Behavioural Brain Research 303 (2016) 85–92

Contents lists available at ScienceDirect

Behavioural Brain Research

journal homepage: www.elsevier.com/locate/bbr

Research report

Altered functional connectivity density in high myopia

Liying Zhai[a], Qian Li[b], Tianyue Wang[a], HongHuan Dong[c], Yanmin Peng[a], Mingxia Guo[a,*], Wen Qin[d], Chunshui Yu[a,d]

[a] School of Medical Imaging, Tianjin Medical University, Tianjin 300203, PR China
[b] Department of Radiology, Tianjin Medical University Cancer Institute and Hospital, National Clinical Research Center of Cancer, Key Laboratory of Cancer Prevention and Therapy, Tianjin 300060, PR China
[c] Department of Magnetic Resonance, Cangzhou Central Hospital, Hebei 061001, PR China
[d] Department of Radiology, Tianjin Medical University General Hospital, Tianjin 300052, PR China

HIGHLIGHTS

- Resting-state FC changes in HM were first detected by FCD mapping and FC analysis.
- HM showed reduced FCD in attention-related areas in PCC/preCun, ITG, SMG and rlPFC.
- HM showed reduced FC between the right SMG and right rlPFC.
- HM showed reduced FC between ventral attention and frontoparietal control networks.

ARTICLE INFO

Article history:
Received 4 December 2015
Received in revised form 16 January 2016
Accepted 20 January 2016
Available online 22 January 2016

Keywords:
Functional magnetic resonance imaging
Functional connectivity density
High myopia
Attention
Rostrolateral prefrontal cortex

ABSTRACT

Abnormal visual experience can affect the brain structure and function. Visual functional performances of high myopia (HM) individuals were observed to be abnormal in contrast to emmetropics, even with a corrected visual acuity. Attention deficits and brain morphological changes have been revealed in the HM, but it is unknown whether there are functional connectivity (FC) alterations. The current study combined the resting-state functional connectivity density (FCD) mapping and seed-based correlation analysis to investigate FC alterations in the brain of HM. In our results, the HM exhibited decreased short- and long-range FCD in the posterior cingulate cortex/precuneus and decreased long-range FCD in the inferior temporal gyrus, supramarginal gyrus and rostrolateral prefrontal cortex. Specially, long-range FCD in the rostrolateral prefrontal cortex showed a significant positive correlation with the uncorrected visual acuity in the HM. Moreover, the HM showed significantly decreased FC not only between the supramarginal gyrus and rostrolateral prefrontal cortex, but also between networks they belong to, the ventral attention and frontoparietal control networks. These results provide evidence for the FC changes in the HM and may help to understand the attention deficits in myopes.

1. Introduction

High myopia (HM), defined as a spherical equivalent equal or less than −6 diopters, is an important public health issue. Globally, HM affects 2.9% of the world's population [1] and its prevalence has increased over the past few decades, especially in the Asia, where HM ranges from 6.3 to 38% [2–5]. Long-term HM can lead to fundus changes [6] and deficits in visual function performance [7], which has been studied extensively. However, little is known about the influence of HM on the brain neural activity.

Previous neuroimaging studies have revealed that structural and functional brain changes not only existed in neuropsychiatric diseases [8,9], but also in diseases with long-term abnormal sensory input [10–15]. Such as in hearing disorders [16,17] and amblyopia [15,18], gray matter reductions were reported. Further studies on amblyopia also detected abnormal functional connectivity (FC) between visual cortex and high-level regions, which indicates a noteworthy impact of abnormal visual experience on the neural

Abbreviations: HM, high myopia; NC, normal controls; fMRI, functional magnetic resonance imaging; FCD, functional connectivity density; FC, functional connectivity; ROI, region of interest; FD, frame-wise displacement; ES, effect size; PCC, posterior cingulate cortex; preCun, precuneus; ITG, inferior temporal gyrus; SMG, supramarginal gyrus; rlPFC, rostrolateral prefrontal cortex; VAN, ventral attention network; FPCN, frontoparietal control network; DMN, default mode network.

* Corresponding author at: School of Medical Imaging, Tianjin Medical University, No. 1, Guangdong Road, Hexi District, Tianjin 300203, PR China.
E-mail address: guomx11@163.com (M. Guo).

http://dx.doi.org/10.1016/j.bbr.2016.01.046
0166-4328/

Table 1
Visual acuity of subjects.

	Left[a]	Right[a]	*t*	*P* value
High myopia (uncorrected)	0.10 ± 0.09	0.10 ± 0.09	0.54	0.59
High myopia (corrected)	1.04 ± 0.08	1.03 ± 0.07	0.57	0.57
Normal controls	1.29 ± 0.32	1.28 ± 0.33	0.13	0.90

[a] Visual acuity was obtained in decimal fractions.

activity of the brain [19,20]. Although with a corrected visual acuity, functional performances of myopic eye, such as contrast sensitivity [21], resolution acuity [22], and even visual attention [23,24], are abnormal in contrast to emmetropics. Thus, it can be inferred that long period of myopic vision may result in changes of brain neural activity in HM as well. Actually, our previous study has shown white matter changes in HM, which occurred not only in visual regions but also in some parietal and frontal areas [25]. Nevertheless, there is not any neuroimaging study about the functional changes in the brain of HM.

Functional connectivity density (FCD) mapping [26,27] is a voxelwise data-driven method which can measure the amount of functional connections between brain regions and it allows the identification of hub regions that play important roles in information processing [26]. Based on the hub regions, FC analysis can be further performed to get insight into the functional organization of the brain. Thus, in this study FCD mapping was used to identify regions with FCD changes in HM and seed-based correlation analysis was performed on those regions to investigate FC changes for further network analysis. Moreover, gray matter volume was also investigated based on the regions showing FCD alterations.

2. Materials and methods

2.1. Subjects

Fifty-nine right-handed students from Tianjin Medical University were recruited for this study and 27 of them were HM (5 males/22 females; range = 21–25 years) with a spherical equivalent ≤ -6.00 diopters. The remaining 32 were emmetropics taken as normal controls (NC, 14 males/18 females; range = 18–25 years). There was no significant difference in age (HM: 23.22 ± 1.34 years versus NC: 22.75 ± 1.72 years; two-sample two tailed *t*-test, $t = 1.16$, $P = 0.25$) or education level (HM: 16.11 ± 1.37 years versus NC: 16.44 ± 1.52 years; two-sample two tailed *t*-test, $t = -0.87$, $P = 0.39$) between the HM and NC groups. Furthermore, visual acuity of the two eyes showed no significant difference within each group (Table 1). Whereas there was significant group difference in uncorrected visual acuity (HM: 0.10 ± 0.09 versus NC: 1.28 ± 0.30; two-sample two tailed *t*-test, $t = 37.60$, $P < 0.001$). In the HM group, the onset age of myopia was no less than 9 years old. They were confirmed to have no other ocular treatments but corrective lenses. All participants were free from neurological diseases and ocular illness. They provided written informed consent prior to participation and the protocol was under the ethics committee of Tianjin Medical University.

2.2. MR imaging

All images were acquired using a Signa HDx 1.5 T MR scanner (GE Medical Systems) in Tianjin Medical University General Hospital. During the scans, there was no light in the room and subjects were instructed to remain stable, to keep their eyes open without wearing glasses or contact lenses and not to think of anything in particular. Resting-state functional magnetic resonance imaging (fMRI) data were obtained using gradient-echo echo-planar imaging (GRE-EPI) sequences with following parameters: repetition time (TR) = 2000 ms, echo time (TE) = 60 ms, flip angle = 90°, matrix = 64 × 64, field of view (FOV) = 22 × 22 cm^2, slice thickness = 5 mm, slice gap = 1 mm, scanning time was 6 min 8 s. Structural images included a T1-weighted 3-dimension spoiled gradient-recalled echo (SPGR) scan: TR = 8.6 ms, TE = 1.8 ms, flip angle = 20°, matrix = 256 × 224, FOV = 24 × 24 cm^2, slice thickness = 1 mm, slice gap = 0, scanning time was 5 min 38 s.

2.3. fMRI data preprocessing

fMRI data were preprocessed using Data Processing Assistant for Resting-State fMRI (DPARSF, http://www.restfmri.net) in Matlab (Math Works Inc., Natick, MA, USA). For the preprocessing of FCD, the first four volumes of each subject were discarded for magnetization equilibrium. The remaining data were corrected for slice timing and realigned to the first volume to correct for head motion. Subject movement was determined to assure head motion of less than 2 mm translations and 2° rotations. Besides, frame-wise displacement (FD) [28] was also calculated as an index of head motion. It summarizes instantaneous changes in head motion. Subjects were excluded if their FD exceeded 0.3. Afterwards, the realigned data were normalized to the standard EPI template and resampled to a voxel size of $3 \times 3 \times 3$ mm^3. Motion-related fluctuations were regressed out from the data using the six realignment parameters. Then, band-pass filtering (0.01–0.08 Hz) was performed on the datasets to reduce the effect of low-frequency drifts and high-frequency physiological noise. For preprocessing of the resting-state FC, the difference was that images were smoothed with a Gaussian kernel of $6 \times 6 \times 6$ mm^3 after spatial normalization. In this study, all subjects were within the limits of head motion.

2.4. Resting-state FCD calculation

According to the method proposed by Tomasi and Volkow [26,27], an in-house script written on Linux platform was used to compute resting-state FCD. Voxels with a signal-to-noise ratio of less than 50 in gray matter regions were not considered in this calculation, aiming to minimize unwanted effects from signal loss artifacts produced near air/tissue interfaces. Pearson's linear correlation was applied to calculate FC. Two voxels with correlation coefficient of $r > 0.6$ were considered functionally connected. For a given voxel x_0, global FCD was defined as the number of significant functional connections that between x_0 and other voxels within the whole brain. For the short-range FCD of x_0, it refers to the number of elements between x_0 and its neighbor voxels. As described by Tomasi and Volkow [27], the long-range FCD was equal to the difference between the global FCD and short-range FCD. To account for the effect of variability across participants, the short- and long-range FCD maps of each individual were scaled by their average strength in the whole brain, respectively. Finally, a Gaussian kernel of $6 \times 6 \times 6$ mm^3 was performed to spatially smooth the normalized FCD data.

2.5. Statistical analysis for FCD

We first estimated spatial distribution of mean short- and long-range FCD in the HM group and NC group, respectively. Then, between-group comparisons of the resting-state FCD were performed in the Statistical Parametric Mapping (SPM8, http://www.fil.ion.ucl.ac.uk/spm/software/spm8/) using general linear model (GLM) analysis, with age, gender and averaged FD included as nuisance covariates. A correction for multiple comparisons was performed by a Monte Carlo simulation, resulting in a corrected threshold of $P < 0.01$ and minimum cluster size of 42 voxels (AlphaSim program with following parameters: single voxel *P* value of 0.01, 5000 simulations, cluster connection radius $r = 5$ mm, full