Assessment of microstructural white matter changes during early development with non-Gaussian diffusion MRI

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INTRODUCTION: The human brain undergoes rapid changes at both macro- and microstructural levels during early stages of development. Diffusion tensor imaging (DTI) is often used to characterize the maturation and myelination processes in the white matter (WM)[1-3], but does not capture the non-Gaussian diffusion properties of water as observed in the brain. Diffusional kurtosis imaging (DKI) is a clinically feasible extension of DTI that quantifies the non-Gaussian diffusion properties in biological tissue through estimation of the diffusional kurtosis. Recently, a WM model was introduced that allows for a direct physical interpretation of the DKI metrics in terms of the characteristics of WM microstructural integrity, including the axonal water fraction (AWF), the tortuosity, and intra- and extra-axonal compartmental diffusivities[4]. In this work, we present initial results for age-related changes in these DKI and WM parameters during the first two years of healthy brain white matter development.

METHODS: This retrospective study included 50 pediatric patients (28 female, 22 male) ranging from 1 day to 754 days in age with no history of neurological dysfunction. All subjects underwent MRI from 2009-2011 on a 1.5 T Avanto Siemens MR scanner. Whole brain DKI data were acquired using 30 diffusion gradient encoding directions and 3 b-values (0, 1000, 2000 s/mm²). Other parameters include: TR/TE: 4500/96 ms, FOV: 230×230 mm², matrix: 88×88×30, slice thickness: 5 mm, gap: 0%, 1 average, time: 4 min, 48 sec. DKI post-processing[5] in Matlab provided parametric maps of the standard DTI metrics of mean diffusivity (MD), axial diffusivity $D_{\parallel}$, radial diffusivity $D_{\perp}$, and fractional anisotropy (FA), as well as the additional DKI metrics of mean kurtosis (MK), axial kurtosis $K_{\parallel}$, and radial kurtosis $K_{\perp}$. The DKI maps were then used to derive WM parametric maps[4] for the AWF, the tortuosity, and the intra-axonal (D_{axon}) and extra-axonal axial (D_{e}) diffusivities. Subsequently, 5 regions of interest (ROIs) in the WM (i.e. the genu, splenium, external capsule (EC), anterior and posterior limb of the internal capsule (IC)) were defined on the FA-map for each subject as shown by the example in Fig. 1(a). Average values of the DKI and WM parameters over each ROI were correlated with subject age X by fitting each parameter value P to a non-linear function ($P = ae^{-bX} + c$).

RESULTS: Non-linear regression showed significant age-related changes for all DTI metrics (except for $D_{\parallel}$), as well as for the additional DKI metrics in all WM ROIs (except for $K_{\parallel}$ in the splenium). Of the WM parameters, significant non-linear changes were found in all WM ROIs for the AWF, tortuosity, while D_{axon} and D_{e} did not significantly change during development. Considerable regional variations are observed in the time course and size of the age-related changes as demonstrated in Fig. 1 (b) for the AWF. The percentage changes averaged over all 5 ROIs are shown in Fig. 1 (c), showing that all kurtosis parameters, as well as the AWF and tortuosity increase, while all diffusivities decrease from age 0 as a baseline. Overall, the highest correlations (Pearson correlation coefficient > 0.9) were found for the AWF, MK and $K_{\perp}$.

DISCUSSION: This first study of the normally developing human brain during early development using DKI demonstrates significant non-linear changes in the DKI parameters. The large relative changes (Fig. 1(c)) and high correlation with age of the DKI parameters suggest an increased sensitivity to changes in tissue microstructure as compared to standard DTI, as has been previously demonstrated in a rodent brain maturation study[6]. The DKI-derived WM integrity parameters for the AWF and tortuosity are specific markers of myelination, and hence show a strong correlation with age. The regional variations in the AWF (Fig. 1(b)) are consistent with known patterns of brain maturation as depicted by FA[2]. The WM parameters D_{axon} and D_{e}, on the other hand, are not sensitive to myelination, but specific markers for the intracellular and extracellular diffusion, respectively. Our results show no appreciable changes in these parameters with age, as would be expected in normal development.

In summary, the increased sensitivity of the DKI parameters, combined with the high specificity of the new WM parameters, makes this non-Gaussian diffusion MRI technique ideally suited for the evaluation of normal brain development, as well as the investigation of pathological stages within the developing brain.

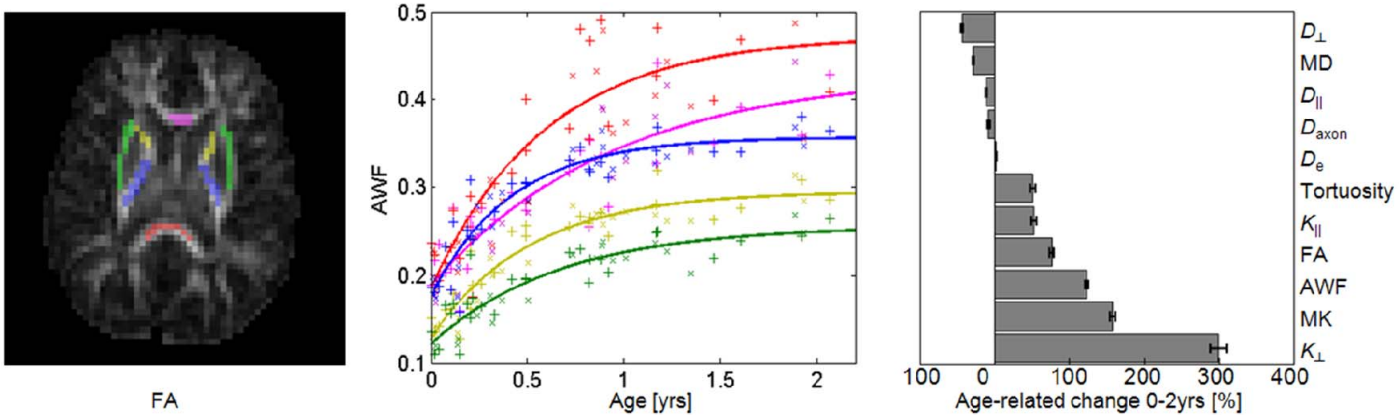

FIGURE 1: (a) FA-map of a 300 days old female showing the studied ROIs: genu in magenta, splenium in red, anterior limb IC in yellow, posterior limb IC in blue and the EC in green; **(b)** Regional variations for the AWF as a function of age where the colors of the data points (+ female, × male) and fitted curves match the color of the ROIs in Fig. 1(a); (**b)** Percentage age-related changes of the DKI and WM parameters during the first 2 years averaged over the 5 ROIs. The error bars represent standard errors.

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