Alterations in Brain Microstructure in ADHD by Diffusional Kurtosis Imaging

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INTRODUCTION:

Attention-Deficit/Hyperactivity Disorder (ADHD) is characterized by excessive inattention, hyperactivity, and impulsivity, either alone or in combination. It is the most studied condition in child mental health, reflecting its high prevalence (3% to 6% of children) and association with significant lifelong impairment. While there is considerable evidence that both total and regional brain volumes are reduced in ADHD children compared to gender and age-matched controls (1), little else is known about brain structural changes associated with ADHD. Diffusion-weighted MRI provides a powerful tool for probing tissue structure and may be able to provide more insight into ADHD-related brain structural changes. To date, however, there have been limited studies published utilizing diffusion-based MRI in ADHD (2). Recently, our laboratory has developed a new diffusion MRI technique called diffusional kurtosis imaging (DKI), which is based on the non-Gaussianity of the diffusion process (3-5). Non-Gaussian diffusion is believed to arise from diffusion barriers, such as cell membranes and organelles, and water compartments and is, therefore, a natural indicator of tissue microstructural complexity. From DKI, one can derive diffusion metrics such as fractional anisotropy (FA), mean diffusivity (MD) and mean kurtosis (MK). We have utilized this novel diffusion imaging method to study the brains of typically developing children (controls) and children with ADHD.

METHODS:

Imaging was conducted on a 3T MR system (Siemens Trio). DKI scans were performed on control children (2 females + 6 males) with a mean age of 16.5 years (range 12.5 to 17.2 years) and children diagnosed with ADHD (2 females + 7 males) with a mean age of 15.7 years (range 12.8 to 16.8 years. ADHD subjects were recruited from the NYU Child Study Center, were either drug naïve (4 of 9 subjects) or off medication on the scan day, and met either current DSM-IV criteria for Combined Type ADHD (5 of 9 subjects) or predominantly Inattentive Type ADHD. The DKI experiments used 30 gradient encoding directions and 6 b-values (0-2500 s/mm^2). Other imaging parameters were: TR = 2300 ms, TE = 108 ms, FOV = 256×256 mm^2, 15 oblique axial slices, voxel size 2×2×2 mm^3, total scan duration ≈ 12 minutes. The diffusion tensor and diffusional kurtosis tensor were computed using a previously described model (4), and parametric maps were calculated for the mean diffusivity (MD), fractional anisotropy (FA), and mean kurtosis (MK). A pre-frontal brain region of interest was manually drawn 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 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. Histograms were normalized against the total number of voxels for each ROI, so that the sum of all values within one histogram equaled unity.

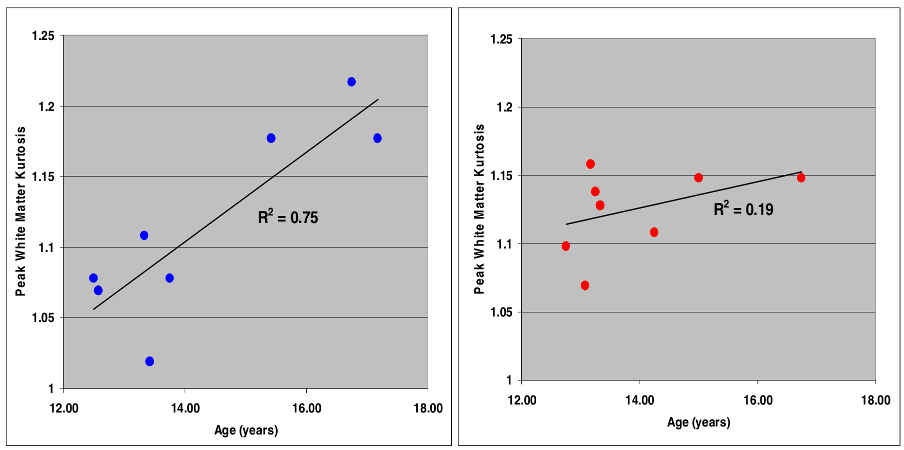

Figure 1: Prefrontal cortex mean white matter kurtosis vs. age for control (left) and ADHD (right) children.

RESULTS and DISCUSSION:

MD and FA values for the two groups were similar and unremarkable. MK values, however, demonstrated different patterns of brain microstructure complexity between control children and ADHD children. The most striking observation was the absence of a significant change in kurtosis with age in the ADHD children as was observed in the control children (Figure 1). Least squares regression was used to characterize and compare ADHD and control children with respect to the association of kurtosis with age and gender. There was no indication of a nonlinear association between kurtosis and age ($p>0.85$) or of a dependence of kurtosis on gender ($p>0.9$). There was a significant age-related increase in mean kurtosis ($p=0.002$), with the rate of increase being significantly lower ($p=0.033$) among ADHD children than among control children. Specifically, kurtosis was observed to increase at a rate of only 0.01 units per year of age among ADHD children and at a more than 3-fold higher rate of 0.03 units per year among control children.

There is now conclusive evidence that ADHD is associated with globally decreased brain volumes relative to age- and sex-matched typically developing controls. These volumetric differences appear to represent a nonprogressive deficit presumably resulting from early genetic and/or environmental factors. It is possible that these volumetric changes are preceded by changes in brain tissue microstructure for which diffusion-based MRI measurements may be sensitive. The results presented above demonstrate the advantages of assessing brain microstructure with DKI. Although these finding are necessarily preliminary given the small samples, it demonstrates the substantial improvement in statistical power associated with DKI. These initial results suggest that children with ADHD differ in developmental trajectory, which necessarily must be examined in a longitudinal manner.

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