

Early white matter maturation: a longitudinal study of normal pediatric subjects from the age of 2 weeks to 4 years

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Introduction: Current DTI based early brain developmental studies [1-6] have revealed 1) the non-linear early postnatal changes in fractional anisotropy (FA) and mean diffusivity (MD), 2) higher FA and lower MD values in central brain region after birth, 3) the development of limbic fibers before the association fibers, and 4) commissural and projection fibers forming from anterior to posterior. Our study consists of several unique features when compared with the previously published ones. First, our work is a longitudinal study which substantially improves statistical power for detecting subtle changes compared to cross sectional studies. Second, full-term healthy subjects without sedation were studied while most of the previous studies employed subjects born pre-maturely and/or scanned for clinical indications. Third, both axial (AD) and radial diffusivities (RD) were examined in this study while most of the previous studies only evaluated fractional anisotropy (FA) and mean diffusivity (MD). Finally, ROI analysis was the method of choice for most of the published studies. As a result, the inhomogeneity of DTI parameters within the same white matter structure may be overlooked. In contrast, our analysis is computational anatomy based, which allows for a detailed evaluation of the maturation patterns of the four DTI parameters (FA, MD, AD and RD).

Methods: This study was approved by institutional review board. Written consents were obtained from parents. Twenty nine (17M, 12F) full-term healthy neonates were recruited for a longitudinal study up to four years. DTI with six encoding directions were acquired after the subjects were fed and swelled to sleep on a warm blanket with proper ear protection. No sedation was used during the imaging session. There were a total of 71 datasets (23 neonates, 18 1-year-old, 23 2-year-old, and 7 4-year-old). All FA images were registered towards a template of a two-year old FA images (not a subject in this study) with an elastic registration technique, HAMMER [7], which considers neighborhood intensity distribution and edges for image alignment instead of image intensity alone. The regression analysis was a generalized estimating equation based framework which is able to handle the missing data problem in a repeated measurement [8]. Initially, age and gender were considered as covariates in the estimating equation ($Y = a_0 + a_1 \cdot \text{age} + a_2 \cdot \text{age}^2 + a_3 \cdot \text{gender}$, age = days-after-brith/365) to fit the data. After no significant relation was detected for gender, the model fitting was repeated with age as the only covariate ($Y = a_0 + a_1 \cdot \text{age} + a_2 \cdot \text{age}^2$) where Y represented FA, MD, AD and RD, respectively. Thus, the coefficients a_0 , a_1 and a_2 represent the changing pattern of a DTI value at birth (age = 0), the velocity (a_1), and acceleration (a_2). In order to preserve the potential inhomogeneous patterns of these DTI parameters, regression analysis was performed directly with the unsmoothed images.

Results: Non-linear maturation patterns were observed for all four DTI parameters (Fig. 1). For FA, the central white matter areas (including the corpus callosum and internal/external capsules) have higher values compared to peripheral white matter at birth (Fig. 1A). The corpus callosum and internal capsule have a positive velocity (Fig. 1B), and a negative acceleration (Fig. 1C). MD has a lower value in the central regions at birth, and higher values in frontal and parietal white matter regions (Fig. 1D). The frontal and parietal white matter regions have a more rapid reduction velocity (Fig. 1E) and positive acceleration (Fig. 1F). In a_0 map of AD (Fig. 1G), the white matter have a higher value, while in a_0 map of RD (Fig. 1J), posterior limb of internal capsule has the lowest value. The velocity and acceleration maps of AD (Fig. 1H and I) and RD (Fig. 1K and L) are very similar to their counterparts in MD.

ROIs with a fixed size (3*3 voxels) were placed at the center of genu, body and splenium of corpus callosum (CC), and bilaterally at internal/external capsules (IC/EC) and putamen. The mean growth curves for these four DTI parameters were plotted in Fig. 2. Genu has a higher FA value than both splenium and body within the whole period (Fig. 2A). At birth, IC has a slightly higher FA value than body, but body's FA becomes higher at around 6 months. EC has a very slow increase in FA value and there is almost no change for FA in putamen. In MD, these brain structures have a descending order of splenium, body, genu, EC, putamen and IC (Fig. 2B). In AD, the descending orders are from splenium, genu, body, IC, EC to putamen (Fig. 2C). The changing pattern in RD is more complex due to crossing points presented before 1.5 years, where the growth curves of splenium and body intercept the growth curves of EC and putamen, and the growth curve of genu crosses IC's (Fig. 2D).

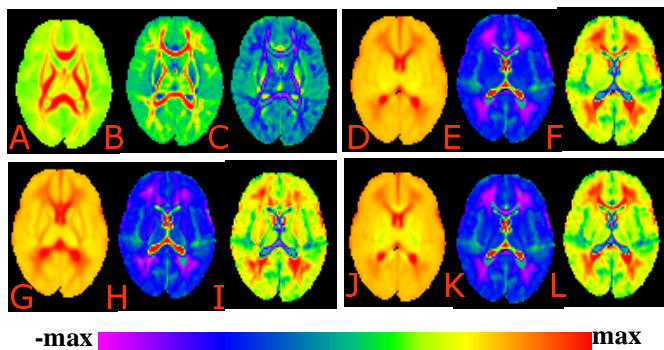


Fig.1. The triple coefficient (a_0 , a_1 and a_2) maps for FA (A,B,C), MD (D,E,F), AD(G, H and I), and RD(J,K and L). **max** was adjusted to different values for different parameters to improve the viewing contrast.

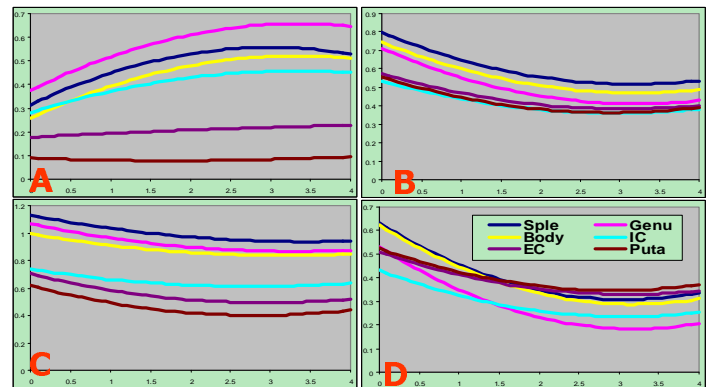


Fig.2. The growth curves for FA (A), MD (B), AD (C) and RD (D).

Discussion: Our computational anatomy based analysis is able to reveal the non-linear maturation patterns of four DTI parameters in a critical time period of early brain development. The inhomogeneity of the maturation patterns within white matter was demonstrated. We also confirmed that genu is more rapidly developed than splenium in CC. Comparing the changes in AD and RD may allow an interpretation of the observed changing pattern with improved specificity. The reduction of RD and AD are very similar in putamen (30% for both RD and AD) and EC (26% for AD and 33% for RD), which may be explained as dominance of brain water reduction. Genu demonstrates largest reduction in RD (61%) compared to splenium (47%) and body (50%), while these three regions have a similar reduction in AD (18% for genu, 17% for splenium, 15% for body), suggesting that the myelination at genu is more rapid whereas splenium and body are in a slower pace. The dynamic and complex growth curves of RD reported in our study also warrants future work to explore the physiological underpinnings of such a complexity in white matter development.

Reference: [1] Mukherjee, et al NANO 2006:16,19-43. [2] Huang et al. Neuroimage.2006 33:27-38. [3] Neil et al, Radiology, 1998;209:57-66. [4] Zhai, et al. Radiology 2003;229:673-81. [5] Mukherjee, AJNR 2002; 23:1445-56. [6] Hermoye et al, Neuroimage 2006;29:493-505. [7] Shen et al, IEEE-TMI, 21(11), 1421-39, 2002. [8] Li et al, SPIE 2009.