. 2011CB707700, 2007CB512500, 2007CB512503, 2009CB521905.

Zhenyu Liu, Intelligent Medical Research Center, Institute of Automation, Chinese Academy of Sciences, Beijing, China (e-mail: liuzhenyu@fingerpass.net.cn).

Jie Tian, Intelligent Medical Research Center, Institute of Automation, Chinese Academy of Sciences, Beijing, China (Corresponding author, phone: 8610-82618465; fax: 8610-62527995; email: tian@ieee.org).

II. METHODS

A. Subjects

After obtaining approval of the Medical Ethics Review Committee of Tongren Hospital and obtaining informed consent in accordance with the Declaration of Helsinki, 21 POAG patients and 22 gender and age-matched healthy volunteers were enrolled in the study. Eleven males and 10 females aged 27–69 years old (mean age 46) were included in the POAG group and were matched with 11 male and 11 female healthy volunteers aged 25–65 years old (mean age 45), included in the control group. There were no statistically significant differences in age and gender between the two groups ($P > 0.05$). Informed written consent was obtained for all participants.

POAG patients were recruited at Beijing Tongren hospital and the healthy subjects were from a community. The patients were recruited into the study based on the clinical diagnostic criteria of POAG: a history of open anterior chamber angle, visual field defects, abnormal optic disk, and increased intraocular pressure [20]. Subjects underwent a thorough history and physical examination including an ophthalmologic examination. Inclusion criteria for the POAG group were: (1) a clinical examination confirming POAG and (2) the presence of a visual field defect. Exclusion criteria for the POAG group included (1) clinical evidence or history of other oculopathy; (2) history of any significant medical, neurological, or psychiatric illness including hypertension and diabetes; (3) use of alcohol, caffeine, or nicotine within the last 3 months. Inclusion criteria of the control group were age and gender matched healthy volunteers to patient group without clinical evidence or history of glaucoma. Exclusion criteria were (1) history of any significant medical, neurological, or psychiatric illness including hypertension and diabetes; (2) the presence of ocular disease by routine clinical ophthalmic test.

B. Data acquisition and preprocessing

Magnetic resonance imaging data were acquired using a 3.0 Tesla Signa (GE) MR scanner. Head movements were prevented by a custom-built head holder. The images were parallel to the AC-PC line and covered the whole brain. The resting state scan lasted for 6 min and 40 s, and acquired 200 resting state volumes. Twenty-eight axial slices were obtained using a T2*-weighted single-shot, gradient-recalled echo planar imaging sequence (FOV = 240 mm x 240 mm, matrix = 64 × 64, thickness = 5 mm, TR = 2000 ms, TE= 35 ms, flip angle = 90°). After the functional run, high-resolution structural information (3D-BRAVO) on each subject was also acquired using 3D MRI sequences with a voxel size of 1 mm3 for anatomical localization (TR = 2.1 s, TE = 4.6 ms, matrix = 256 x 256, FOV = 240 mm x 240 mm, flip angle = 13°, slice thickness = 1 mm).

Standard professional data processing software, Data Processing Assistant for Resting-state fMRI (DPARSF 1.0, http://restfmri.net/forum/DPARSF), was used for data analysis. DPARSF is plug-in software run on a matrix laboratory platform (MATLAB R2008a) and is based on statistical parametric mapping (SPM 5, http://www.fil.ion.ucl.ac.uk/spm) and a resting-state fMRI data analysis toolkit (REST 1.5, by Song et al., http://www.restfmri.net).

The preprocessing steps are illustrated as follows. After converting DICOM files to NIFTI images, the first 10 time points were discarded. Slice timing and head motion correction were then performed. The remaining data was then normalized to Montreal Neurological Institute (MNI) space by using echo planer imaging (EPI) templates and resampling to 3-mm isotropic voxels. After smoothing with a 4-mm full width half maximum (FWHM) Gaussian kernel, the linear trend of time courses was removed. A default mask made from SPM5's a priori mask named brainmask.nii, which covers whole brain contained gray matter (GM), white matter (WM), and cerebrospinal fluid (CSF), was used with a threshold of 50% [21]

C. Data Analysis

The ALFF analysis was carried out using the REST software. The calculation procedure was the same as that reported in the previous studies [22, 23]. Specifically, a filtered time series was transformed to the frequency domain with a fast Fourier transform; thus the power spectrum was obtained. Because the power of a given frequency is proportional to the square of the amplitude of this frequency component, the square root was calculated at each frequency of the power spectrum and the averaged square root was obtained across 0.01–0.1 Hz at each voxel. This averaged square root was taken as the ALFF measurement. For standardization, the ALFF of each voxel was further divided by the global mean of ALFF values. The standardized ALFF of each voxel then has a value of about 1 and this standardization procedure is analogous to that used in PET studies [24].

Voxel wise two-sample t-tests were employed to compare the differences in ALFF between POAG patients and healthy controls. And correlations between ALFF and HAP scores of POAG patients were also investigated.

III. RESULTS

ALFF results across all subjects of the two groups during resting state are shown in Figure 1 ($p < 0.05$, FDR correction). The major regions of DMN exhibited significant higher ALFF values than other brain regions during the resting state, i.e. the medial temporal lobe, posterior cingulate cortex, precuneus, medial prefrontal cortex, and inferior parietal lobe.

We then made a comparison between POAG patients and healthy controls to find the regions showing abnormal ALFF values in POAG patients during the resting state (Figure 2). The results of two sample t test revealed that POAG patients showed significant ALFF values increase in the right medial frontal gyrus and superior motor area, and decrease in the right occipital lingual gyrus, right inferior temporal gyrus, and left precentral gyrus at $P < 0.01$ (Alphasim corrected, $p<0.05$, 54 voxels).

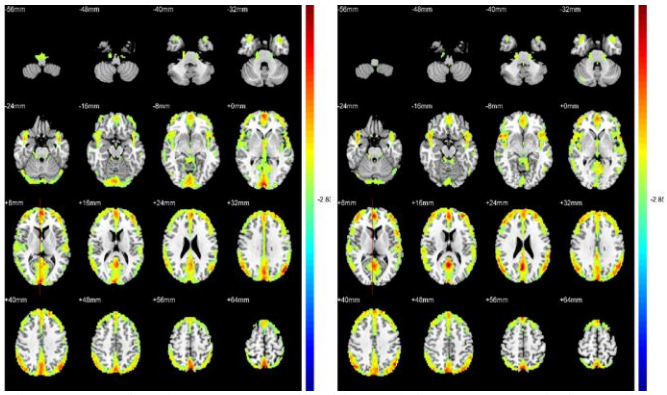

Figure 1. Results of ALFF across all subjects of the two groups during resting state ($p < 0.05$, FDR correction).

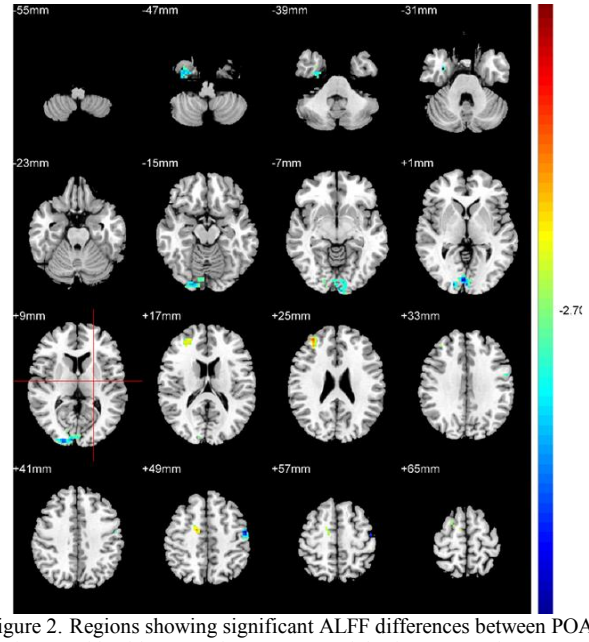

Figure 2. Regions showing significant ALFF differences between POAG patients and healthy controls at p<0.01 (Alphasim corrected, p<0.05, 54 voxels)

In addition, we investigated the correlations between ALFF and Hodapp-Anderson-Parrish (HAP) scores for POAG patients (Figure 3). The results showed that the ALFF of the right superior frontal gyrus was positive correlated with HAP scores and the ALFF of the right precentral gyrus, the left occipital lobe and the left postcentral gyrus were negative correlated with HAP scores at p<0.01 (Alphasim corrected, p<0.05, 154 voxels).

IV. DISCUSSION AND CONCLUSION

POAG is a kind of neurodegenerative disease with brain structures alteration. In recent years, the functional alteration in the brain with POAG has attracted more attention, for the pattern of brain functional alteration could help a lot in understanding the underlying mechanisms. In the present study, we employed the ALFF values to investigate the alteration of regional spontaneous activity in POAG patients and the correlations between ALFF and POAG stages.

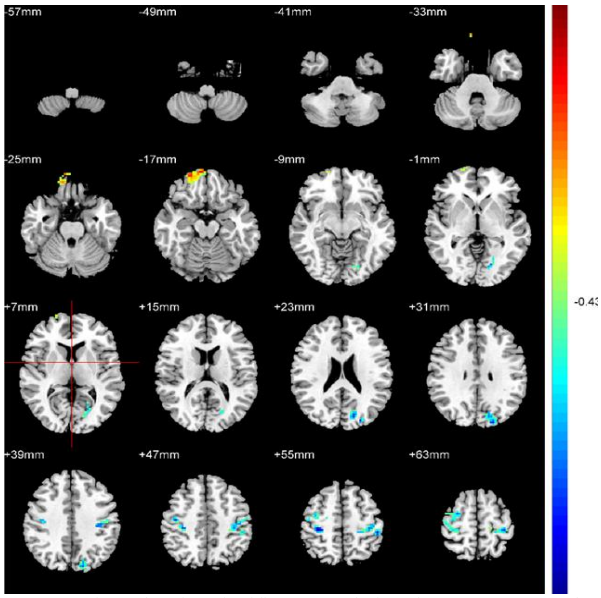

Figure 3. Regions showing significant correlations between ALFF and HAP scores for POAG patients at p<0.01 (Alphasim corrected, p<0.05, 154 voxels)

BA17 is defined as primary visual cortex (PVA) that directly connected with RGC. And BA18 and BA19 are defined as higher visual cortices that receive input information from PVA. The primary visual cortex receives informations from lateral geniculate nucleus and then sends it out through two distinct anatomical streams [25]. In the present study, ALFF in right BA17, right fusiform gyrus and right inferior temporal gyrus decreased. The reduction of spontaneous neural activity in BA17 indicated that the function of primary and higher visual cortices were impaired. And it was in accord with a recent study of regional homogeneity [26] and prior studies of proton magnetic resonance spectroscopy [27]. ITG and fusiform gyrus are components of the ventral stream of visual system, the decreased spontaneous neural activity in these areas might suggest dysfunction in visual stimuli processing, and memory recall and object identification. However, the dysfunction of dorsal stream was not observed.

The reduction of spontaneous neural activity could be found out of the visual cortices, including left postcentral gyrus, left precentral gyrus and right cerebellum posterior lobe. Postcentral gyrus and precentral gyrus constitute the motor and sensory network which was associated with PVA spontaneous activity [16]. And it was reported that this network would have decreased functional connectivity and reduced regional homogeneity in patients with POAG [17, 26]. The CPL plays an important role in fine motor coordination, specifically in the inhibition of involuntary movement.

In addition to the brain areas of decreased ALFF, areas of increasing ALFF were noted. Our results showed that the ALFF in right medial frontal gyrus and right superior motor area increased. The supramarginal gyrus is associated with language perception and processing. And the superior frontal gyrus is involved in self-awareness, and might be inactivated by sensorimotor processing. So the alteration could be interpreted by the reduction of spontaneous neural activity in precentral gyrus and postcentral gyrus. The medial prefrontal

cortex is a subsystem of the default-mode network, participating in self-relevant mental simulations. However, to this moment, there was no evidence for the involvement of posterior DMN in patients of POAG. In clinical studies, some percentage of patients with POAG were suffered from depression, hysteria, schizophrenia and paranoia [7]. Based on this, the alteration in these areas should be considered as primary dysfunction rather than secondary changes.

There are several parameters to evaluate the severity of POAG in clinical practice. And among them, HAP system was widely used in previous studies, especially in those of MRI. In the present study, we found that the HAP scores were negatively correlated with the spontaneous neural activity in left occipital cortex, bilateral temporal area, left postcentral gyrus and precentral gyrus. The middle temporal is known as V5, which plays a major role in the perception of motion. Our results showed that the spontaneous neural activity in visual cortex gradually decreased as the progression of POAG course. And the alteration in motor and sensory network was also correlated with the progression. However, the correlation between the HAP score and the dysfunction in brain regions associated with cognition and emotion was still not clear. For we found the ALFF in superior frontal gyrus and fALFF in left rectus gyrus and right precuneus increased as the disease developed, while the fALFF in insula and anterior cingulate gyrus was negatively correlated with HAP score.

In summary, the results of this study have revealed that the abnormality of spontaneous brain activity in patients with POAG exists in visual cortex as well as in distal brain regions associated with sensation, motion, emotion and psychology. And the abnormal spontaneous neural activity in different brain regions could be better detected by specific frequency bands. These findings might contribute to a better understanding of the pathophysiology of POAG.

REFERENCES

[1] Y. H. Kwon, J. H. Fingert, and M. H. Kuehn, "Primary Open-Angle Glaucoma REPLY," New England Journal of Medicine, vol. 360, pp. 2679-2680, Jun 18 2009.

[2] H. A. Quigley, "Medical Progress - Open-Angle Glaucoma," New England Journal of Medicine, vol. 328, pp. 1097-1106, Apr 15 1993.

[3] R. J. Casson, G. Chidlow, J. P. M. Wood, J. G. Crowston, and I. Goldberg, "Definition of glaucoma: clinical and experimental concepts," Clinical and Experimental Ophthalmology, vol. 40, pp. 341-349, May-Jun 2012.

[4] H. A. Quigley and A. T. Broman, "The number of people with glaucoma worldwide in 2010 and 2020," British Journal of Ophthalmology, vol. 90, pp. 262-267, Mar 2006.

[5] M. C. Leske, A. Heijl, M. Hussein, B. Bengtsson, L. Hyman, E. Komaroff, et al., "Factors for glaucoma progression and the effect of treatment - The Early Manifest Glaucoma Trial," Archives of Ophthalmology, vol. 121, pp. 48-56, Jan 2003.

[6] G. R. Howell, I. Soto, R. T. Libby, and S. W. M. John, "Intrinsic axonal degeneration pathways are critical for glaucomatous damage," Experimental Neurology, vol. 246, pp. 54-61, Aug 2013.

[7] M. Pache and J. Flammer, "A sick eye in a sick body? Systemic findings in patients with primary open-angle glaucoma," Survey of Ophthalmology, vol. 51, pp. 179-212, May-Jun 2006.

[8] N. Gupta and Y. H. Yucel, "Glaucoma as a neurodegenerative disease," Current Opinion in Ophthalmology, vol. 18, pp. 110-114, Mar 2007.

[9] N. Gupta, L. C. Ang, L. N. de Tilly, L. Bidaisee, and Y. H. Yucel, "Human glaucoma and neural degeneration in intracranial optic nerve, lateral geniculate nucleus, and visual cortex," British Journal of Ophthalmology, vol. 90, pp. 674-678, Jun 2006.

[10] A. K. Zikou, G. Kitsos, L. C. Tzarouchi, L. Astrakas, G. A. Alexiou, and M. I. Argyropoulou, "Voxel-Based Morphometry and Diffusion Tensor Imaging of the Optic Pathway in Primary Open-Angle Glaucoma: A Preliminary Study," American Journal of Neuroradiology, vol. 33, pp. 128-134, Jan 2012.

[11] W. W. Chen, N. L. Wang, S. P. Cai, Z. J. Fang, M. Yu, Q. Z. Wu, et al., "Structural Brain Abnormalities in Patients with Primary Open-Angle Glaucoma: A Study with 3T MR Imaging," Investigative Ophthalmology & Visual Science, vol. 54, pp. 545-554, Jan 2013.

[12] C. Y. Li, P. Cai, L. P. Shi, Y. Lin, J. Q. Zhang, S. Q. Liu, et al., "Voxel-based Morphometry of the Visual-related Cortex in Primary Open Angle Glaucoma," Current Eye Research, vol. 37, pp. 794-802, Sep 2012.

[13] A. Miki, T. Nakajima, M. Takagi, M. Shirakashi, and H. Abe, "Detection of visual dysfunction in optic atrophy by functional magnetic resonance imaging during monocular visual stimulation," American Journal of Ophthalmology, vol. 122, pp. 404-415, Sep 1996.

[14] G. P. Qing, S. D. Zhang, B. Wang, and N. L. Wang, "Functional MRI Signal Changes in Primary Visual Cortex Corresponding to the Central Normal Visual Field of Patients with Primary Open-Angle Glaucoma," Investigative Ophthalmology & Visual Science, vol. 51, pp. 4627-4634, Sep 2010.

[15] M. D. Fox and M. E. Raichle, "Spontaneous fluctuations in brain activity observed with functional magnetic resonance imaging," Nature Reviews Neuroscience, vol. 8, pp. 700-711, Sep 2007.

[16] K. Wang, T. Jiang, C. S. Yu, L. X. T. J. Li, Y. Liu, Y. Zhou, et al., "Spontaneous activity associated with primary visual cortex: A resting-state fMRI study," Cerebral Cortex, vol. 18, pp. 697-704, Mar 2008.

[17] H. Dai, J. N. Morelli, F. Ai, D. Z. Yin, C. H. Hu, D. R. Xu, et al., "Resting-state functional MRI: Functional connectivity analysis of the visual cortex in primary open-angle glaucoma patients," Human Brain Mapping, vol. 34, pp. 2455-2463, Oct 2013.

[18] X. N. Zuo, A. Di Martino, C. Kelly, Z. E. Shehzad, D. G. Gee, D. F. Klein, et al., "The oscillating brain: Complex and reliable," Neuroimage, vol. 49, pp. 1432-1445, Jan 15 2010.

[19] N. K. Logothetis, J. Pauls, M. Augath, T. Trinath, and A. Oeltermann, "Neurophysiological investigation of the basis of the fMRI signal," Nature, vol. 412, pp. 150-157, Jul 12 2001.

[20] C. Fleming, E. P. Whitlock, T. Beil, B. Smit, and R. P. Harris, "Screening for primary open-angle, glaucoma in the primary care setting: An update for the US Preventive Services Task Force," Annals of Family Medicine, vol. 3, pp. 167-170, Mar-Apr 2005.

[21] Y. Chao-Gan and Z. Yu-Feng, "DPARSF: a MATLAB toolbox for "pipeline" data analysis of resting-state fMRI," Frontiers in systems neuroscience, vol. 4, 2010.

[22] H. Yang, X. Y. Long, Y. H. Yang, H. Yan, C. Z. Zhu, X. P. Zhou, et al., "Amplitude of low frequency fluctuation within visual areas revealed by resting-state functional MRI," Neuroimage, vol. 36, pp. 144-152, May 15 2007.

[23] Y. F. Zang, Y. He, C. Z. Zhu, Q. J. Cao, M. Q. Sui, M. Liang, et al., "Altered baseline brain activity in children with ADHD revealed by resting-state functional MRI," Brain & Development, vol. 29, pp. 83-91, Mar 2007.

[24] M. E. Raichle, A. M. MacLeod, A. Z. Snyder, W. J. Powers, D. A. Gusnard, and G. L. Shulman, "A default mode of brain function," Proceedings of the National Academy of Sciences of the United States of America, vol. 98, pp. 676-682, Jan 16 2001.

[25] M. A. Goodale and A. D. Milner, "Separate visual pathways for perception and action," Trends Neurosci, vol. 15, pp. 20-5, Jan 1992.

[26] Y. Song, K. Mu, J. Wang, F. Lin, Z. Chen, X. Yan, et al., "Altered spontaneous brain activity in primary open angle glaucoma: a resting-state functional magnetic resonance imaging study," PLoS One, vol. 9, p. e89493, 2014.

[27] K. C. Chan, K. F. So, and E. X. Wu, "Proton magnetic resonance spectroscopy revealed choline reduction in the visual cortex in an experimental model of chronic glaucoma," Exp Eye Res, vol. 88, pp. 65-70, Jan 2009.