

Altered Brain Microstructure in Adolescents with ADHD: A Voxel-Based DKI Analysis

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INTRODUCTION:

Attention-deficit hyperactivity disorder (ADHD) is the most common neurodevelopment childhood disorder affecting approximately 8-12% of children worldwide and is characterized by abnormally heightened inattention, impulsivity and hyperactivity, either alone or in combination. Of the children diagnosed with ADHD, 15% persists with the full-blown disorder into adulthood while another 65% show persistence of some symptoms (1). The neurophysiology of ADHD is only beginning to be understood however substantial evidence have identified the frontal-striatal-cerebellar circuit as the primary site of disruption (2, 3). Recently, our laboratory developed a new diffusion MRI technique called diffusion kurtosis imaging (DKI), which is based on the non-Gaussianity of the diffusion process (4-6). 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, diffusion metrics such as fractional anisotropy (FA), mean diffusivity (MD), and mean kurtosis (MK) can be extracted. In a previous cross-sectional study, our laboratory applied DKI to investigate age-related differences in white and gray matter microstructure complexity of adolescents with ADHD compared to typically developing controls (TDC). Using region of interest (ROI) analysis of the prefrontal cortex, we found that while TDCs displayed dynamic white and gray matter microarchitectural changes from age 12 to 18 years, adolescents with ADHD had stagnant measures throughout this period (7). With the addition of more subjects and utilizing a more robust whole brain voxel-based analysis, this follow up study aimed to identify where the principle regions of dynamic changes occur in controls but are lacking in the ADHD adolescents.

METHODS:

This study involved 11 adolescents with ADHD (9 males) with a mean age of 14.5 years (range: 12.9-17.6 years) and 9 TDCs (6 males) with a mean age of 14.8 years (range: 12.6-17.9 years). ADHD subjects were recruited from the NYU Child Study Center, were either drug naïve (5 of 11) or off medication on the scan day and met

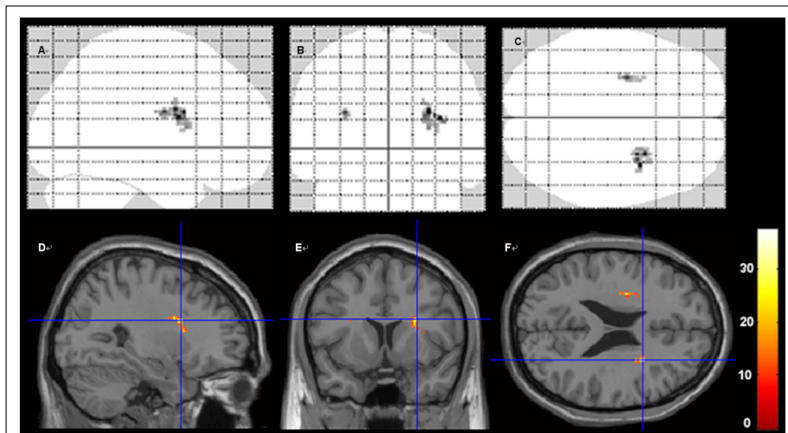


Figure 1. Mean kurtosis voxel-based analysis of typically developing controls (TDC) and ADHD patients

either current DSM-IV criteria for Combined Type ADHD (7 of 11) or Predominantly Inattentive type ADHD. Imaging was conducted on a 3T MR system (Siemens Trio). DKI experiments used 30 gradient encoding directions and 6 b-values (0, 500, 1000, 1500, 2000, 2500 s/mm²). Other parameters include: TR/TE: 2300/108 ms, FOV: 256 x 256 mm², matrix: 128 x 128 x 15, voxels: 2 x 2 x 2 mm³, 2 averages, time: 11 min, 57 sec. Anatomical T1-weighted MPRAGE images were acquired with: TR/TE: 2250/2.61 ms, matrix: 226 x 448 x 160, voxels: 0.7 x 0.6 x 1 mm³, time: 9 min, 13 sec. The diffusion tensor and kurtosis tensor were computed using a previously described model (5), and parametric maps were calculated for the mean diffusivity (MD), fractional anisotropy (FA), and mean kurtosis (MK). Whole brain voxel-based analysis was performed following the methods described in Good et al. (8) using SPM5 (Wellcome Department of Imaging Neuroscience). For each subject, the non-diffusion weighted images (b=0 s/mm²) were coregistered to the T1-weighted images and the resulting affine rigid-body transformation matrix was applied to each of the parametric maps. The T1-weighted images were then normalized with a nonlinear warp to common stereotatic space using the MNI ICBM 152 template. The resulting matrix was applied to the coregistered parametric maps for normalization. A skull stripped binary mask was created from the normalized T1-weighted images by combining binarized WM and GM segmented data. A group mask was generated from overlaying all the individual binary masks within each group. This group mask was used to skull strip the normalized parametric maps to ensure a one-for-one voxel match for all of the datasets. Linear regression analysis was carried out for all sets of images using SPM5. Voxel-wise two sample t-tests and F-tests were performed to detect voxels where the slope of diffusion data differs for each group with age as a covariate. Significance values were set at p<0.001 height threshold, using a cluster size of no less than 75 voxels.

RESULTS and DISCUSSION:

Voxel-based whole brain MK F-test analysis revealed a significant group by age interaction in two clusters in the right and left frontal lobes: a right hemisphere cluster with 181 contiguous voxels (MNI 152 coordinates x=28, y=10, z=24) and a left hemisphere cluster of 91 voxels (MNI 152 coordinates x= -30, y= -4, z= 24). These two clusters spanned the right and left regions of the internal capsule (anterior limb), the corona radiata and the superior longitudinal fasciculus. Figure 1 shows the F-contrast of significant voxel clusters superimposed on a glass brain (A-C) and on the standardized MNI Colin27 anatomical brain (D-F). Similar analysis using both FA and MD data showed no significant interactions. Overall, the voxel-based results confirm the prevailing theory that ADHD is predominantly a white matter disorder affecting the frontostriatal circuitry (2-3). The stagnant development of the prefrontal cortex in ADHD adolescents observed in our previous ROI analysis seems to be localized to key pathways that serve as relays between the cortex and the striatum as well as between frontal and parietal cortices. Given the small cross-sectional nature of the study, interpretation of the results should be made with caution however the results do align with the growing evidence that ADHD has an aberrant developmental trajectory. Characterization of this age-related development on the level of white and gray matter microarchitecture is crucial in teasing out which specific circuitry is affected. Application of DKI to this investigation is warranted as it has shown to be highly sensitive to detecting these tissue properties. Future direction of the study includes collection of more subjects including younger cohort as well as follow up longitudinal analysis of current subjects in order to comprehensively assess the age-dependent relationship of this observed aberrant development.

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