Diffusion Abnormalities in Young Drug Naive ADHD Children

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Background: ADHD is one of the most common neuropsychiatric disorders, with a prevalence of 5-10% in school age children. Numerous structural studies attest to the fact that ADHD is a neurodevelopmental disorder characterized by deficits in multiple, inter-connected brain areas, such as limbic and fronto-striato-cerebellar networks. Unlike structural studies, far less is known about potential developmental abnormalities in white matter (WM). This is important given the fact that ADHD patients have dopamine (DA) dysfunction and DA has been reported to have a direct role in modifying the proliferation, migration, and/or differentiation of oligodendrocytes[1], the cell type responsible for axonal myelination. Despite the link between DA and myelination, little is known about the developmental trajectory of WM in the ADHD brain. To our knowledge this is the first DTI study in a group of young ADHD children (7-11 years old) who were completely drug naive.

Materials and Method: Participants consisted of 20 drug-naïve ADHD patients and 25 demographically matched (age, gender, handedness, SES, ethnicity, IQ) healthy controls (HC). Images were obtained on GE 1.5 T magnet with 25 non-linear gradient directions for b=1000 obtaining 23 contagious slices parallel to AC-PC plane with 5 mm thickness covering the whole brain. The details of the image registration and voxelwise analysis have been published and described in detail elsewhere. Following completion of the image registration procedures, we obtain a spatially normalized FA volume for each subject. Voxels with the high statistical significance were thresholded from the final t-map differences obtained comparing the normalized FA volumes between groups. To reduce the false positive rate due to multiple comparisons, we set an extent threshold of at least 100 contiguous voxels at a false discovery rate corrected.

Results: Voxelwise analysis results were superimposed on the averaged normalized 3D of all subjects and are presented in Figures 1. Results show areas where ADHD naïve children showed increased FA (≥100 contiguous connected voxels (cc), fdr corrected $p<0.05$; uncorrected $p<0.003$) as compared to their matched HCs. **Figure 1** depicts clusters of increased FA abnormalities along the fronto-striato-ponto-cerebellar circuit and along the limbic network (orbital frontal, anterior cingulate, posterior cingulate, and temporal lobe). Pearson's correlation analysis showed significant positive correlations ($r=.67$; $p<.004$) between the left cerebellum FA values and Conner's parent hyperactivity/impulsivity raw scores (**Figure 2**).

Conclusion: Involvement of the fronto-striata-ponto-cerebellar and limbic circuits in ADHD children has been well documented in prior ADHD neuroimaging reports. Recent DTI studies report both high and low FA in many brain regions when comparing ADHD subjects and matched controls. The discrepancies in the findings and inconsistent brain areas reported may be due to the broad age ranges studied, failure to control for medication status, comorbid conditions, poorly matched comparison groups (e.g. IQ), and/or suboptimal imaging methodology. The increased FA finding may indicaticate that ADHD children have a different WM trajectory that is delayed compared to HCs. Positive correlations of the FA cluster in the left cerebellum with hyperactivity scores shows that increased FA is a sign of brain abnormality in these unmedicated children. We believe the WM abnormalities reported here may be due to dopamine dysfunction along with a delay in normal brain developmental processes of synaptic pruning and cell and axonal elimination that are followed by active periods of myelination.

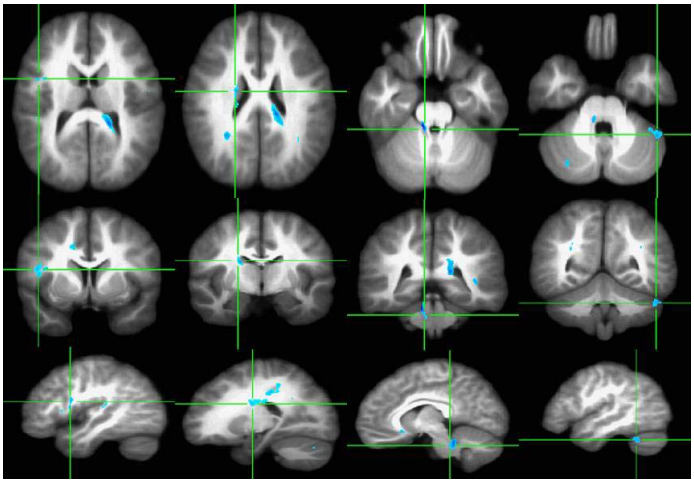

Figure1. Significant clusters of high FA (blue areas) are superimposed on average 3D of all subjects.

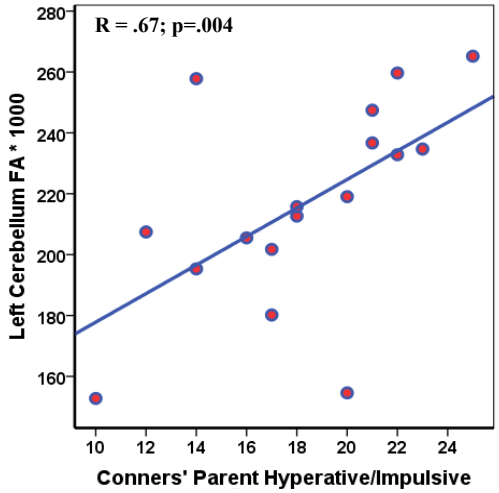

Figure 2. Correlation of the left cerebellar FA and Conners' Parent Hyperactivity/Impulsivity raw scores. Higher FA correlated with higher hyperactivity symptoms in ADHD children.

1. **Bongarzone, E.R., et al., *Identification of the dopamine D3 receptor in oligodendrocyte precursors: potential role in regulating differentiation and myelin formation.* J Neurosci, 1998. 18(14): p. 5344-53.**