Single Center to Evaluate and Compare Anisometropic Amblyopia in Adults Using Blood Oxygenation Level-Dependent Functional Magnetic Resonance Imaging and Diffusion Kurtosis Imaging

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Background: Anisometric amblyopia results from the unequal ability to focus between the right and left eyes. Blood oxygenation level-dependent functional magnetic resonance imaging (BOLD-fMRI) measures the proportion of oxygenated hemoglobin in specific areas. Diffusion kurtosis imaging (DKI) is a method of diffusion tensor imaging that estimates the skewed distribution of water diffusion probability. We aimed to evaluate and compare 11 adult patients with anisometric amblyopia (AA) with 13 normally sighted healthy controls (HC) using BOLD-fMRI and DKI.

Material/Methods: Eleven adults with AA (age range 20-49; mean age 29.18±8.089) and 13 HC adults (age range 22-50; mean age 28.00±5.79) were recruited. DKI scanning used a single excitation echo-planar imaging sequence and a region of interest to obtain DKI parameters for optic radiation; the corpus callosum was manually placed, including mean kurtosis (MK), fractional anisotropic (FA), and mean diffusivity (MD) values; and BOLD data used a gradient-echo echo-planar imaging sequence.

Results: The AA group had lower MK and FA of bilateral optic radiation than the HC group (P=0.008 and P=0.006, respectively) and higher MD than the HC group (P=0.005). The MK of the corpus callosum in the AA group was lower than that of HC group (P=0.012). Compared with the non-dominant eyes of the HC group, the amblyopic eyes in the AA group had less activation range and intensity in Brodmann areas 17, 18, and 19.

Conclusions: The combined use of DKI and BOLD-fMRI detected microstructural changes associated with local visual pathways and identified damage to the visual cortex in patients with amblyopia.

Keywords: Amblyopia • Anisometropia • Magnetic Resonance Imaging

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**Background**

Amblyopia is a visual development disease which is caused by interference, deprivation, and inhibition during the visual development period in one or both eyes. When investigating the physiological mechanisms associated with this disease, in addition to eye abnormalities, abnormal neural activities in specific brain regions were also detected in patients with amblyopia [1,2]. Anisotropic amblyopia is when the dioptric power of the right and left eyes is different (spherical equivalent difference ≥2.00D), and due to images of objects forming with different resolution or size in the retina, the images of the 2 eyes cannot be merged into 1 object image. Therefore, the image of the eye with a larger diopter is actively suppressed by the center of the cortex, resulting in amblyopia [3]. Anisotropic amblyopia is more common and severe in hyperopic anisometropia cases than is myopic anisometropia [4]. If patients with anisometric amblyopia can detect amblyopia in time and correct their vision, the prognosis is good; however, it is more common that such amblyopia often has delayed treatment due to good monocular vision. Animal experiments and functional magnetic resonance imaging (fMRI) have confirmed the presence of historical changes in the hypothalamus in patients with amblyopia [5,6]. Li et al pointed out the decrease of brain-derived neurotropic factor in the lateral geniculate body in kittens with form-deprivation amblyopia [5]. Dai et al found that the amplitude of low-frequency fluctuation of resting state functional magnetic resonance imaging (rs-fMRI) in the bilateral frontal, temporal, and occipital lobes in children with monocular amblyopia was lower than that in the healthy control group. The weakened primary visual cortex functional connectivity was mainly concentrated in the frontal lobe and angular gyrus [7]. In summary, it was found that patients with amblyopia can have abnormalities from the lateral pathway to the visual center.

Diffusion kurtosis imaging (DKI), as a straightforward extension of diffusion-weighted imaging and diffusion tensor imaging techniques, can sensitively detect changes in the microstructure of tissues and provide better diffusion characteristics for nerve tissues (white matter and gray matter), regardless of normal or pathological conditions [8,9]. The technology of DKI was developed after the recognition that the diffusion distribution of water molecules in tissues is an abnormal distribution and after the application of fourth-order tensors to the transformation process of magnetic resonance imaging. DKI can quantify the displacement deviation between the real water molecule diffusion and the ideal, normal distribution diffusion; characterize the limited degree of water molecule diffusion and the inhomogeneity of diffusion; and can more sensitively detect changes in tissue microstructure [10]. Song et al recruited 8 patients with anisometric amblyopia and 15 healthy participants and found significant decreases in the fractional anisotropy (FA) values and the voxel numbers of optic radiations, which suggested that the visual radiation (especially the posterior visual radiation) of patients with anisotropic amblyopia has dysplasia, and that its integrity, compactness, and directionality are reduced [11]. However, so far, DKI technology has not been applied to the study of brain structure in adult patients with anisotropic amblyopia.

Blood oxygenation level-dependent functional magnetic resonance imaging (BOLD-fMRI) technology can detect changes in the blood oxygen content of neuronal activity areas. It infers with neuron activity indirectly by detecting changes in blood oxygenation in the area of neuron activity.

The basic principle is that the influence of neuronal activity on local cerebral blood flow and oxygen consumption does not match, which can cause changes in the concentration of deoxyhemoglobin near the active cortex and result in changes in magnetic resonance signals [12]. BOLD-fMRI can perform functional imaging of brain tissue and observe specific functional changes in a certain part of the brain. In terms of amblyopia research, BOLD-fMRI technology can indicate the characteristics of amblyopia damage at the overall level and locate the visual cortex directly, thereby inferring the function abnormality of amblyopia from the cortical aspect [13,14]. It has been proven that cortical damage in patients with amblyopia is not limited to the primary and higher visual cortex, but that patients with amblyopia also have optic radiation and structural abnormalities of the white matter neural network in multiple vision-related brain regions [15].

Therefore, this study from a single center aimed to evaluate and compare 11 adult patients with anisotropic amblyopia with 13 normally sighted adults using the techniques of BOLD-fMRI and DKI.

**Material and Methods**

**Participants**

This study was approved by the Ethics Committee of the First Affiliated Hospital of Jinan University (approval no. [2015] Ethics Approval Section 061). The study observed the tenets of the Declaration of Helsinki, and informed consent for participation was obtained prior to the start of the study. All questions and concerns were addressed before the consent forms were signed. In this study, the participants were adults recruited from the Ophthalmology Department of the First Affiliated Hospital of Jinan University. Eleven adults with anisotropic amblyopia (AA group; 4 men, 7 women; age range, 20 to 49 years; mean age 29.18±8.08 years) and 13 normally sighted adults (HC group; 5 men, 8 women; age range, 22 to 50 years; mean age 28.00±5.79 years) were recruited in this study. Amblyopia was
defined as the best corrected visual acuity difference of more than 2 logarithms of the minimum angle of resolution lines between the 2 eyes. All patients had myopic anisometropic amblyopia, defined as a spherical equivalent difference of the 2 eyes of more than 2 diopter (D). The age of the healthy group was matched with the patient group, and inclusion criteria was defined as best corrected visual acuity of each eye at least 0.0 logarithms of the minimum angle of resolution. All participants underwent a complete ophthalmologic examination, and none showed signs of strabismus or other organic disease. The general information of patients with amblyopia is shown in Table 1.

### MRI Data Acquisition

**Imaging Equipment and Parameters**

fMRI was performed on a 3.0-Tesla MR scanner (General Electric, USA) with 8-channel phased-array head coils within 1 week after the eye examination. T1-weighted images were bias-corrected and segmented into grey matter, white matter, and cerebrospinal fluid, and then affine normalized to MNI space. Tissue class images were then non-linearly normalized using the high-dimensional diffeomorphic anatomical registration through exponentiated Lie Algebra (DARTEL) algorithm to study-specific templates created by DARTEL. The transformation matrix was then applied for fMRI maps. Mean modulated and smoothed grey matter maps were used to generate a group grey matter mask and applied as a mask for analyzing functional differences in between-group comparisons.

The scan parameters were as follows: (1) Whole brain anatomy image scan: 3DT1BRAVO sequence, repetition time (TR) 8.2 ms, echo time (TE) 3.2 ms, flip angle 12°, matrix 256×256, number of excitations (NEX) 1.0, layer thickness 1.2 mm, layer spacing 0, and field of view (FOV) 24 cm; (2) DKI scanning adopted excitation echo-planar imaging (EPI) sequence, TR 5000 ms, TE 98 ms, matrix 128×128, FOV 24, NEX 2.0, layer thickness 4.0 mm, layer spacing 0, applying dispersion gradient in 75 directions, b=2500 s/mm², and scan time 13 min 25 s; and (3) BOLD data adopted gradient-echo echo-planar imaging (GRE-EPI) sequence, TR 2000 ms, TE 35 ms, flip angle 90°, matrix 64×64, NEX 1.0, layer thickness 3 mm, layer spacing 1 mm, and FOV 24.

**Data Processing of DKI**

The data were transferred to the AW45-2 post-processing workstation and processed by Functool processing software. The delineation and measurement of regions of interest (ROI) referred to classic neuroanatomical descriptions and related literature reports. The ROI was a circle with a diameter of 3.0 mm. The

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**Table 1. General information of amblyopia patients.**

| No. | Gender | Age | VA (logMAR) | Diopter | BCVA (logMAR) | Amblyopia eye |
|-----|--------|-----|-------------|---------|---------------|---------------|
|     |        |     | Right       | Left    | Right         | Left          |               |
| 1   | Male   | 23  | -0.1        | 1.0     | PL            | +5.50D/-1.00D*20° | -0.1          | 0.4           | Left          |
| 2   | Female | 20  | 0.7         | 1.2     | -3.00D        | -4.00D/-4.00D*175° | 0.0           | 0.3           | Left          |
| 3   | Male   | 26  | 0.7         | 0.5     | -3.50D/-0.25D*40° | +0.50D*90°      | -0.1          | 0.5           | Left          |
| 4   | Female | 26  | 0.1         | 0.7     | -1.00D        | +4.50D         | -0.1          | 0.7           | Left          |
| 5   | Male   | 38  | 0.0         | 0.4     | -1.00D        | +3.75D         | -0.2          | 0.2           | Left          |
| 6   | Female | 29  | -0.2        | 1.0     | PL            | +4.50D         | -0.2          | 0.2           | Left          |
| 7   | Female | 28  | 1.2         | 0.1     | +8.50D        | +1.75D/+0.50D*125° | 0.7           | 0.0           | Right         |
| 8   | Female | 29  | 1.4         | 0.7     | -13.00D/-3.50D*25° | -6.50D/2.55D*5° | 0.2           | 0.0           | Right         |
| 9   | Male   | 23  | 0.7         | 0.2     | +5.00D        | -1.00D         | 0.3           | 0.0           | Right         |
| 10  | Female | 49  | 1.0         | 0.2     | +4.50D/-1.25D*115° | +1.25D         | 0.7           | -0.1          | Right         |
| 11  | Female | 30  | 0.7         | -0.1    | -0.75D        | +0.50D/-0.75D*106° | 0.2           | -0.1          | Right         |

VA – visual acuity; BCVA – best correct visual acuity; PL – plano lens; D – diopter.
software can measure the mean kurtosis (MK), fractional anisotropic (FA), and mean diffusivity (MD) values in the corresponding ROI. The optic radiation ROI was chosen to be the optic radiation that runs along the triangle of the lateral ventricle, measured 3 times in 3 consecutive levels, and the average value was selected; the ROI of the corpus callosum was selected at the basal ganglia level, and the bilateral symmetry of the knees and compressions of the corpus callosum was taken, respectively. When selecting the ROI, it was necessary to avoid the surrounding gray matter and cerebrospinal fluid as much as possible.

Data Processing of BOLD

fMRI data preprocessing was performed using SPM8 (http://www.fil.ion.ucl.ac.uk/spm). First, all functional images were corrected for slice timing as well as head movement. Participants with excessive head movement >1.5 mm of displacement or >1.5 of rotation in any direction were discarded. A high-pass filter with a cut-off of 128 s was applied to remove low-frequency temporal drifts, normalized to the MNI template and spatially smoothed with an isotropic Gaussian kernel of 4-mm full-width half-maximum.

Data Analysis

DKI Statistical Analysis

SPSS26.0 statistical software was used for data analysis. The MK value, FA value, and MD value of the white matter of each group are expressed as mean±standard deviation. The paired t test was performed to compare the difference of optic radiation MK, FA, and MD between the left and right sides in the HC group and the amblyopic side and the normal side in the AA group. The difference of MK value, FA value, and MD value in the same part of the HC group and the anisometropic AA group were analyzed and evaluated by 2-sample t tests. P<0.05 was considered statistically significant.

BOLD Statistical Analysis

The comparison of the activation range and intensity of the amblyopic eye in the AA group and the non-dominant eye of the normal group, and the comparison of the activation range and intensity of the non-amblyopia eye in the AA group and the dominant eye of the normal group were done with 2-sample t tests in the Statistical Parametric Mapping software version 8 (SPM8) basic model to obtain the intergroup difference. The threshold of the activation range was set to 10 pixels and the number of activated pixels in the cerebral cortex represented the activation range. The statistical value t of the t test represented the activation intensity, and the larger the t value, the higher the activation intensity.

Results

DKI Results

Comparison of Visual Radiation on Both Sides of AA Group and AA Group

In the HC group, there was no statistical difference in the MK, FA, and MD values of the bilateral vision radiation. The same results were also shown in the AA group (Figure 1).
Comparison of Bilateral Visual Radiation Between the HC Group and AA Group

The MK and FA values of the bilateral optic radiation in the AA group were significantly lower than those in the HC group ($P=0.008$, $P=0.006$, respectively); the MD value was increased compared with that of the HC group ($P=0.003$) (Table 2, Figure 2).

Comparison of Corpus Callosum Between HC Group and AA Group

In the genu of the corpus callosum, there was no significant difference in the MK, FA, and MD values between the AA group and HC group. In the splenium of the corpus callosum, the MK value in the AA group was significantly lower than that of the HC group ($P=0.012$); however, there was no significant difference in the FA and MD values, compared with the HC group (Table 2, Figure 2).

Results of BOLD-fMRI Stimulation

Brain Activation Area in the HC Group and AA Group

In our study, patients with anisometric amblyopia and healthy control participants had extensively activated bilateral visual regions and bilateral limbic lobes (Figure 3). The most obvious area of dominant eye activation was located in Brodmann 17, namely the cuneiform lobe and lingual gyrus. In addition, the middle occipital gyrus, precuneus cortex, fusiform gyrus, superior frontal gyrus, middle frontal gyrus, middle temporal gyrus, inferior temporal gyrus, posterior parietal gyrus, and other areas had different degrees of activation.

Table 2. Comparison of MK, FA and MD values of optic radiation and corpus callosum between anisotropic amblyopia group and healthy control group.

Changes in the Brain Activation Area Between the Amblyopic Eyes in the AA Group and the Non-Dominant Eye in the HC Group

Compared with the non-dominant eye in the HC group, the activation intensity of the Brodmann 17, 18, and 19 areas of the amblyopic eye in the AA group were all reduced, and the differences in the 18 and 19 areas were more significant (see Table 3). The brain areas lower than the HC group were mainly located in the middle occipital gyrus, tongue gyrus, cuneiform lobe, middle temporal gyrus, and superior frontal gyrus (Figure 4).

Changes in the Brain Activation Area Between the Non-Amblyopic Eyes in the AA Group and the Dominant Eye in the HC Group

Compared with that of the dominant eyes of the HC group, the activation intensity of Brodmann 17 and 18 areas of the normal eye in the AA group were reduced, and the reduction in area 18 was more obvious (Table 4). The brain areas that were lower than the HC group were mainly in the lingual gyrus and cuneiform lobe (Figure 5).

Discussion

In our study, we found that the MK values of bilateral visual radiation and the corpus callosum in patients with anisometric amblyopia were lower than those of healthy controls. The activation range and intensity of fMRI visual stimulation were reduced in patients with anisometric amblyopia, both the extrastriate cortex and striated cortex were affected, and the extrastriate cortex was more damaged.
Brain Structure Changes in Patients with Anisometropic Amblyopia

Relationship Between Abnormal Optic Radiation and Anisometropic Amblyopia

This study used DKI technology to study the development of optic radiation, and the results showed that the bilateral optic radiation MK and FA values of the AA group were lower than those of the HC group, and the MD value was increased compared with that of the HC group. This indicates that the microstructure complexity of bilateral visual radiation in patients with anisometropic amblyopia may decrease, which may be related to the changes in the density, direction, myelin sheath, and other aspects of the visual radiation fiber. In previous studies [16,17], it was confirmed that the cells of the lateral geniculate body of amblyopia are shrunken and their function is impaired and that optic radiation is composed of fibers emitted after the lateral geniculate body. Therefore, the optic radiation of patients with amblyopia may have dysplasia and abnormal fiber projection, which reduces its complexity.

Animal models have proven that staying in the dark will delay the myelination of the optic nerve, and researchers speculate that the process of myelination may be related to light stimulation [18]. The transmission of visual information in patients...
Figure 3. Analysis activation diagram of irritation group of amblyopia eye in amblyopia group, surface, sagittal, coronal, cross-sectional view. Brodmann 17, 18, 19 area activation and vitreous brain activation map.

Table 3. The stimulus activation map of the non-dominant eye in the healthy control group and amblyopic eye in the amblyopia group.

| Cluster | Number of pixels | Activate areas                  | BA partition | T     | MNI coordinates |
|---------|------------------|--------------------------------|--------------|-------|-----------------|
| 1       | 1573             | Right middle occipital gyrus   | 19           | 42.16 | 58 -74 -2       |
| 2       | 256              | Middle occipital gyrus         | 19           | 15.77 | -47 -73 -5      |
| 3       | 207              | Left lingual gyrus             | 19           | 11.54 | -16 -70 -3      |
|         |                  | Right cuneiform                | 19           | 4.21  | 19 -65 39       |
| 4       | 325              | Right lingual gyrus            | 18           | 18.55 | 11 -83 3        |
|         |                  | Right lingual gyrus            | 18           | 2.76  | 17 -88 -19      |
| 5       | 189              | Left cuneiform                 | 17           | 4.79  | -10 -92 3       |
| 6       | 119              | Right middle temporal gyrus    | 3.97         | 43    | -70 17          |
| 7       | 106              | Left upper forehead            | 3.21         | -16   | 40 50           |
Table 4. The stimulus activation map of the dominant eye in the healthy group and the contralateral eye in the amblyopia group.

| Cluster | Number of pixels | Activate areas          | BA partition | T   | x    | y    | z    |
|---------|------------------|-------------------------|--------------|-----|------|------|------|
| 1       | 1321             | Left cuneiform          | 18           | 8.56| -10  | -89  | -15  |
|         |                  | Right lingual gyrus     | 18           | 6.48| 18   | -85  | -20  |
| 2       | 474              | Left lingual gyrus      | 18           | 6.94| -8   | -88  | -18  |
| 3       | 226              | Right cuneiform         | 17           | 3.41| 12   | -90  | -14  |
with anisometric amblyopia is reduced, which is similar to what occurs with animals raised in the dark in animal models, and abnormal visual information can affect the normal formation of optic radiation myelin. Therefore, the change of myelin sheath may be one of the reasons for the decrease of optic radiation MK and FA values and the increase in MD value. Optic radiation is a part of the visual pathway. Its dysplasia can lead to the inability of visual information to be better transmitted to the visual cortex, which in turn leads to the weakening of the synchronized activity of the visual cortex neurons. This may be one of the aspects of the pathogenesis of amblyopia.

**Relationship Between Abnormal Corpus Callosum and Anisometric Amblyopia**

The corpus callosum, located at the bottom of the longitudinal fissure of the brain, is the largest white matter fiber bundle in the human brain. It integrates the information of the cerebral hemispheres on both sides, coordinates the activities of the cerebral hemispheres on both sides, and connects the motor language center, motor co-existence, and audiovisual area, which is especially important for the transmission of visual information. In this study, the MK value of the corpus callosum in the AA group was lower than that of the HC group, and the differences of FA and MD values were not statistically significant. We speculate that there may be changes
in the microstructure of the corpus callosum in patients with anisometropic amblyopia.

The optic zone is located around the corpus callosum, and there is a wide distribution of corpus callosal neurons and corpus callosal fiber endings. They are mainly concentrated near the junction of Brodmann 17 and 18 [19]. It is inferred that the fibers of the corpus callosum are related to the visual zone and may be one of the reasons for the decrease of stereo vision in patients with amblyopia. Only through the corpus callosum can neurons in the visual cortex within a certain area of the visual cortex receive binocular information. The MK value is a dimensionless parameter that reflects the degree of diffusion limitation and does not depend on the spatial orientation of the tissue structure. Compared with the FA value and the MD value, it can better reflect the diffusion characteristics of the tissue [20]. This also reflects the good application prospects of DKI.

**Functional Impairment of Visual Cortex in Patients with Anisometropic Amblyopia**

Through the BOLD-fMRI study, we found that when the amblyopic eyes of adult patients with amblyopia and anisometropia receive visual stimulation, the activation range and intensity of the primary visual cortex and the higher visual cortex were reduced compared with the HC group, and the Brodmann 18 and 19 areas were significantly reduced. When the contralateral eye of patients with amblyopia received visual stimulation, the activation range and intensity of the primary visual cortex and the higher visual cortex were reduced compared with the HC group, and the Brodmann 18 area was significantly reduced. This result suggests that both the amblyopic eye and the contralateral eye in patients with anisometropic amblyopia have damage to the primary and high-level visual cortex, and the primary damage is to the high-level visual cortex. This is consistent with previous literature reports. Previous studies have found that patients with amblyopia have damage not only to the primary visual cortex, but also to the higher visual cortex [15,21]. Li also found that the V1 area of most patients with amblyopia was significantly affected, and the visual cortex damage involved the expansion of the striate cortex [22]. There are 2 channels for the conduction of visual information in the advanced visual cortex: one is the dorsal channel ("where" channel), and the path is V2-V3-V3a/V5/V7, which mainly involves spatial motor function analysis; the other is the ventral channel ("what" channel), and the path is V2-VP-V4/V8, which mainly involved information processing such as shape, structure, and color. The dorsal pathway and ventral pathway were confirmed to have functional impairment in patients with amblyopia [23,24].

In patients with anisometropic amblyopia, due to the large diopter difference between the eyes, the object images of the 2 eyes cannot be merged into a single one, and the amblyopic eyes are inhibited. The visual pathway cannot obtain enough visual information stimulation, and functional changes occur. The advanced visual cortex is the center that integrates complex visual information into conscious perception. Therefore, the reduction of the input of visual information will also affect the damage of its neuronal structure and function. Cerebral cortex neurons can be divided into simple cells, complex cells, and super-complex cells according to the characteristics of their receptive fields. Super-complex cells are mainly distributed in Brodmann 18 and 19. Therefore, histologically, the extrastriate cortex is more sophisticated and complex than the striate cortex. It is speculated that the high-grade extrastriate cortex of patients with amblyopia may be more vulnerable to damage during visual development. It has also been found clinically that amblyopia not only damages central vision, but also damages image perception, kinesthesia, color perception, and text perception [25-27]. The extrastriate cortex is the center responsible for processing this visual information. We speculate that the cause of non-amblyopic eye damage in patients with amblyopia may be related to the interaction of the eyes, but the mechanism needs to be further studied. However, because of the small number of participants included in this study, verification by a large-sample, multicenter analysis is still needed in a future study.

There were some limitations in our study: DKI can probe microstructural changes in tissues, and the selection of DKI regions of interest is influenced by human factors and has a certain degree of subjectivity during data post-processing; BOLD-fMRI technology also has certain defects and limitations, such as head movement easily causing experimental errors; BOLD-fMRI can only indirectly reflect the functional activity of neurons through changes in blood flow and oxygen content, and the results are affected by the state of blood vessels. The next step in the study of the mechanism of amblyopia needs to repeatedly verify the research results and combine it with the research methods of single-neuron electrophysiology, morphology, and psychophysics.

**Conclusions**

This study showed that the combined use of DKI and BOLD-fMRI could detect microstructural changes associated with local visual pathways and identify damage to the visual cortex in patients with amblyopia.

**Declaration of Figures’ Authenticity**

All figures submitted have been created by the authors, who confirm that the images are original with no duplication and have not been previously published in whole or in part.
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