Abnormal spontaneous brain activity in patients with non-arteritic anterior ischemic optic neuropathy detected using functional magnetic resonance imaging

Peng-De Guo[1], Peng-Bo Zhao[2], Han Lv[3], Feng-Yuan Man[4], Yan Su[2], Jing Zhao[1], Ming Liu[1], Yun-Xiang Chen[1], Yan Wang[1], Hai-Qin Hua[1], Ling-Ling Cai[5], Jian Zhou[2]

[1]Department of Radiology, Dongfang Hospital, Beijing University of Chinese Medicine, Beijing 100078, China;
[2]Department of Ophthalmology, Dongfang Hospital, Beijing University of Chinese Medicine, Beijing 100078, China;
[3]Department of Radiology, Beijing Friendship Hospital, Capital Medical University, Beijing 100050, China;
[4]Department of Radiology, The People's Liberation Army Rocket Force General Hospital, Beijing 100088, China;
[5]Dongfang Hospital, Beijing University of Chinese Medicine, Beijing 100078, China.

To the Editor: Non-arteritic anterior ischemic optic neuropathy (NAION), characterized by a sudden onset of unilateral painless visual loss and a swollen optic disc, is the most common form of acute optic neuropathy in patients over 50 years of age.[1] The pathogenesis of NAION remains unclear, but most histopathological studies support the concept of vasculopathic occlusion in the region of the short posterior ciliary arteries.[2] Functional magnetic resonance imaging (fMRI) is one of the most widely used non-invasive techniques for measuring brain function over time *in vivo*. To the best of our knowledge, only one study has investigated the effects of stimulating the affected eye in the extra-visual areas in NAION in humans.[3] However, this previous study only examined task-state fMRI, and lacked a measure of resting-state fMRI (rs-fMRI). Thus, it remains unclear whether regional spontaneous brain changes are limited to the visual system.

Thirty-one patients with NAION (20 males, 11 females, aged from 35 to 79 years, mean age 52.74 ± 11.29 years) and 31 normal controls (NCs) (20 males, 11 females, aged from 33 to 66 years, mean age 50.97 ± 8.20 years) matched in age and gender were enrolled in the study treated at Dongfang Hospital, Beijing University of Chinese Medicine between June 2015 and November 2017. Sixteen of the 31 patients exhibited unilateral NAION (eight in the left eye and eight in the right eye) with 15 patients exhibiting bilateral NAION (in both eyes, either sequentially or simultaneously). All NAION patients met the following criteria: (1) presenting with sudden, painless and monocular visual loss or successively bilateral visual loss; (2) receiving standardized treatment and evaluation in our hospital; (3) no history of hypertension, coronary artery disease, drug addiction, or sleep disorder; and (4) no contraindication from MRI scans, such as claustrophobia or irremovable metal in the body. All patients and NCs underwent eyesight testing, intraocular pressure measurement, optical coherence tomography (OCT) to measure retinal nerve fiber layer (RNFL) thickness, and visual field analysis.

All patients and NCs underwent MRI (1.5 Tesla, Philips Intera Achieva system, Royal Philips, Amsterdam, the Netherlands) while wearing a black blinder and sponge earplugs before hospital treatment. High-resolution structural images were obtained using a three-dimensional brain volume technique. Resting-state fMRI was obtained using an echo planar imaging pulse sequence with each scan: matrix 64 × 64, field of view 20 cm × 20 cm, slice thickness 3.6 mm, space between the slices 0.72 mm, number of excitations 1, repetition time/echo time 3000/30, flip angle 90°, 35 slices, dynamic scan 100 times, total scan time of 5.06 min. Subjects were asked to remain motionless with their eyes open, and not to think of anything specific during the scan, particularly during functional scans.

Resting state fMRI data were obtained using Data Processing Assistant for Resting-State fMRI (DPARSF) software (http://www.rfmri.org/DPARSF_V2_3), which is based on Statistical Parametric Mapping (SPM8), and the Resting-State fMRI Data Analysis Toolkit (REST) (http://www.rfmri.org/DPARSF_V2_3). Sequential preprocessing included removing the first 10 volumes for adapting to the scan environment and signal instability,

Access this article online

Quick Response Code:

Website: www.cmj.org

DOI: 10.1097/CM9.0000000000000134

Correspondence to: Prof. Jian Zhou, Department of Ophthalmology, Dongfang Hospital, Beijing University of Chinese Medicine, Beijing 100078, China
E-Mail: zhj9667@126.com

Chinese Medical Journal 2019;132(6)

Received: 25-10-2018 **Edited by:** Qiang Shi

slice timing and head motion correction. Any subjects with head motion >1.5 mm maximum displacement or rotation motion >1.5° in the *x*, *y*, or *z*-axis was excluded. Using these criteria, four patients were excluded. The remaining fMRI series was then spatially normalized for the purpose of ensuring dataset comparability at the group level and coregistered to standard stereotactic Montreal Neurological Institute (MNI) space (resampling voxel size, 3 mm × 3 mm × 3 mm).

After pre-processing, fMRI images were smoothed with a Gaussian kernel of 4 mm × 4 mm × 4 mm full-width at half maximum. To remove the effects of low-frequency drift, physiological high-frequency respiration, and cardiac noise, temporal bandpass filtering (0.01–0.08 Hz) and linear trend removal were performed on all pre-processed data. Individual amplitude of low-frequency fluctuation (ALFF) maps were generated for each data series.

REST was used for statistical analysis. Two-sample *t* tests were used for comparisons between patients and normal controls, with gender, age, and duration of disease as covariates of no interest. We corrected the significance level of multiple comparisons using a false discovery rate (FDR)-corrected threshold of $P < 0.05$ for analysis of differences between NAION patients and NCs. The results were presented using Xjview toolbox (http:www.alivelearn.net/xjview) and REST software. Finally, Pearson correlation analyses were performed using SPSS 17.0 software (SPSS, Inc., Chicago, IL, USA) to explore the correlation between abnormal ALFF values and clinical parameters.

Compared with NCs, NAION patients showed lower ALFF values in the right insula, right inferior frontal gyrus and bilateral middle frontal gyrus, and higher ALFF values in the right precuneus [Supplementary Table 1, http://links.lww.com/CM9/A18 and Figure 1A]. In NAION patients, the ALFF values in the right middle frontal gyrus were positively correlated with right RNFL values ($r = 0.42$, $P = 0.02$) [Figure 1B].

The default mode network (DMN) is comprised of medial prefrontal cortex (ventral medial prefrontal cortex and anterior cingulate cortex), medial parietal cortex (posterior cingulate), precuneus, lateral temporal parietal cortex (superior gyrus, angular gyrus, and superior temporal sulcus), parahippocampal gyrus and hippocampal formation.[4] The DMN plays a key role in many brain functional networks, and DMN activity is negatively correlated with many brain functions, such as vision, hearing, and somatesthesia. In addition, the DMN is believed to be closely associated with a range of phenomena, such as anxiety, cognition, memory, and depression. The DMN in the brain is active, with high metabolic rates during the resting-state condition. In patients with glaucoma, Liu and Tian[5] reported abnormal activity in the right medial frontal gyrus. Furthermore, patients with optic neuritis were found to have lower ALFF values in the medial frontal gyrus, bilateral medial frontal gyrus/anterior cingulate.[6] Based on these findings, it has been proposed that optic neuritis may lead to DMN damage. In the present study, we found that, compared with NCs, patients with NAION had lower ALFF values in the right insula, right inferior frontal gyrus, and bilateral middle frontal gyrus, but higher ALFF values in the right precuneus. As an important feature of rs-fMRI, ALFF provides more information to aid the understanding the NAION-related functional reorganization. Rather than examining each individual area, the brain is examined as a whole entity, recognizing that damage in one region may lead to dysfunction in other brain regions. Therefore, the decreased ALFF values in the present study indicate that NAION may lead to DMN dysfunction, whereas increased ALFF values in the right precuneus may reflect compensation to maintain the stability of the internal network.

A previous study reported that the inferior frontal gyrus plays an important role in audiovisual communication.[7] In another study, patients with advanced primary open-angle glaucoma were found to exhibit decreased blood-oxygen-level dependent (BOLD) values in inferior frontal gyrus.[8] In the present study, we found that patients with NAION exhibited lower ALFF values in right inferior

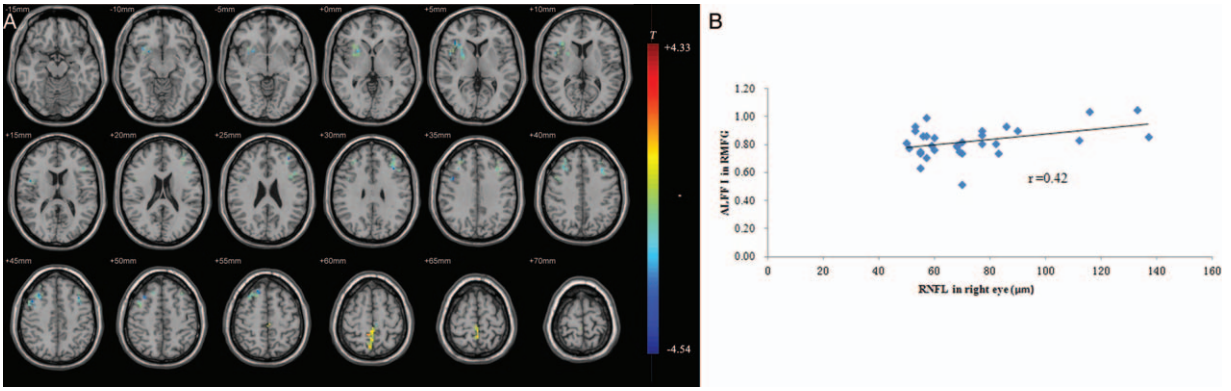

Figure 1: (A) Altered ALFF in NAION patients in comparison with normal controls. Compared with NCs, the ALFF in patients with NAION were lower in the right insula, right inferior frontal gyrus, bilateral middle frontal gyrus and higher ALFF value in the right precuneus. (B) Correlations between the RNFL in the right eye and ALFF values in right middle frontal gyrus ($n = 31$; $r = 0.42$, $P = 0.02$). ALFF: Amplitude of low-frequency fluctuation; NAION: Non-arteritic anterior ischemic optic neuropathy; NCs: Normal controls; *r*: Pearson correlation coefficient; RMFG: Right middle frontal gyrus; RNFL: Retinal nerve fiber layer.

frontal gyrus, which may reflect functional damage in these regions.

Furthermore, the precuneus plays a pivotal role in the DMN. Recent fMRI studies in healthy subjects have suggested a central role for the precuneus in a wide spectrum of highly integrated tasks, including visuospatial imagery, spatial awareness, and consciousness.[9] A previous study reported significant increases in precuneus activation in a patient with advanced primary open-angle glaucoma.[8] In addition, strong interactions between the precuneus/posterior cingulate region and the left inferior parietal lobe with DMN have been reported.[10] Consistent with these findings, in the present study, we found that activity in the right precuneus was significantly increased in NAION patients compared with NCs, indicating alterations of the DMN in NAION patients. Therefore, increased ALFF values in the precuneus, as part of the DMN, may also reflect a type of spatial vision enhancement in NAION patients, which in turn enhances the processing capability of visual space.

In addition, the middle prefrontal cortex also is a subsystem of the DMN, which is involved in the self-relevant mental simulation. In the present study, we observed some areas exhibiting lower ALFF values in bilateral middle frontal gyrus in NAION patients compared with NCs. Furthermore, ALFF values in the right middle frontal gyrus exhibited a positive correlation with right RNFL values. This finding suggests that NAION may involve substantial damage to the middle frontal gyrus. Thus, homolateral RNFL in the middle frontal gyrus may provide a useful index, providing insight into the neural mechanisms underlying NAION.

In conclusion, the current study revealed that patients with NAION exhibited abnormalities in spontaneous brain activity, including a positive correlation with homolateral RNFL. These findings indicated that NAION may affect the hub position of the brain functional network-DMN. The current results provide potentially important information for improving our understanding of the inherent neural mechanisms underlying NAION.

Declaration of patient consent

The authors certify that they have obtained all appropriate patient consent forms. In the form the patients have given their consent for their images and other clinical information to be reported in the journal. The patients understand that their names and initials will not be published and due efforts will be made to conceal their identity, but anonymity cannot be guaranteed.

Funding

The work was supported by grants from the Basic Scientific Research Program from Beijing University of Chinese Medicine (No. 2015-JYB-JSMS107) and the Capital Characteristic Clinical Project (No. Z171100001017206).

Conflicts of interest

None.

References

1. Biousse V, Newman NJ. Ischemic optic neuropathies. N Engl J Med 2015;372:2428–2436. doi: 10.1056/NEJMra1413352.
2. Knox DL, Kerrison JB, Green WR. Histopathologic studies of ischemic optic neuropathy. Trans Am Ophthalmol Soc 2000;98:203–220. discussion 221–222.
3. Aguirregomozcorta M, Mancini L, Jenkins TM, Hickman SJ, Ciccarelli O, Plant GT, *et al*. A longitudinal functional MRI study of non-arteritic anterior ischaemic optic neuropathy patients. J Neurol Neurosurg Psychiatry 2011;82:905–913. doi: 10.1136/jnnp.2009.194563.
4. Andrews-Hanna JR, Reidler JS, Sepulcre J, Poulin R, Buckner RL. Functional-anatomic fractionation of the brain's default network. Neuron 2010;65:550–562. doi: 10.1016/j.neuron.2010.02.005.
5. Liu Z, Tian J. Amplitude of low frequency fluctuation in primary open angle glaucoma: a resting state fMRI study. Conf Proc IEEE Eng Med Biol Soc 2014;2014:6706–6709. doi: 10.1109/EMBC.2014.6945167.
6. Huang X, Cai FQ, Hu PH, Zhong YL, Zhang Y, Wei R, *et al*. Disturbed spontaneous brain-activity pattern in patients with optic neuritis using amplitude of low-frequency fluctuation: a functional magnetic resonance imaging study. Neuropsychiatr Dis Treat 2015;11:3075–3083. doi: 10.2147/NDT.S92497.
7. Plakke B, Hwang J, Romanski LM. Inactivation of primate prefrontal cortex impairs auditory and audiovisual working memory. J Neurosci 2015;35:9666–9675. doi: 10.1523/JNEUROSCI.1218-15.2015.
8. Chen WW, Wang N, Cai S, Fang Z, Yu M, Wu Q, *et al*. Structural brain abnormalities in patients with primary open-angle glaucoma: a study with 3T MR imaging. Invest Ophthalmol Vis Sci 2013;54:545–554. doi: 10.1167/iovs.12-9893.
9. Mailo J, Tang-Wai R. Insight into the precuneus: a novel seizure semiology in a child with epilepsy arising from the right posterior precuneus. Epileptic Disord 2015;17:321–327. doi: 10.1684/epd.2015.0759.
10. Fransson P, Marrelec G. The precuneus/posterior cingulate cortex plays a pivotal role in the default mode network: Evidence from a partial correlation network analysis. Neuroimage 2008;42:1178–1184. doi: 10.1016/j.neuroimage.2008.05.059.

How to cite this article: Guo PD, Zhao PB, Lv H, Man FY, Su Y, Zhao J, Liu M, Chen YX, Wang Y, Hua HQ, Cai LL, Zhou J. Abnormal spontaneous brain activity in patients with non-arteritic anterior ischemic optic neuropathy detected using functional magnetic resonance imaging. Chin Med J 2019;132:741–743. doi: 10.1097/CM9.0000000000000134