Underdevelopment of Optic Radiation in Children With Amblyopia: A Tractography Study

SHENG XIE, GAO LANG GONG, JIANG XI XIAO, JIN TANG YE, HAI HUA LIU, XIAO LING GAN, ZI TIAN JIANG, AND XUE XIANG JIANG

• PURPOSE: To detect the abnormalities of the optic radiation (OR) in children with amblyopia by diffusion tensor imaging (DTI) and tractography.

• DESIGN: Prospective, nonrandomized clinical trial.

• METHODS: Fourteen children with amblyopia and 14 normally sighted children underwent DTI scanning. After the ORs were reconstructed by using tractography algorithm, voxels through which the anterior parts of ORs passed were determined for their values of fractional anisotropy (FA). The paired *t* test was applied to compare their mean FA values of right OR and left OR in the control group. For the amblyopia group, analysis of variance was conducted to determine the effect of laterality and vision status on the FA values. In addition, the voxel numbers of anterior and posterior parts of both ORs were calculated. The Student *t* test was used to compare the average FA of bilateral ORs and voxel numbers between the two groups.

• RESULTS: Comparison demonstrated left-higher-than-right asymmetry in both amblyopic children and normal children. We found no significant difference of average FA between the amblyopic group (0.4832 ± 0.0225) and control group (0.4770 ± 0.0273). Voxel numbers of the anterior parts of both ORs were not significantly different between the two groups, whereas voxel numbers of their posterior parts in the controls were more than that of amblyopic children.

• CONCLUSION: Tractography showed more voxels in the posterior ORs of normal children than in the amblyopic children, indicating that normal children have better development of the ORs. The underdevelopment of the ORs might reflect the dysfunction of visual cortex in children with amblyopia. (Am J Ophthalmol 2007; 143:642–646. © 2007 by Elsevier Inc. All rights reserved.)

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From the Department of Radiology (S.X., J.X.X., J.T.Y., X.X.J.); and Department of Pediatric Ophthalmology (H.H.L., X.L.G.), Peking University First Hospital; and National Laboratory of Pattern Recognition, Institute of Automation, Chinese Academy of Sciences, Beijing, China (G.L.G., Z.T.J.).

Inquiries to Sheng Xie, Radiology Department, Peking University First Hospital, 8 Xishiku St, Xicheng District, Beijing, 100034 China; e-mail: ouyangxu2004@vip.sina.com

AMBLYOPIA IS A DEVELOPMENTAL DISORDER THAT results in vision deficits. It has been well established that amblyopia represents functional and morphologic effects of vision deprivation on the visual cortex and the lateral geniculate nucleus.[1–4] However, most of this evidence came from animal models, and the neuroanatomic information about the changes of brain structures in human remained limited. In recent years, great effort has been made in this field by using neuroimaging modalities, but the work was commonly involved with the adult subjects.[5–8] Because of unavailability of children subjects and their inability to cooperate, studies in humans concerning development of the visual system were scarce.

Magnetic resonance (MR) imaging has been used to examine the normal patterns of brain maturation and myelination. But conventional MR imaging usually reveals unremarkable findings about amblyopia. Diffusion tensor imaging (DTI) is a newly developed MR technique, which can provide both structural and functional information about the white matter quantitatively.[9] During the process of brain maturation, there is decrease of total water content and progression of myelination. Because these maturational changes result in altered water diffusion, the information regarding the magnitude and severity of any observed alternations in anisotropy may be valuable for understanding the pathophysiologic characteristics of developmental abnormality.[10,11] One previous study has compared DTI data from a patient suffering from septo-optic dysplasia with those healthy control subjects and showed obvious reduction in anisotropy of visual fiber tracts in the patient.[12] Based on diffusion tensor images, tractography was developed to extract connectivity information in vivo.[13–16] Optic radiation (OR) has been tracked with this technique and the results have been validated with anatomical evidence.[17,18] By using this technique, marked geniculocalcarine tract differences were found between five early-blinded people and seven normally sighted volunteers.[19] In light of previous studies, one might presume that amblyopia will result in changes of visual fiber tracts related to the abnormality of visual cortex. Because OR is the fiber tract connecting the lateral geniculate nucleus and visual cortex, we hypothesized that abnormalities might be detected in this fiber tract in amblyopia. With the technique of DTI and tractography, we tried to identify the abnormalities of the OR in children with amblyopia in this study.

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TABLE 1. Information of Amblyopic Subjects

Subject	Amblyopia	Distance Acuity (logMAR)		Refractive Error		Eye Deviation, Arc	
		Left	Right	Left	Right		
Child 1	Anisometropia	0.6	1.0	+3.50	+2.00	Orthotopia	0
Child 2	Strabismic	1.2	0.1	+1.50	+1.50	Esotropic	+15
Child 3	Strabismic	0.1	0.5	+9.00	+7.50	Esotropic	+25
Child 4	Strabismic	0.2	1.0	+6.50	+2.0	Exotropic	−40
Child 5	Anisometropia	0.6	1.0	+1.00	0	Orthotopia	0
Child 6	Anisometropia	0.4	0.5	+5.00	+4.25	Orthotopia	0
Child 7	Anisometropia	1.0	0.7	+6.00	+7.50	Orthotopia	0
Child 8	Anisometropia	0.7	0.7	+2.50	+2.25	Orthotopia	0
Child 9	Strabismic	0.4	1.0	+3.50	+2.75	Esotropic	+20
Child 10	Anisometropia	0.4	0.4	+0.50	−0.50	Orthotopia	0
Child 11	Anisometropia	1.0	0.1	+1.50	+5.00	Orthotopia	0
Child 12	Anisometropia	0.6	0.6	+0.50	−0.50	Orthotopia	0
Child 13	Strabismic	0.3	1.0	+5.25	+1.25	Esotropic	+15
Child 14	Anisometropia	0.1	1.0	+5.00	+1.00	Orthotopia	0

METHODS

• **SUBJECTS:** Fourteen pediatric patients with amblyopia (six males, eight females; age range, 4 to 8 years; mean age 5.8 years) and 14 normally sighted children (10 males, four females; age range, 3.5 to 9 years; mean age 5.8 years) were recruited in this study. Informed consent for participation was obtained from every subject's parents and the ethics committee at Beijing University approved all the protocols used in this study. The amblyopic children were recruited by physician referral from the pediatric ophthalmology service at Peking University First Hospital. First the children with vision problems completed an ophthalmologic exam that included tests of ocular motility, dilation, fundus exam, autorefraction, and visual evoked potentials. After the diagnosis of amblyopia was confirmed, they were referred to MR scanning before amblyopia treatment. Patients with a known organic brain disorder or with specific clinical evidence of neurologic dysfunction were excluded from this series. Five children had strabismus amblyopia and nine had anisometropic amblyopia. Their results are summarized in Table 1. Controls were recruited from the children who underwent MR imaging examination for other purposes unrelated to vision problems. Four were volunteers, five were referred to MR scanning because of headache, two were scanned for trauma, one was scanned for dwarfism, and the other two were for febrile convulsion. They were confirmed to have normal visual acuity and to be free of neurologic conditions. The two groups were matched for age.

• **MR DATA ACQUISITION:** All MR imaging was performed on a 3.0-Tesla MR scanner (GE Signa 3.0T HD, Milwaukee, Wisconsin, USA). Conventional axial T2-weighted images were obtained previously to rule out the presence of any detectable lesion in their brains. Diffusion tensor imaging was acquired with a single-shot echo planar imaging sequence. The diffusion sensitizing gradients were applied along 15 noncollinear directions with b value of 1000 seconds/mm^2, together with an acquisition without diffusion weighting ($b = 0$). Thirty contiguous axial slices were acquired with 3-mm thickness and no gap. The acquisition parameters were as follows: repetition time = 6200 milliseconds; echo time = 71.1 milliseconds; matrix = 128 × 128; field of view = 24 × 24 cm; number of excitation [NEX] = 2. After that, high-resolution 3-dimensional spoiled gradient recalled pulse [SPGR] images (repetition time = 7.8 milliseconds, echo time = 3.2 milliseconds, TI = 450 ms, field of view = 22 × 22 mm, matrix = 256 × 256, slice thickness = 1.6 mm, NEX = 1) covering the whole brain were also obtained. Head motion was minimized with restraining foam pads offered by the manufacturer. MR images were reviewed by a radiologist to confirm that all data sets were uncontaminated by head motion artifacts.

• **DATA PROCESSING:** Each subject's DTI dataset was transferred to a personal computer running DTI studio (Johns Hopkins University, Baltimore, Maryland, USA), which was designed to reconstruct all tracts using fiber assignment by continuous tracking algorithm. All tracts in the data set were first reconstructed by seeding each voxel that had a fractional anisotropy (FA) greater than 0.15. The propagation was continued until they reached a voxel with an FA less than 0.15 or turned at an angle greater than 70 degrees. To extract the OR from all tracts, we manually defined the first target regions containing bilateral ORs on the coronal color-tensor slice showing occipital horns of the lateral ventricles. Another region containing white matter of both occipital lobes was prescribed as the second target region in the coronal color-

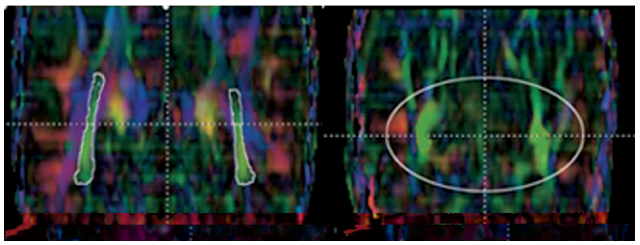

FIGURE 1. The regions defined for tracing the optic radiations (ORs) in the controls and children with amblyopia. (Left) Regions containing the ORs in the coronal color-tensor map showing occipital horns of the lateral ventricles were defined to extract the ORs. (Right) Another region containing white matter of both occipital lobes was prescribed as target region in the coronal color-tensor map at the level of middle calcarine sulcus.

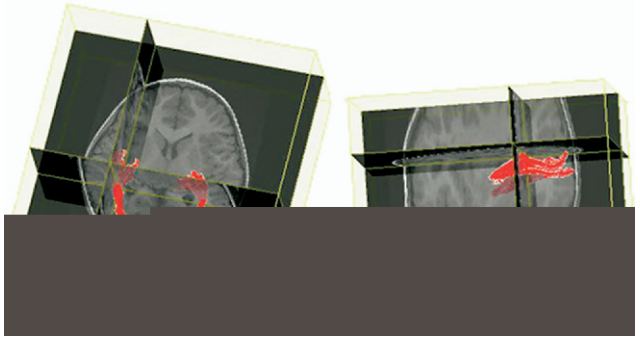

FIGURE 2. The reconstructed fibers of optic radiations (ORs) were depicted in the coregistered 3-dimensional T1-weighted images in a subject. The value of fractional anisotropy was extracted from every voxel along the course of the OR.

tensor slice at the level of middle calcarine sulcus (Figure 1). All tracts passing these two regions were saved as the preliminary results of ORs. But some association fibers still existed (e.g., inferior longitudinal fasciculus) in them; so considerable attention was given to exclude those fibers projecting to lobes other than occipital lobes. Under this criterion, our traced ORs would include the fibers extending into the primary visual cortex (V1) and the secondary visual cortex (V2) (Figure 2).

The following procedure was taken to extract the measurement of the ORs. The OR was first subdivided into two parts: anterior and posterior. The anterior part of OR was defined to range from the posterior edge of corpus callosum to the half length of occipital lobe, whereas posterior part included the remaining part. Because anisotropy in the posterior parts of ORs is more vulnerable to partial volume effect, only FA values in the anterior parts of ORs were averaged as the typical anisotropic index for bilateral ORs, respectively. Additionally, numbers of traced voxels in the anterior parts and posterior parts of both ORs were also calculated.

TABLE 2. The Mean and Standard Deviations of Fractional Anisotropy and Voxel Numbers of the Optic Radiation in Amblyopes and Controls

Index	Amblyopia Group	Control Group
FA of left OR	0.4974 ± 0.0243	0.4932 ± 0.0394
FA of right OR	0.4690 ± 0.0274	0.4608 ± 0.0260
Average FA	0.4832 ± 0.0225	0.4770 ± 0.0273
Voxel number of anterior ORs	2873 ± 746	3355 ± 665
Voxel number of posterior ORs	1208 ± 449	1798 ± 660
Voxel number of whole ORs	4081 ± 1040	5153 ± 1072

FA = fractional anisotrophy; OR = optic radiation.

• **STATISTICAL ANALYSIS:** To investigate the FA difference between bilateral ORs, paired *t* test was conducted to compare their FA values in the control group. For the amblyopia group, analysis of variance was used to detect the effects of side and vision status (amblyopic or fellow) on their FA values. Then FA values of bilateral ORs were averaged for comparison between the two groups. A two-tailed Student *t* test was carried out to compare average FA values and voxel numbers of both ORs from the patients with the corresponding quantities from the controls. In addition, histograms were generated for each group to show the distribution of the voxels with regard to FA values.

RESULTS

THERE WAS NO STATISTICAL DIFFERENCE IN AGE BETWEEN the two groups (5.8 years ± 1.4 for children with amblyopia, 5.8 years ± 1.9 for controls).

Significant difference of FA values was detected between the two sides of ORs in the controls ($t = 4.16$, $P = .001$). In the amblyopia group, the effect of vision status and vision-by-side interaction effect were not evident along the ORs, whereas the side difference was significant ($F = 6.33$, $P = .02$). It showed that left OR had greater FA than right OR in both groups. No difference of voxel numbers, in both anterior and posterior parts, was found between the two sides of ORs in the controls and the patients.

We found no significant difference of average FA between the amblyopic group and control group ($t = 0.65$, $P = .52$). Voxel numbers of the anterior part of both ORs were not significantly different between the two groups, though they showed some tendency ($t = 1.81$, $P = .08$). In contrast, more traced voxels existed in the posterior ORs of control group, which had achieved significance ($t = 2.77$, $P = .01$). As to the voxel number of whole ORs concerned, statistical significance still existed between the

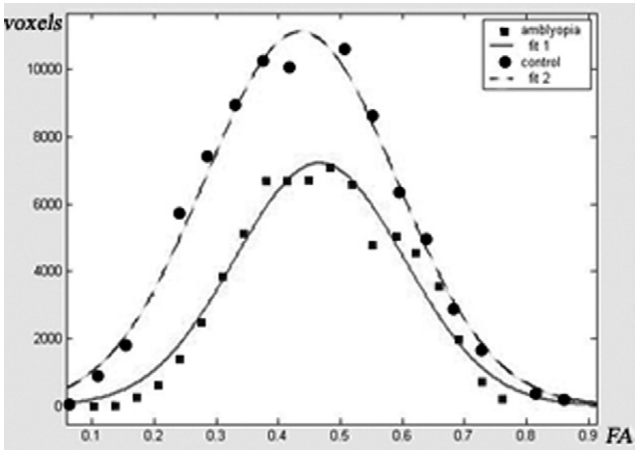

FIGURE 3. Fractional anisotropy (FA) histograms of the control group (dashed line) and amblyopic group (solid line). Number of voxels vs fractional anisotropy in the whole traced optic radiations (ORs). The curves can be fitted by theoretical Gaussian curves, representing the distribution of fractional anisotropy of traced voxels in both optic radiations. The Gaussian curves of the two groups are similar and symmetrical in their configuration, but the one of control group is much higher than that of amblyopia group.

two groups ($t = 2.69$, $P = .01$). The mean and standard deviations of FA and voxel numbers are reported in Table 2. FA histograms of whole ORs for patients and controls are illustrated in Figure 3. They were fitted with Gaussian curve, and height difference was observed between the curves.

DISCUSSION

DIFFUSION TENSOR IMAGING HAS BEEN CONSIDERED AS A useful method in the evaluation of brain development. It is believed that FA can provide microstructural information on white matter development.[10] Tractography, a technique based on DTI, allows us to extract the trajectories of certain fiber tracts in vivo. Although tractography may be affected by image resolution and signal-to-noise ratio, it frequently generates results that are reasonable and reproducible.[12] Tractography of the ORs has been verified with anatomical knowledge.

In our study, tractography showed more voxels in the posterior parts of bilateral ORs of normal children than in that of the amblyopes, which indicated that normal children had better development of the ORs, especially in their periphery. As we know, the brains of children undergo an extended period of postnatal maturation, with increase of the white matter and progression of myelination. Recent advances in neuroscience provided evidence of the influence of training on the development of white matter.[20,21] Amblyopia, no matter what etiology underlies it, exhibits abnormalities in the visual cortex and lateral geniculate nucleus (LGN) histologically and neurophysiologically. Most visual evoked potential studies routinely reported reduced and distorted VEPs in human amblyopes, suggesting dysfunction of the visual pathway.[22,23] It has been demonstrated in the animal model that induction of myelination is triggered by neural activity and myelination of the optic nerve is decelerated by rearing in the darkness.[24,25] Therefore, low visual activity in amblyopes might hinder their ORs from maturation. Because ORs were bidirectional, we believed that the underdevelopment observed in the ORs of amblyopia probably was related to changes both in the visual cortex and the LGN. Besides, perhaps the underdevelopment of the ORs will in turn lead to the prolongation of neural transmission and impair the connection between the occipital lobe and LGN.

However, statistical analysis failed to detect significant difference in FA between the two groups. The anisotropic diffusion in white matter might be affected by myelination, axonal thickness, or amount of parallel organization of axons, or a combination of these three factors.[26] In the study of Bengtsson and associates, intensive musical practice led to measurable DTI changes in deep cerebral white matter.[27] They proposed that increased myelination, caused by neural activity in fiber tracts during training, is one mechanism underlying the observed FA increases. Therefore, one might expect that well developed OR will show greater FA. However, the average FA is contributed by every traced voxel in both ORs in our study. The voxels in the edges of OR will have lower FA because of partial volume effect and more nonparallel fibers in a voxel. It is possible that the more voxels with low FA in the control group make the average FA decreased. Another possibility is that our sample is too small and our patients are relatively mildly affected. To better demonstrate the distribution of FA values in ORs, we built the histograms for the two groups. It can be inferred from the histograms that the average FA may not be significantly different between them. The Gaussian curves of the two groups are similar and symmetrical in their configuration, although the one of control group is much higher than that of amblyopia group.

Another interesting result in our study is the remarkable lateralization of FA in bilateral ORs. This left-higher-than-right asymmetry has been observed in other tracts of normal subjects, indicating that there is developmental imbalance between the two hemispheres.[28] Some neurologic disease can reduce this asymmetry, as revealed by some studies.[29] However, we did not find the loss of FA asymmetry between the bilateral ORs in amblyopes. It may be related to the fact that the OR receives combination of visual inputs from both eyes.

It is of note that our quantitative results should not be viewed as real reflection at an anatomic level. And it remains unclear how closely these changes in the ORs correlate with vision impairment and neurophysiologic results. In addition, the connections between the occipital

lobe and other cortical regions deserve exploration to understand the development of neural network of complex visual functions.

In summary, our results indicated that amblyopia can cause functional underdevelopment of the ORs in children. In turn, the underdevelopment of the ORs might play a key role in the neural mechanism of amblyopia. Our findings also suggest that DTI and tractography may provide valuable insight into the role of early experience on the structure and function of the human brain.

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