Evidence of Pronounced Surface Deformation of the Subcortical Caudate Nucleus in Attention Deficit Hyperactivity Disorder Boys with a Comorbid Reading Disability

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Background: ADHD is one of the most common childhood neurodevelopmental disorders characterized by three main symptom domains of inattention, hyperactivity and impulsivity. ADHD is also highly heterogeneous regarding behavioral and cognitive deficits including reading ability where reading disability (RD) coexists in approximately 20-40% of cases. There is evidence of shared deficits between ADHD with RD (ADHD+RD) and RD in processing/naming speed and working memory, which are not present in ADHD without RD (ADHD-RD)[1,2]. However, the neuropathology differentiating ADHD+RD from ADHD-RD is poorly understood. The most consistent neuroimaging observation in ADHD is a reduction in the subcortical caudate nucleus. The striatum, which includes the caudate nucleus and putamen, plays a critical role in the integration of cognitive- and motor control-related frontal areas through corticostriatal pathways[3]. Because cortical projections to the striatum are highly topographically organized[3], assessing morphological deformation in the shape of the caudate and putamen may provide inferences to which corticostriatal pathways are implicated. The striatum has not been implicated in RD; however, it is unclear whether specific alterations in the deformation along the surface of the caudate and putamen are present in ADHD+RD that differentiate from ADHD-RD and healthy control (HC) individuals, which is the objective of this study.

Methods: ADHD+RD (N=14, combine type=13, inattentive type=1; age 9.4±2.3 yrs), ADHD-RD (N=19, combine type=13, inattentive type=6; age 10.0±2.7 yrs) and HC (N=20; age 10.4±2.3 yrs) boys underwent a T_1-weighted structural MRI examination. The right and left caudate and putamen structures were automatically segmented using FSL FIRST[4] followed by manual editing to correct for segmentation errors. The segmented caudate and putamen volume masks were converted to 3D surface maps and rigidly aligned to a standard template surface map using SPHARM-PDM[5]. For each individual, a deformation surface map was estimated by computing the distance difference at each vertex along the surface map relative to the standard template surface map. The deformation maps were then compared statistically between groups using SurfStat[6] with age as covariate. The results of shape analyses were corrected for multiple comparison correction using the false discovery rate method. Additionally, group differences in the caudate and putamen volumes were examined using an ANCOVA analysis with age and intracranial volume (ICV) as covariates.

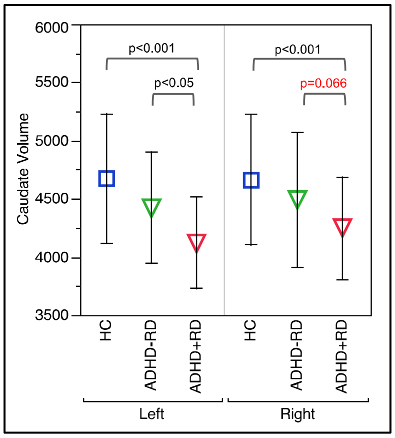

Fig1: ANCOVA analysis showing showed significantly smaller caudate volume in ADHD+RD relative to HC and ADHD-RD.

Results: Regarding volume differences, the caudate nucleus was significantly smaller bilaterally combining the ADHD boys compared to HC boys (left: p=0.006; right: p=0.038). Subgroup analyses showed significant main effects of diagnosis bilaterally (left p=0.003; right p=0.022). Post-hoc analysis showed a significant reduction in the caudate nucleus volume in ADHD+RD boys compared to HC boys (left: p<0.001; right: p=0.006) and compared to ADHD-RD (left only: p=0.036) (Fig1). Putamen did not show any significant group differences in volume. Analysis of surface deformations showed significant compression clusters in the anterior medial (left: no. vertices=156, t=4.39, p=0.032; right: no. vertices=3, t=3.10, p=0.043) and posterior superior (left: no. vertices=14, t=3.71, p=0.032; right: no. vertices= 4, t=3.25, p=0.038) caudate surface in all ADHD boys relative to HC boys. Subgroup analysis of surface deformation showed greater extending significant compression clusters in the anterior medial (left: no. vertices=343, t=5.48, p=0.0022; right: no. vertices=27, t=3.38, p=0.014) and posterior superior (left: no. vertices=185, t=4.20, p=0.0049; right: no. vertices=47, t=4.46, p=0.0049) caudate surface of ADHD+RD boys compared to HC boys (Fig2). There were no significant clusters between ADHD-RD and HC boys. Also, the putamen did not show any significant group or sub-group differences in the shape deformation maps.

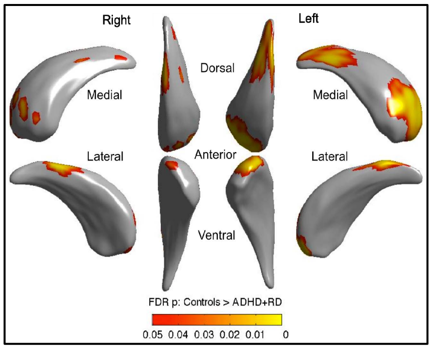

Fig2: Shape analysis showing significant compression clusters bilaterally in the anterior medial and posterior superior caudate surface in ADHD+RD relative to HC.

Discussion: Consistent with other studies, the volume analysis showed, in general, significant bilateral caudate volume reductions in all ADHD boys compared to HC boys; however, the reduction was at a greater extent in ADHD+RD boys and not in ADHD-RD compared to HC boys. The surface shape analysis showed greater specificity to where in the caudate nucleus local surface compressions are present. Specifically, results that primarily were driven by ADHD+RD boys showed surface deformation bilaterally in the anterior medial and posterior superior areas of the caudate nucleus; an effect that was more apparent on the left side. Considering the topographically organized caudate, the surface deformation in the anterior medial portion of the caudate may implicate connections from the inferior frontal/ventral prefrontal cortex, which includes Broca's language area, while the surface deformation in the posterior superior caudate may implicate connections from the dorsal prefrontal/premotor cortex. Further studies using diffusion tensor imaging (DTI) will help to corroborate these findings.

Reference: [1]McGrath LM, Pennington BF, Shanahan MA, et al. *J. of Child Psychology and Psychiatry, and Allied Disciplines.* 2011;52:547-557. [2]Willcutt EG, Betjemann RS, McGrath LM, et al. *Cortex.* 2010;46:1345-1361. [3]Haber SN, Calzavara R. *Brain Res Bull.* 2009;78:69-74. [4]Patenaude B, Smith SM, Kennedy DN, Jenkinson M. *Neuroimage.* 2011;56:907-922. [5]Styner M, Oguz I, Xu S, et al. Insight J. 2006;(1071):242-250. [6]Chung MK, Worsley KJ, Nacewicz BM, et al. Neuroimage. 2010;53:491-505.