Changes in DTI parameters in the optic tracts of macaque monkeys with monocular blindness

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HIGHLIGHTS

- DTI can noninvasively and quantitatively detect damage in the optic tracts of neonatal monocular blind macaque monkeys.
- The damage included the integrity destruction of white matter tracts and axonal degeneration and demyelination.
- The damage was gradual and irreversible process, and the degree of degeneration between the left and right optic tracts was not synchronized over time.

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ABSTRACT

For humans and non-human primates, the alteration of the visual pathway's white matter fibers after visual deprivation has been partially explored. However, the changes in the optic tracts after the transection of the optic nerve have not been well characterized. In the current study, we attempted to investigate the differences in optic tracts between normal and unilateral optic nerve transected macaque monkeys using diffusion tensor imaging (DTI). Four healthy neonatal macaque monkeys were randomly divided into 2 groups, with 2 in each group. Group A served as a control group, and Group B underwent unilateral (right eye) optic nerve transection to produce monocular blindness. Sixteen months (Group B\textsuperscript{16M}) and thirty-two months (Group B\textsuperscript{32M}) after optic nerve transection, diffusion tensor imaging was performed on all monkeys. Then, we compared fractional anisotropy (FA), mean diffusivity (MD), axial diffusivity (AD) and radial diffusivity (RD) in bilateral optic tracts between Group A and Group B and between Group B\textsuperscript{16M} and Group B\textsuperscript{32M}. In both Group B\textsuperscript{16M} and Group B\textsuperscript{32M}, when compared with normal monkeys in Group A, FA was decreased and MD, AD and RD were increased in the bilateral optic tracts of monkeys with monocular blindness. Furthermore, compared with Group B\textsuperscript{16M}, FA was reduced and MD, AD, RD were more obviously increased in the bilateral optic tracts of Group B\textsuperscript{32M}, and noticeable differences in MD, AD and RD were found between the left and right optic tracts in group B\textsuperscript{32M}. We believe that the results of this study would be helpful in investigation of the histological abnormalities of the integrity damage, axonal degeneration and demyelination of optic tracts in macaque monkeys with monocular blindness by DTI parameters in noninvasively and quantitatively.

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1. Introduction

For humans and non-human primates, the optic nerve is part of the central nervous system (CNS) and the pathway to transfer visual information from the retina to the brain [1]. It is not surprising that the absence of vision from birth or the loss of vision later in life has huge consequences, both anatomically and functionally. After visual deprivation, the axonal proteins and lipids of the optic nerve fibers are destroyed and nerve fibers degenerate [2]. The hydrophilicity of the myelin sheath increases with neuroglial cell proliferation. Finally, the axons rupture, demyelinate and atrophy [2]. The alteration of the visual pathway’s white matter fibers after visual deprivation has been partially explored [2–5], but detailed information on alterations in the optic tracts is lacking, especially the changes after the transection of the optic nerve [6–8]. In contrast to the known anatomical changes in the white matter tracts that are relevant to the visual system after retinal ischaemia, optic neuritis and glaucoma in humans [9–11], little is known about the effects in the optic tracts of blindness in neonatal non-human primates.

Diffusion tensor imaging (DTI) is a magnetic resonance imaging technique that can characterize the directional properties of the diffusion of water molecules. The visualization of white matter tracts is based on the principle that diffusion is restricted by fibrous microstructures [12,13]. Diffusion tensor-based tractography is currently the only existing technique that can visualize white matter tracts in vivo. DTI can quantitatively measure the anterior visual pathway (i.e., retina, optic nerves, chiasm, and optic tracts) using fractional anisotropy (FA), mean diffusivity (MD), axial diffusivity (AD) and radial diffusivity (RD) [14,15]. Therefore, numerous studies have used this modality to investigate normal or abnormal brain development in humans and non-human primates [16–18]. The decrease of axial diffusivity in the optic nerve was detectible by diffusion tensor imaging after acute demyelinating optic neuritis [19]. Sidek S et al. [11] reported a FA decrease and MD increase in the optic nerve and optic radiation of patients with severe glaucoma, which may be due to the degeneration of neural tissue. Furthermore, DTI also has been applied to humans with acquired binocular blindness and early blindness (who lost vision within 1 year), which suggested that there was no axonal degeneration of the optic radiation in late onset blindness [3]. However, no studies on neonatal monocular blind non-human primates have observed the changes of the optic tracts of the visual pathway.

Therefore, our study utilized macaque monkeys to establish a neonatal monocular blindness model to investigate anatomical and functional changes of the bilateral optic tracts in the visual pathway of monocular blind subjects by detecting changes in the parameters of diffusion tensor imaging with a 3T MR scanner. Such alterations in FA, MD, AD and RD maybe valuable to reveal the integrity of the cerebral white matter within visual pathways of a monocular blindness macaque monkey model. To our knowledge, we are the first to report on the optic tract of macaque monkeys with early monocular blindness using DTI.

2. Subjects and methods

2.1. Ethics statement

The study was approved by the Committee on the Ethics of Animal Experiments of the Eye & ENT Hospital, and was carried out in strict accordance with the recommendations in the Guide for the Care and Use of Laboratory Animals of Pudan University and local and international ethical guidelines. The housing of the monkeys protocol was clearly described in a previously published paper [20]. All of the monkeys were raised in suitable environ-ment with a balanced diet and freely available water. Furthermore, skilled veterinarians supervised their health. Prior to the optic nerve transection, the monkeys were anesthetized with 0.3 ml of a ketamine-xylazine mixture (10 mg/kg body weight). Postoperatively, each monkey received cefotaxime (75 mg/kg body weight) and an analgesic, diclofenac sodium (1 mg/kg body weight), twice daily for 5 days. None of the monkeys were sacrificed during the study.

2.2. Animal preparation and experimental protocol

Healthy neonatal macaque monkeys (N = 4) were randomly divided into 2 groups, with 2 in group A (Monkey 1 and Monkey 2) and 2 in group B (Monkey 3 and Monkey 4). There was no significant difference in the mean age between the normal and monocular blindness groups. In this study, optic nerve transection was performed in the right eye of two monkeys in the experimental group (Group B, Monkey 3 and Monkey 4) at postnatal day 40 under anesthesia induced by a 0.3 ml ketamine-xylazine mixture to establish the monocular blindness model. The optic nerve transection protocol was clearly described in a previously published paper [20]. Briefly, under an operating microscope, we bluntly transsected and dissected the tissues around the eyeball until the optic nerve was clearly exposed. Then, a small section of the optic nerve was removed from the surgical eye when we transected the optic nerve to ensure that the optic nerve was completely transected. Finally, the eyeball was reset into the orbit again, and the incision was sutured. This operation is believed to result in fewer morphological changes and less surgical trauma than the monocular enucleated model. Separate, healthy macaque monkeys were kept as a control group (group A, Monkey 1 and Monkey 2); 16 and 32 months after the operation, diffusion tensor imaging was performed of all the monkeys.

2.3. MRI (Diffusion tensor tractography)

The anesthetized macaque monkeys were placed in a knee coil in a supine position with their heads in the central location. Thin sheets were used to keep the monkeys warm at approximately 38°C. All experiments were performed on a Siemens–Magnetom Verio 3.0T scanner. Diffusion images were acquired with a spin-echo version of echo planar imaging (EPI) sequence. High-resolution T1-weighted images were acquired with the 3D MPRAGE sequence for the structural identification of the optic tract. The DTI imaging parameters were: TR = 4600 ms, TE = 82 ms, slice thickness = 2.0 mm, no inter-slice gap, 25 slices, FoV = 140 mm × 140 mm, voxel size = 1.8 × 1.8 × 2.0 mm3, b-value = 0 and 1000 s/mm2, 20 diffusion directions, and 5 averages.

2.4. Data post-processing

The diffusion tensor imaging datasets were analyzed on a Siemens MR post-processing workstation (Siemens–Magnetom Verio, 3.0T MR, Germany). The images for each monkey were independently evaluated by two experienced radiologists. Fractional anisotropy (FA) and mean diffusivity (MD) are general measures used to quantitatively characterize the microstructural changes in white matter fiber bundles, and axial diffusivity (AD) and radial diffusivity (RD) can provide additional information regarding tissue microstructure and axon and myelin pathology [9,21]. The regions of interest (ROIs) were positioned on T1 Weighted Images, FA, MD, AD and RD maps. A single, small circular ROI was placed mid-length of the center part of the visualized optic tract on the axial section. This process was repeated for all monkeys.
The percentage change of FA, MD, AD and RD values between group A and group B (B16M and B32M) were compared.

3. Results

The changes of the FA, MD, AD and RD values for the bilateral optic tracts between the normal (Group A) and monocular blindness (Group B) groups, including Group B16M and Group B32M, are illustrated in Table 1, Figs. 1–3. In Group B16M, when compared with Group A, the FA value was decreased by 30%, whereas MD and RD were increased by 8% and 16% in the left optic tract, respectively. The FA value was decreased by 28%, and MD and RD increased by 9% and 14%, respectively, in the right optic tract. In Group B32M, compared with normal monkeys, we found that FA decreased (left optic tract was decreased by 46%, right optic tract was decreased by 49%) in monocular blindness monkeys, whereas MD, AD and RD were increased by 63%, 52%, and 69%, respectively, in the left optic tract and 54%, 41%, and 60%, respectively, in the right optic tract. In addition, we also observed the variations of these DTI parameters between Group B16M and Group B32M and between the left and right optic tract in Group B16M and Group B32M, respectively. Compared with Group B16M, FA was further reduced, whereas MD and RD were further increased and AD was increased in the bilateral optic tracts of Group B32M; moreover, the changes of MD, AD and RD of the left optic tract were greater than those of the right optic tract in Group B32M. Additionally, there were no obvious differences between the left optic tract and right optic tract in Group B16M, whereas the differences of MD, AD and RD in the left optic tract were more dramatic than those in the right optic tract of Group B32M.

4. Discussion

Alterations of the visual pathway have been investigated in blind humans [4,8,22], but to our knowledge, comparable in vivo examination of optic tract changes in neonatal macaque monkeys after unilateral optic nerve transection has not been reported. DTI metrics provide quantification of the different aspects of diffusion that relate to the underlying microstructure [14]. DTI potentially detected the damage to the myelin sheath or axons of the white matter fibers [9,23], and FA provides information regarding the directionality of diffusion and reflects a level of fiber integrity and

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### Table 1

| P    | Left optic tracts | PC of group B vs group A | Right optic tracts | PC of group B vs group A |
|------|-------------------|--------------------------|--------------------|--------------------------|
| FA   | Group A B16M      | 0.534 ± 0.021            | 50%                | 0.501 ± 0.002            |
|      | Group B B16M      | 0.373 ± 0.021            | 30%                | 0.359 ± 0.015            |
|      | Group B B32M      | 0.286 ± 0.100            | 46%                | 0.255 ± 0.034            |
| MD   | Group A B16M      | 0.774 ± 0.039            | 8%                 | 0.746 ± 0.025            |
|      | Group B B16M      | 0.844 ± 0.057            | 63%                | 0.818 ± 0.052            |
|      | Group B B32M      | 2.106 ± 0.447            | 52%                | 1.608 ± 0.170            |
| AD   | Group A B16M      | 1.289 ± 0.023            | 52%                | 1.202 ± 0.037            |
|      | Group B B16M      | 1.207 ± 0.062            | 5%                 | 1.142 ± 0.052            |
|      | Group B B32M      | 2.711 ± 0.264            | 41%                | 2.048 ± 0.264            |
| RD   | Group A B16M      | 0.608 ± 0.098            | 16%                | 0.690 ± 0.036            |
|      | Group B B16M      | 0.728 ± 0.099            | 49%                | 0.750 ± 0.146            |
|      | Group B B32M      | 1.944 ± 0.613            | 60%                | 1.505 ± 0.160            |

P: parameter.
Group A: Normal group.
Group B16M: The monocular blindness group sixteen months after right optic nerve transection.
Group B32M: The monocular blindness group thirty-two months after right optic nerve transection.

Abbreviations: FA, fractional anisotropy; MD, mean diffusivity; AD, axial diffusivity; RD, radial diffusivity.

MD, AD, and RD are given in 10⁻³ mm²/s. FA is unitless. All values are mean ± s.d. PC: percentage change.

↑↑↑: increased; decreased 0–30%; ↑↑↑↑: increased; decreased 31–50%; ↑↑: increased/decreased more than 51%. The normal values in the normal group were increased/decreased compared with the monocular blind group.

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Fig. 1. Normal macaque monkey in Group A Regions of interest (ROIs): Red circles in the right optic tract and green circles in the left optic tract are marked on the axial T1WI (a), color FA map (b), MD map (c), AD map (d), and RD map (e), and the corresponding values of the DTI parameters (f) are shown. (For interpretation of the references to colour in this figure legend, the reader is referred to the web version of this article.)
coherence. It has been reported that FA values correspond to the integrity as well as the orientation of tissue microstructure, including the myelin sheath, microtubule, and microfiber [24]. MD is the spatially averaged magnitude of water diffusion, measuring the total molecular motion averaged over all directions [25,26]. The AD value was sensitive to axon degeneration and RD was sensitive to both demyelination and remyelination [9,27].

In our study, greatly reduced FA value and increased MD value could be detected along the bilateral optic tracts in Group B16M and Group B32M, which is consistent with previous study that showed decreased FA and increased MD in the optic tracts, optic radiation and the calcarine sulcus of early blind humans [28]. It has been reported in many disease groups, including Alström Syndrome and glaucoma, that reduced FA and increased MD is a typical phenomenon of white matter demyelination, axonal loss or axonal reorganization of fibers [29,30]. Therefore, our results indicate that the degeneration of white matter within the visual pathway in models of visual loss has occurred, and the fiber integrity and coherence of the optic tract have been damaged. Meanwhile, optic tract fibers shrunk and atrophied; thus, extracellular spaces enlarged and water content increased, which were in accordance with what has been seen in the same changes of optic nerve integrity in individuals with binocular blindness [2]. Accordingly, our results were likely due to the modification of neural structures during critical periods of neurodevelopment of monocular blind monkeys [30]. Additionally, there was a greater change in FA than in MD in Group B16M, which was consistent with previous studies regarding the decrease of FA and the increase of MD in the bilateral optic nerve and optic radiation of glaucoma patients with low vision [11]. Therefore, our results showed that FA is a more sensitive and reliable biomarker than MD as an indicator of the assessment of optic tract damage in group B16M.

The AD value reflects axonal degeneration, while the RD value reflects demyelination. Our study showed an increase in RD value in the bilateral optic tracts of group B16M and an increase in the RD and AD values in the bilateral optic tracts of group B32M when compared with group A. These observations were in accordance with previous studies [31,32] that showed that when the right optic nerve was transected, the axonal arrangement was damaged and the integrity of the axon sheath was lost. This loss then resulted in a decrease in resistance from the barrier restriction along the direction of the fiber tract, which could be reflected by DTI parameters.
that showed an increase in AD [2,9]. In addition, the destruction of the myelin sheath that led to the magnitude of water molecules diffusing perpendicular to the fiber tract was increased, which can be found and reflected by the increase of RD [2,9,33]. Therefore, in our study, the increase of AD and RD can indicate the axonal degeneration and demyelination of fibers in the optic tracts after optic nerve transection, respectively. Furthermore, we found that the changes in RD were more remarkable than those in AD in both group B16M and B32M. Thus, we speculated that two possible mechanisms may account for the alterations between RD and AD in the optic tract of the monocular blind monkeys. One is that demyelination is superior to axonal degeneration after optic nerve transection, and the other involves the immaturity of the axon and the myelination of the optic tract due to early visual optic nerve transection [1,16,34]. However, further investigation with a larger sample size is recommended.

Moreover, the variations in the DTI parameters between group B16M and group B32M and between the left and right optic tracts within group B32M were all dramatic differences in our study. Compared with group B16M, FA was further reduced, whereas MD, AD, and RD were further increased in the bilateral optic tracts in group B32M. This was more obvious in the left optic tracts than in the right optic tracts. Because patients with glaucoma could be regarded as partial deafferentation models of the visual system [34], decreased FA and increased MD, AD and RD in the optic nerve were observed in these patients. Our findings were consistent with previous studies on glaucoma patients [11,32]. These results could indicate that the destruction of white matter integrity, such as axonal degeneration and demyelination, could occur in the bilateral optic tracts after the unilateral transection of the optic nerve. In addition, we also found that the FA value showed a progressive decreasing trend and MD, AD, and RD showed a progressive increasing trend over time after the transection of the right optic nerve, which could suggest that the degeneration of fibers in the optic tracts after optic nerve transection was gradual and irreversible [35].

Additionally, in group B32M, MD, AD and RD in the left optic tract were higher than those in the right optic tract, while there was no obvious difference between the left and right optic tract in group B16M, which indicated that the degree of degeneration between the contralateral and ipsilateral optic tract are not synchronized over time. In the early stage of right optic nerve transection, the presence of axonal loss and myelin disintegration in the bilateral optic tracts were similar, but in the late stages of right optic nerve transection, axonal degeneration and demyelination in the contralateral optic tract were more severe than in the ipsilateral optic tract. This difference may be due to the following factors. First, Mikhalil et al. reported that there was an initial decrease in the stimulation of the deprived eye followed by the potentiation of the responsiveness to stimulation of the non-deprived eye in monocular blind young mice; therefore, intensive practice could lead to measurable DTI changes and result in lower MD, AD and RD in the right optic tract relative to the left optic tract [37]. Second, because the nasal part of the right optic nerve fibers (57%) in normal macaques cross to the left side and the temporal part of the right optic nerve fibers (43%) do not cross to the left side [38], in monkeys that underwent right optic nerve transection, the left optic tract included the nasal part (57%) of the right optic nerve fibers, while the right optic tract included the temporal part (43%) of the right optic nerve fibers, so the quantity of abnormal fiber bundles in the left optic tract was greater than in the right optic tract, which indicated that a greater changes in the left optic tract appeared when the right optic nerve was transected. Third, developmental immaturity due to the visual deprivation during the critical developmental period may be implicated in the mechanism behind the differences between the left and right optic tracts in monocular blind monkeys. Immature white matter fiber damage was positively correlated with the duration of blindness, and the left optic tract was more damaged due to visual loss of the right eye than the right optic tract [37,39]; therefore, the damage to the left optic tract was more serious than that of the right optic tract in group B32M, but was not obvious in group B16M. However, a larger sample is needed in future studies to further validate our results.

There were some limitations in the current study. First, the number of samples was limited (N = 2 for each group), and statistical analysis could be performed. Therefore, further investigation with a larger sample size is recommended in the future. Second, we only investigated DTI parameters of the optic tract in the visual pathway, and in future studies, we hope to detect these parameters in other regions of the visual pathway. Third, all of these findings were not confirmed by histology. In a future study, we hope that we will be able to detect histological changes to further validate our study.

In conclusion, our results demonstrated that DTI parameters can noninvasively and quantitatively detect damage to the integrity of white matter tracts and axonal degeneration and demyelination in the optic tracts of neonatal monocular blind macaque monkeys. These changes were gradual and irreversible, and the degree of degeneration between the left and right optic tracts was not synchronized over time. Such alterations could provide valuable information to investigate the histological abnormalities of the visual pathway after optic nerve transection in neonatal macaque monkey models.

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