Diffusion MRI Detects Different Developmental Trajectory in the Thalamus of Adolescents with Attention-Deficit Hyperactivity disorder (ADHD) Compared with Typically Developing Controls

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INTRODUCTION: The thalamus is a major subcortical relay station which mediates communication among brain regions related to memory, consciousness, motor, attention, perception, and the integration of thought processes [**1,2**]. Since the neuroanatomical basis of attention deficit-hyperactivity disorder (ADHD) is postulated to involve the frontal cortical-basal ganglia-thalamic-cerebellar circuits [**3,4**], we decided to examine the microstructural integrity of the thalamus in adolescents with ADHD using diffusion MRI, including a new technique called diffusional kurtosis imaging (DKI) [**5,6,7,8**]. The diffusional kurtosis is of interest as an indicator of the diffusional heterogeneity generated by diffusion barriers, such as cell membranes and organelles, which can indicate the degree of diffusion restriction or tissue complexity.

METHODS: Twenty-one adolescents (age range = 12-18 yr) were recruited from the NYU Child Study Center. The ADHD group included twelve adolescents (9 males, 3 females ; mean age =15 yr) diagnosed with ADHD according to DSM-IV criteria for Combined Type or Predominantly Inattentive type ADHD, and were either drug naïve or off medication on the scan day. The typically developing control group (TDC) included nine adolescents (5 males, 4 females; mean age =14 yr). The protocol was approved by the institutional review board of NYU Langone Medical Center. Written informed consent was received from parental and legal guardians of all subjects. DKI scans were performed on a 3T Siemens Trio MR system, using 30 gradient encoding directions and 6 b-values (0-2500s/mm^2). Other imaging parameters were: TR/TE=2300/108ms, FOV=256×256mm^2, 15 oblique axial slices, voxel size 2×2×2 mm^3 and 2 averages. Anatomical T1-weighted MPRAGE images were acquired with: TR/TE: 2250/2.61 ms, matrix: 226x448x160 and voxel size 0.7×0.6×1 mm^3. The DKI dataset was used to calculate parametric maps for the mean diffusivity (MD), fractional anisotropy (FA), axial diffusivity (D_{ax}), radial diffusivity (D_{ra}), mean kurtosis (MK), axial kurtosis (K_{ax}), and radial kurtosis (K_{ra}) [**7,8**]. Rectangular regions of interest were drawn on both right and left thalamus on the b=0 images, on three consecutive slices by the same reader (WRG). To assure the same anatomical level in all subjects, the central slice was determined to be at the level of the anterior horns of the lateral ventricles, adding one slice before and one after. To minimize partial volume effect voxels with MD >2 were excluded from the analysis. Group means (+/- s.d) for all diffusion metrics were calculated. Unpaired t-tests were performed to compare groups' means ($p < 0.05$) of the diffusion metrics. The relationship between mean diffusion metrics and age was evaluated by Pearson's correlation ($p < 0.05$).

RESULTS and DISCUSSION: Group comparison showed no significant mean difference between TDC and ADHD adolescents for all diffusion metrics. The age-related correlation analysis showed a negative correlation for D_{ax} (-0.76; p= 0.017), and a positive correlation for K_{ax} (0.84; p= 0.005) for the TDC group. Although MD and D_{ra} showed a negative trend, and MK showed a positive trend, they were not significant ($p>0.05$). There was no age-related correlation with any of the diffusion metrics for the ADHD group. The thalamus is a morphologically heterogeneous grey matter region with several major nuclear groups traversed by a band of myelinated fibers that forms the frontal-striatal-thalamic-cerebellar connections. The data presented here shows that for a typically developing adolescent in this age range (12-18 yr), there is a decrease in axial diffusivity (D_{ax}) and an increase in axial kurtosis (K_{ax}) in the thalamus, which may represent the continuing myelination and changes in cell-packing density that occurs during normal brain development. On the other hand, there were no significant age-related diffusion changes in the ADHD group. Although it is not known what the morphological differences in the thalamus of ADHD children are, we may speculate that it could represent differences in the axonal fibre pathway, in cell-packing distribution and/or in the degree of myelination, which could change the normal thalamus microarchitecture. We have previously reported that TDCs display dynamic pre-frontal cortex microarchitectural changes during the same age range (12-18 yr), while adolescents with ADHD shows stagnant measures throughout this period [**9,10**]. It is important to mention that one mechanism controlling the development of the thalamocortical projections is believed to be the axon–axon interactions with cortical efferents axons in the internal capsule [1], which may suggest that the developmental changes seen in the thalamus and pre-frontal cortex in ADHD adolescents are part of the same neurobiological process of the disease. Although these findings are necessarily preliminary given the small samples, and its interpretation should be made with caution, they suggest that there may be a difference in the trajectories of structural development in the thalamus between typically developing and ADHD adolescents, which must be examined in a longitudinal manner.

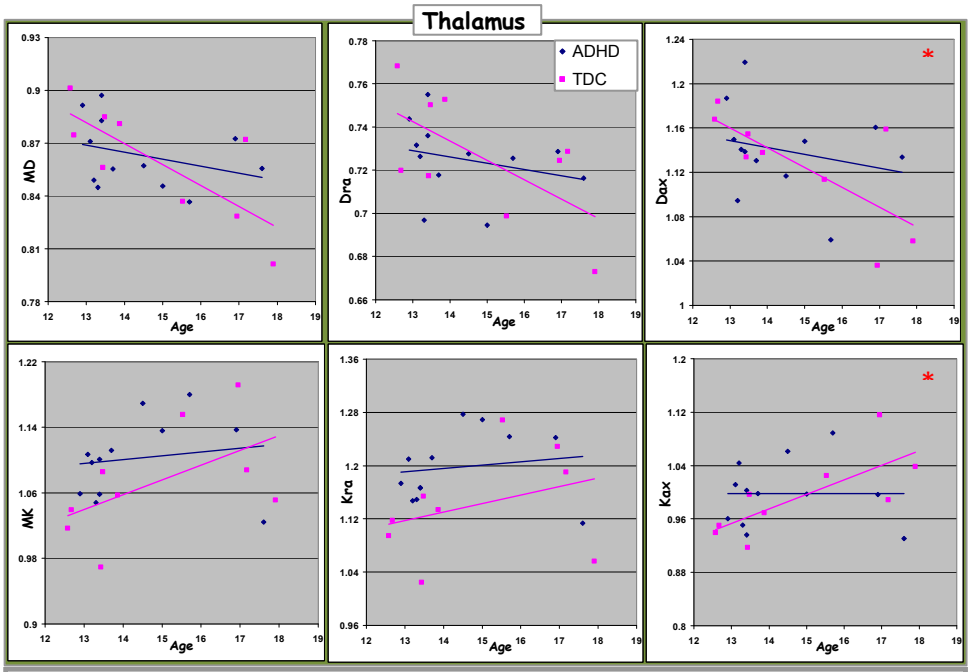

Figure 1. Significant (*) age- related correlation was detected for the TDC group for the following indices: D_{ax}: negative correlation (-0.76; p= 0.017). K_{ax}: positive correlation (0.84; p= 0.005). TDC: typically developing control; D_{ax}: axial Diffusivity; K_{ax}: axial kurtosis.

References: **1**.Vanderhaeghen and Polleux. Trends Neurosci. 2004; 27(7):384-91; **2.** Haber and Calzavara. Brain Res Bull. 2009; 78(2-3):69-74. **3.** Krain and Castellanos. Clin Psychol Rev. 2006; 26(4):433-44. **4.** Kelly et al. Curr Psychiatry Rep. 2007; 9(5):401-7. **5.** Jensen and Helpern. Proc Intl Soc Mag Reson Med 2003;11: 2154. **6.** Helpern et al. Proc Intl Soc Mag Reson Med 2009; 17:3493. **7.** Jensen et al. MRM 2005; 53:1432. **8.** Lu et al. NMR Biomed 2006; 19:236. **9.** Helpern et al. Proc Intl Soc Mag Reson Med 2007; 15:1580. **10.** Helpern et al. Proc Intl Soc Mag Reson Med 2009; 17:1270

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