DTI Study of Development and Aging of the Optic Nerve in Rhesus Monkeys

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Introduction: Optic nerve (ON) disorders can cause unilateral or bilateral visual failure in children and adults, and are difficult to assess clinically. Diffusion tension imaging (DTI) provides a non-invasive means to assess and evaluate ON abnormality [1] and has demonstrated its sensitivity in several studies of ON development and related pathologies in humans and animals [2-5]. Non-human primates show the closest similarity in brain structure and functionality with human and are the ideal model in the studies of ON abnormalities including axonal and myelin damage. However, chronic changes in the ON during development and aging in monkey model have not been characterized systemically with DTI. In this study, we used non-human primate model to ascertain ON development and aging with DTI.

Materials and Methods: Thirty healthy rhesus monkeys (2 weeks to 27 years old) were divided into 2 groups for imaging: (i) 2 weeks to 6 years old, and (ii) 6 to 27 years old. Animals in group (i) were scanned with a single-shot diffusion tensor imaging (DTI) sequence with parallel imaging (GRAPPA) with an 8-channel phase-array knee coil (INVIVO, Orlando, FL). The imaging parameters were: TR = 5000 ms/TE = 86 ms, FOV = 83mm×83 mm, data matrix = 64×64, slice thickness = 1.3 mm, 60 directions. The monkeys in group (ii) were scanned with a multi-shot double-echo DTI sequence by using a Siemens Extremity CP knee coil. The imaging parameters were: TR = 6970 ms/TE = 104 ms, FOV = 141mm×141 mm, data matrix = 128×128, slice thickness = 1.1 mm and diffusion directions = 60. During MRI scans, animals were immobilized with a custom-built monkey head holder under anesthesia (1-1.5% isoflurane). End-tidal-CO_2, inhaled CO_2, O_2 saturation, blood pressure, heart rate, respiration rate, and body temperature of animals were monitored continuously and regulated. For analysis, the imaging data from all animals were pooled together and divided into 6 subgroups: 2 weeks, 3 months, 20-23 months, 6-7 years, 20-22 years and 23-27 years. DTI data were motion-corrected, averaged and processed for apparent diffusion coefficient (ADC) and fractional anisotropy (FA) maps using SPM, FSL and custom developed software written in Matlab. ADC and FA maps were interpolated to facilitate subsequent data analysis. The region of interest (ROI) was selected on 3 coronal slices located at the anterior quarter of the ON manually for both eyes. Mean values of ADC and FA in the ROI were calculated for both ONs from each animal. The group (ii) results were normalized to the results in the group (i). One-way ANOVA and Pearson correlation were used for statistical analysis.

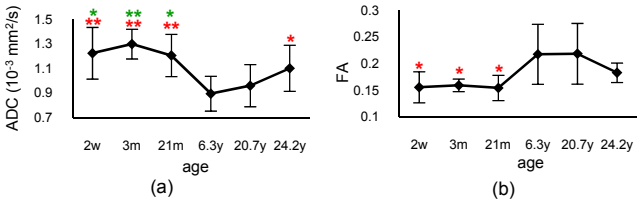

Fig. 1 Mean ADC (a) and FA (b) values of optical nerve of monkeys at different ages. *: $p < 0.05$; **: $p < 0.01$. Red star denotes significant difference from 6-7 years old monkey subgroup; Green star denotes significant difference from 20-22 years old monkey group. Error bars are the standard deviation.

Results and Discussion: Fig. 1 shows the changes of the mean ADC and FA values of ON with age. One-way ANOVA detected significant changes of ADC ($F(5,60) = 12.09$, $p < 0.001$) and FA values ($F(5,60) = 6.62$, $p < 0.001$) due to aging. ADC value decreased significantly from $1.22 \pm 0.21 \times 10^{-3}$ mm^2/s at 2 weeks, $1.30 \pm 0.12 \times 10^{-3}$ mm^2/s at 3 months and $1.20 \pm 0.17 \times 10^{-3}$ mm^2/s at 20-23 months to $0.89 \pm 0.14 \times 10^{-3}$ mm^2/s at 6-7 years of age ($p < 0.001$). FA increased significantly from 0.16 ± 0.03 at 2 weeks, 0.16 ± 0.01 at 3 months and 0.15 ± 0.02 at 20-23 months to 0.22 ± 0.06 at 6-7 years of age ($p < 0.05$). This suggests that the axonal maturation happens between 21 months and 6.3 years. Significant difference was also found for ADC value between the first 3 subgroups and the 20-22 years old subgroup ($0.96 \pm 0.17 \times 10^{-3}$ mm^2/s) and no significant difference was found between the subgroups of 6-7 years old and 20-22 years old, indicating that ON degeneration had not occurred at 20-22 years of age. During aging, significant increase of ADC was observed for old monkeys at 23-27 years of age ($1.09 \pm 0.22 \times 10^{-3}$ mm^2/s, $p < 0.05$) compared with adolescent monkeys at 6 years old, whereas no significant change was observed for FA. This indicates that ON degeneration may occur at ~24 years of age.

During the period from 2 weeks to 6-7 years, ADC of the ON showed significant negative correlation ($p < 0.001$) and FA showed significant positive correlation with age ($p < 0.001$, Fig 2). This is consistent with the results shown in Fig. 1 and indicates that axonal maturation and ON fiber myelination happens before the age of 6 years in Rhesus monkeys. ADC was observed to have a significant positive correlation with age ($p < 0.01$) after 6 years of age, while no significant correlation was found between FA and age in this age range. This result is consistent with One-way ANOVA result (Fig. 1), indicating ON degeneration.

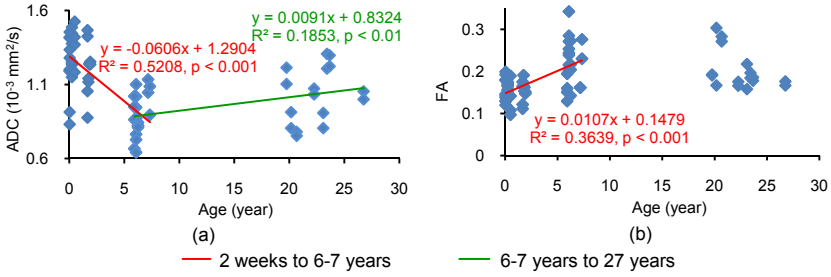

Fig. 2 Pearson correlation (a) between ADC value and age; (b) between FA value and age.

Conclusion: ADC and FA evolution in the ON of monkeys during development and aging was investigated systematically with DTI. Significant changes were found between 21 months with 6 years of age, but not observed in the ON in early development. Furthermore, DTI revealed age-related changes in older rhesus monkeys that may represent axonal and myelin degeneration. DTI may provide a means to evaluate ON disorders or injury.

References: [1] Lystad et al., ultrasound Clin 3:257–266, 2008. [2] Xu et al., NMR Biomed. 21(9):928-940, 2008. [3] Wheeler-Kingshott et al., Mag. Reson. Med. 56:446-451, 2006. [4] Kolbe et al., NeuroImage 45:679-686, 2009. [5] Coimbra et al., Proc. Intl. Soc. Mag. Reson. Med. 17:1074, 2009.