Age-Related Patterns of Change in Brain Microstructure by Diffusional Kurtosis Imaging

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INTRODUCTION: The normal brain undergoes structural changes during the human life span with the patterns of change in gray and white matter differing substantially in development and aging. These patterns of changes in brain tissue microstructure follow the process of continuous myelination and later on gray matter loss and white matter degeneration. The ability to quantitatively characterize age-related changes in brain structure *in vivo* has the potential to improve our understanding of the relationship between structure and cognitive ability that change during the human life span and perhaps improve our ability to differentiate and diagnosis numerous neurological diseases. Recently, our laboratory has developed a generalization of diffusional tensor imaging (DTI) called diffusional kurtosis imaging (DKI), which quantifies the non-Gaussian nature of the diffusion process resulting from tissue microstructure diffusion barriers, such as cell membranes (1; 2; 3). We have used DKI to investigate age-related pre-frontal brain microstructure in three groups of normal subjects. Histograms of DKI-derived metrics (fractional anisotropy, FA; mean diffusivity, MD; mean kurtosis, MK) were obtained and MK histograms are shown to have distinct patterns for each age-range and a distinct signature for CSF, gray matter and white matter.

METHODS: The experiments were conducted on a 3T MR system (Trio, Siemens Medical Solutions). DKI scans were performed on a total of 19 normal subjects consisting of three groups: 1) children (ages 12-17 yrs; n=7); 2) young adult (ages 29-44 yrs; n=6) and 3) cognitively intact elderly (ages 63-85 yrs; n=6). The DKI experiments used 30 gradient encoding directions and 6 b-values (0-2500s/mm2). Other imaging parameters were: TR=2300ms, TE=108ms, FOV=256x256mm^2, 15 oblique axial slices, voxel size 2x2x2mm^3, total scan duration 11'57". The diffusion tensor and diffusion kurtosis tensor were computed using a previously described model (3), and parametric maps were calculated for FA, MD and MK. A pre-frontal brain region of interest (ROI) was manually draw in five slices containing a large portion of the frontal lobe; the ROI extended from the most anterior point containing brain tissue in each slice until the dorsal border of the genu of the corpus callosum. Histograms were calculated for each subject using all of the voxels within the ROI. The MD used value intervals (bins) ranging from 0 to 3 μm^2/ms at 0.047 μm^2/ms increments (bin size). The FA used bins ranging from 0 to 1 (dimensionless) with a bin size of 0.016. The MK used bins ranging from 0 to 2 (dimensionless) with a bin size of 0.031. The histograms were then normalized against the total number of voxels for each subject, so that the sum of all values within one histogram equals unity. ROI drawing and histograms were obtained using ImageJ (http://rsb.info.nih.gov/ij/).

RESULTS and DISCUSSION: Shown in Figure 1 are the FA, MD and MK histograms from each group. Since the DKI data fitting gives the kurtosis as well as the FA and diffusion coefficients, all the diffusion data were derived from a single dataset. The FA histograms show a reduced FA for the older adult group but little difference is apparent between the children and the younger adult group. Although the MD histograms are similar for all three groups (peak MD values ~ 0.75-1.31), the elderly group demonstrates a wider distribution of values. The MK histograms however, show distinct peaks for gray matter (~0.75) and white matter (~1.25) for all 3 groups. This is a major advantage of MK over FA since FA provides little if any information about gray matter structure. Additionally, the MK data demonstrate several interesting features: the white matter kurtosis for the younger adult group (red) is shifted to a higher kurtosis value than either the older adult group (yellow) or the children (blue), consistent with an overall higher degree of microstructural complexity; the white matter kurtosis for the older adult group and the children are similar suggesting comparable microstructural complexity; the peak gray matter kurtosis value for the children is lower compared to either adult group indicating a reduced gray matter microstructural complexity for this group. Differences in gray-to-white matter voxel fraction ratio are also evident in the kurtosis histograms. Children have the highest ratio followed by the younger adult group followed by the older adult group. This order is predicted from post-mortem studies. Least squares regression was used to examine the relationships of MK and FA with age and gender. The regression models to predict both FA and MK included gender as a classification factor and age as a continuous factor. Gender was observed to have a significant main effect on MK mean ($p=0.040$), with males having significantly higher mean MK values than females of the same age, but not on FA ($p>0.18$). In a further analysis, peak white matter kurtosis values were plotted versus age for all three groups (Figure 2). The children demonstrate a strong correlation ($R^2 = 0.75$) with kurtosis increasing with age. This is consistent with the intense myelination that is taking place during this age range. The kurtosis value for the white matter peak for the adults, taken together as one group, shows a consistent albeit less robust decline with age. This is most likely representative of white matter degradation known to occur during this age range. These data demonstrate the application of diffusional kurtosis measurements and highlights its significant advantage of allowing for the quantification of microstructural complexity in both gray and white matter in the developing and aging brain.

Figure 2

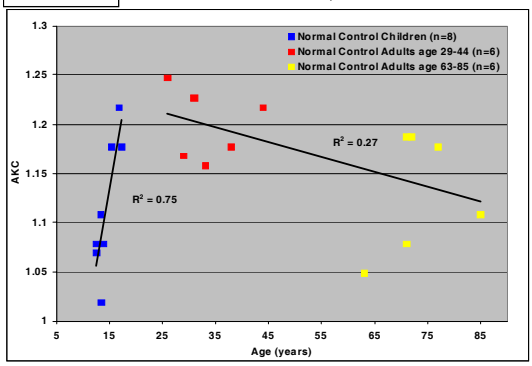
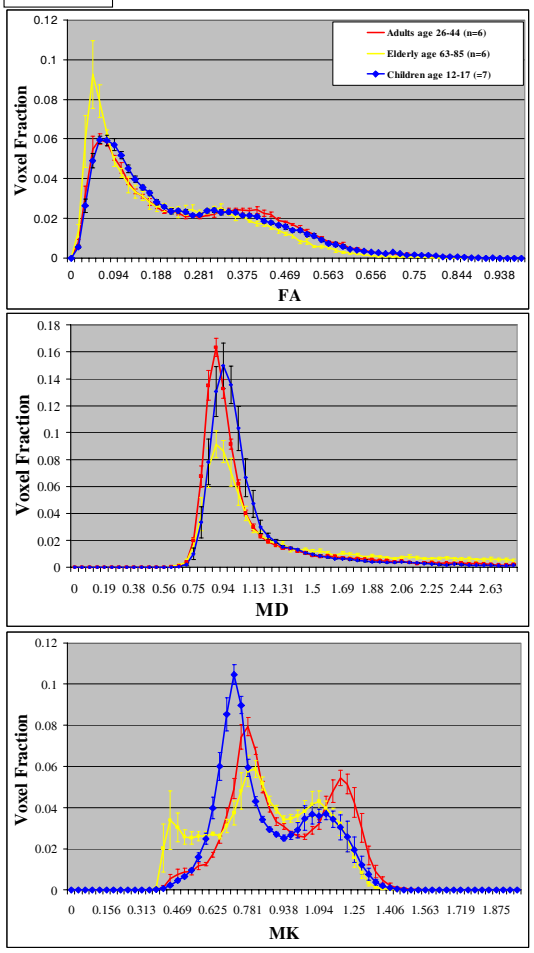


Figure 1



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