Characterization of Optic Nerve Development in Rhesus Monkeys with DTI

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Introduction: Optic nerve is the continuation of the axons of ganglion cells in the retina and plays a critical role in the visual pathways. Diffusion tensor imaging (DTI) provides a non-invasive means to investigate optic nerve abnormality and has demonstrated its sensitivity in several preliminary studies of optic nerve in humans and animals [1-4]. Several investigations on the optic nerve development were conducted with humans and animals postmortem [5-7], but no *in vivo* results have been reported. In this study, we used DTI to characterize the optic nerve development of Rhesus monkeys from 2 weeks old (infant) to 6 years old (adults).

Materials and Methods: 3 healthy young rhesus monkeys were scanned at the ages of 2 weeks, 3 months, 6 months and 1 year. Additional older rhesus monkeys, at the ages of 2 (n = 7), 3 (n = 5), 4 (n = 5), and 6 (n = 5) years old, were scanned for comparison. All scans were performed on a Siemens Trio 3T with an 8-channel phase-array volume coil using double spin-echo single-shot EPI sequence for DTI acquisition with parameters: TR = 5000 ms / TE = 86 ms, FOV = 83 mm × 83 mm, data matrix = 64 × 64, slice thickness = 1.3 mm, b-value = 0, 1000 s/mm^2, 60 directions. Animals were lying on their backs and immobilized with a custom-built holder under anesthesia (1-1.5% isoflurane) with physiological parameters monitored continuously.

Mean diffusivity (MD), fractional anisotropy (FA), axial diffusivity ($\lambda_{\parallel}$) and radial diffusivity ($\lambda_{\perp}$) maps were derived from the DTI data with FSL. Regions of interest (ROIs) were selected manually using MRIcro 1.4 (Fig. 1). The changes of the DTI parameters during optic nerve development were fitted to the equation $MD\ (or\ \lambda_{\parallel}, \lambda_{\perp}, \mathrm{FA}) = C + Ae^{-age/t}$ [8] with OriginPro 8.5.0 SR1, where t is a time constant indicating the rate of development. C and A are fitting parameters. The time to maturity for each parameter is defined as the time to reach 90% of the maximum development – the asymptotic value of each parameter. Repeated ANOVA and one-way ANOVA with SPSS were utilized for statistical analysis.

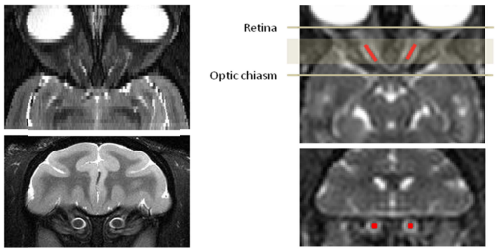

Fig. 1 (a) High resolution T2 weighted image (0.3 mm * 0.3 mm * 1.1mm) of the optic nerve of an adult monkey. (b) Region of interest (ROI) was selected manually on the coronal slices located between the anterior and posterior quarters of the optic nerve (the shaded area) for both eyes. The ROI only includes the central pixel of the optic nerve cross-section on the selected slices. The base image is the MD map of one of the 6-year-old subjects.

Results: Fig. 2 shows the change of MD, $\lambda_{\parallel}$, $\lambda_{\perp}$ and FA with age. The time constants (t) for FA, $\lambda_{\perp}$, MD and $\lambda_{\parallel}$ were 0.6, 1.3, 1.5 and 2.3 years (or 8, 15, 18, 28 months), respectively, and the corresponding time to maturity was 18, 35, 43, 65 months, respectively. FA increased as much as 160%, while $\lambda_{\perp}$, MD and $\lambda_{\parallel}$ decreased 52%, 35% and 11% from 2 weeks to 6 years. Repeated ANOVA for the DTI measures from the 3 young subjects at 4 ages did not show any significant changes. One-way ANOVA for the DTI measures from all the subjects are illustrated in Fig. 3. Significant changes in FA ($F_{(7, 26)} = 10.60$, $p < 0.05$), $\lambda_{\perp}$ ($F_{(7, 26)} = 11.54$, $p < 0.05$), MD ($F_{(7, 26)} = 8.22$, $p < 0.05$) and $\lambda_{\parallel}$ ($F_{(7, 26)} = 3.44$, $p < 0.05$) were observed starting at 1, 2, 3 and 3 years of age, respectively.

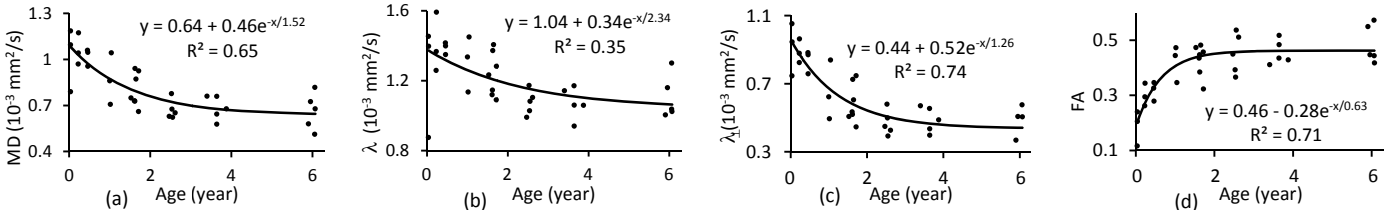

Fig. 2 The changes of (a) MD, (b) $\lambda_{\parallel}$, (c) $\lambda_{\perp}$ and (d) FA with age were fitted with an exponential function $MD\ (or\ \lambda_{\parallel}, \lambda_{\perp}, \mathrm{FA}) = C + Ae^{-age/t}$ [8].

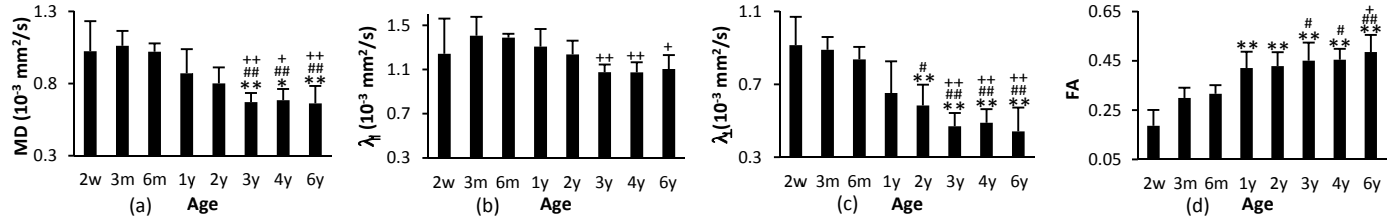

Fig. 3 (a) MD, (b) $\lambda_{\parallel}$, (c) $\lambda_{\perp}$ and (d) FA values of monkey optic nerve at different ages and one-way ANOVA results. *, # and +: significant difference in comparison with subgroups at ages of 2 weeks, 3 months and 6 months, respectively. Single symbol: $p < 0.05$; double symbols: $p < 0.01$. Error bars represent standard deviation.

Discussion and conclusion: In this study, DTI was employed to characterize the development of optic nerve in rhesus monkeys from infant (2 weeks old) to adulthood (6 years old). The results demonstrated that the progression of the optic nerve diffusion parameters followed an exponential trajectory, consistent with the finding in the white matter development of human brain [8]. The different time constants of FA, $\lambda_{\perp}$, MD and $\lambda_{\parallel}$ indicate different time dependency of each diffusion parameter during the early optic nerve development. The diffusion property dependency on time may be used to characterize the normal development of optic nerve, as optic nerve typically consists of a bundle of neuronal fibers and the diffusion parameter changes reflect the progression of neuron myelination. Also, the time to maturity of all the four DTI parameters is comparable with the previous reports on postmortem examination of rhesus monkey optic nerves.

In conclusion, the present study revealed the diffusion parameter property in the early optic nerve development, and all of the results suggest that DTI can be a robust means to access optic nerve non-invasively.

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