Development of axonal pathways in preadolescent children

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***Introduction*:**
Studies indicate that abnormal brain development during childhood increases the risks for various cognitive and psychiatric disorders. Therefore understanding normal brain development is of great importance to study these abnormalities. We have previously reported our findings on changes in cortical gray matter in normally developing children and we extended that investigation to explore changes in major pathways of the cerebral white matter (WM). Previous studies reported cerebral WM changes from childhood to early adulthood using DTI [1]. A review of DTI studies of WM development can be found in the paper by Cascio et al [2]. However, most of those studies reported average Fractional Anisotropy (FA) or Mean Diffusivity (MD) values in selected ROIs or fiber tracts and a few used voxel based morphometry to search the whole brain for evidence of age associated changes. Our study focused on a narrow age range during late childhood, which is a critical phase in cognitive development. Furthermore, we conducted whole brain analysis to study changes in FA and MD along all major fiber tracts. We also utilized higher spatial and directional resolution DTI on a large population of children to achieve increased sensitivity and specificity. Our findings illustrate changes in fiber pathways of the brain at a higher detail than previously reported.

***Methods*:**
A normative sample of 132 children between the ages of 6 and 10 years underwent MRI scans in 3T Philips Achieva system. The study was approved by the IRB of the university and written consents were obtained from the parents. DTI was acquired using SE-EPI pulse sequence with 32 non-collinear gradient directions with b=800 and a single acquisition with b=0 for reference. The whole brain was acquired with 60 axial slices using FOV=$224\times224mm^2$ and $1.75\times1.75\times2mm^3$ voxel size, NEX=1. TR/TE=9290ms/55ms, SENSE=2.4. Structural MRI scans were reviewed by a radiologist and subjects with an evidence of intraventricular hemorrhage, periventricular leukomalacia, and/or low-pressure ventriculomegaly were excluded from analysis. Correction of eddy current effects and motion was performed using 12 parameter affine transformations. The Fractional Anisotropy (FA) and Mean Diffusivity maps were generated using FDT toolbox of FSL software (http://www.fmrib.ox.ac.uk/fsl/) [3]. The FA maps were processed and analyzed using Tract Base Spatial Statistics (TBSS) software in FSL [4]. In the first step of TBSS, a nonlinear registration tool aligned FA maps from all subjects into the subject-specific template that we generated from our data set. In the next step, a mean FA skeleton was created, which represents the centers of all tracts common to the group. In the final step, FA maps from each subject were projected onto this skeleton. The pixel-wise correlation between age and FA or MD values across subjects were investigated using a permutation test [5], which tests the statistical significance of pixel-wise differences between the two groups for correct labeling of the data against random re-labelings of the same data. Approximately 5000 permutations were tested for this study. All results reported here are thresholded at $p<0.05$ corrected for multiple comparisons using FWE.

***Results*:**
Fig.1 illustrates major fiber tracks in which FA increased and MD decreased significantly with age. In this figure T1 weighted MNI152 standard brain was used as the background and each fiber track is overlaid in green. Then the statistical maps were masked by each fiber track to illustrate the statistically significant changes in that particular track. Age-associated changes in FA and MD are overlaid in hot (red-yellow) and cold (blue-cyan) colors, respectively.

***Discussion*:**
In this study we have demonstrated that most of the major axonal pathways undergo significant age-associated changes between ages 6 and 10. These changes are probably driven by the ongoing synaptogenesis as well as myelination. These results also show that these fiber tracks develop in synchrony with the cortical maturation during this period. For instance, Sowell et al [6] showed that the visual, parietal, motor, sensory and prefrontal cortices underwent significant maturational changes between 5 and 11 years. The fiber tracts that showed age-associated changes in our study are the major connections to those the cortical areas. Interestingly, all major fiber tracks, except uncinate, showed similar increase in FA and decrease in MD values, indicating that they possibly undergo similar maturational changes. However, there were no discernible age-associated changes in FA values along the whole uncinate while MD decreased significantly. Similar observations were reported in some other DTI literature and they suggested that this finding possibly indicated that the three eigenvalues of diffusion decreased proportionally, resulting in the same FA values but a decrease in MD values. This may indicate that the uncinate is possibly undergoing slightly different structural changes during this period.

References: [1] *Barnea-Goraly et al, Cereb. Cortex15:1848-1854, 2005*; [2] *Cascio et al, J . Am. Acad. Child Adolesc. Psychiatry, 46:2, 2007*; [3] *Smith SM et al NeuroImage, 23:208-219 (2004)*; [4] *Smith SM et al NeuroImage 31:1487-1505 (2006)*; [5] *Nichols TE and Holmes AP Human Brain Mapping, 15:1-25 (2002)*. [6] *Sowell et al. J. Neuroscience, 24:8223-8231, 2004*.

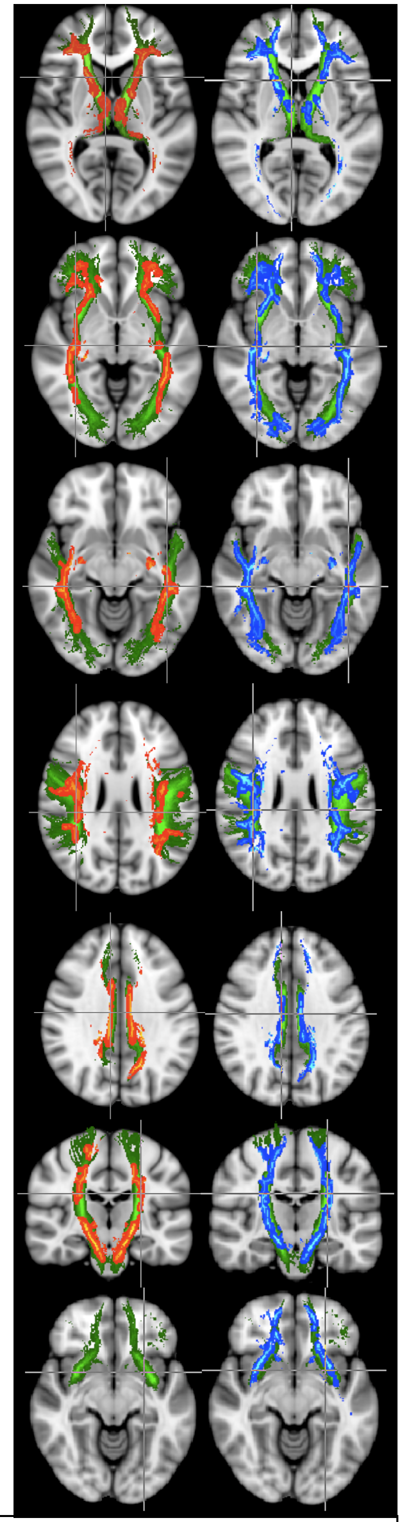

Fig.1. Major fiber tracts that showed statistically significant increase in FA (left column) and decrease in MD (right column) with age. Note that uncinate did not show an increase in FA but a significant decrease in MD was detected. Top to bottom: Thalamic projections, IFO, ILF, SLF, cingulum, CST and uncinate.

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