Preliminary Evidence of Pronounced Thinning in the Cortex of Attention Deficit Hyperactivity Disorder Boys with a comorbid Reading Disability

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Target Audience: Researchers who are interested in developmental disorder are likely to be interested in the findings of this study.

Background: ADHD is one of the most common childhood neurodevelopmental disorders characterized by three main symptom domains including inattention, hyperactivity and impulsivity. ADHD is also highly heterogeneous in terms of behavioral impairments and deficits in executive functions and cognitive control as well as in reading ability where reading disability (RD) coexists in approximately 25-45% of cases[1]. Studies assessing neuropsychological measures have shown deficits in different cognitive abilities but to a greater extent in ADHD children with comorbid RD (ADHD+RD) compared to ADHD children without RD (ADHD-RD)[2]. There is evidence of shared deficits between ADHD+RD and RD without ADHD in naming speed, verbal reasoning and working memory, which are not present to the same extent in ADHD-RD[2]. Moreover, ADHD+RD children have shown relatively greater impairments in response inhibition and processing speed compared to ADHD-RD[2]. Regarding morphological differences, structural MRI studies have reported significant cortical thinning in the dorsal prefrontal cortex[3], parietal cortex[3] and right anterior cingulate cortex[4] in ADHD relative to healthy controls (HC). While there is clear evidence of greater cognitive deficits in ADHD+RD than ADHD-RD, the neuropathology differentiating ADHD+RD from ADHD-RD from the perspective of cortical morphology remains poorly understood, which is the main objective of this study. In this preliminary three-subject group study assessing cortical thickness, we hypothesize greater and more widespread alterations in cortical thickness in ADHD+RD children and to a lesser degree in ADHD-RD children both compared to healthy control (HC) individuals.

Methods: ADHD+RD (N=15, combine type=14, inattentive type=1; age 9.4±2.5 yrs), ADHD-RD (N=24, combine type=15, inattentive type=9; age 10.6±2.4 yrs) and HC (N=26; age 10.4±2.4 yrs) boys underwent a T_1-weighted structural MRI examination. Seven separate volumes with different inversion times were collected on 3T Siemens Verio scanner (TR=2200ms, TE=2.88ms, flip-angle=13º, FOV=200x256mm^2, 208 axial slices, slice thickness=0.8 mm, matrix=250x320, GRAPPA=2 for parallel imaging, and scan-time=6min/volume) and averaged offline after realigning to the first volume[5]. The averaged volumes were filtered using structurally adaptive non-local means filter to improve SNR[6]. Cortical surface reconstruction and cortical thickness measurements were conducted using the automated pipeline in Freesurfer[7,8]. The errors in skull stripping and white matter segmentation were edited manually slice-by-slice by an trained rater who was blinded to the participant's diagnosis. Each participant's thickness maps were registered to a study specific average subject and smoothed with Gaussian kernel of 20mm. The thickness maps were then compared statistically between groups using a generalized linear modeling (GLM) methodology within SurfStat[9] with age as covariate.

Results: Based on uncorrected p-values for multiple comparisons, ADHD-RD children showed significant clusters of thinner cortex in the right middle/inferior temporal cortex, right medial orbitofrontal, right superior parietal cortex, left inferior temporal cortex and bilateral dorsal prefrontal cortex compared to HC boys (left of Fig 1). As expected, ADHD+RD children showed significant and widespread clusters of thinner cortex in the dorsal prefrontal, orbitofrontal, parietal and temporal cortices bilaterally and in the right cingulate cortex compared to HC boys (right of Fig 1). In contrast, relative to HC, ADHD-RD groups showed significant clusters of thicker cortex in the right postcentral, left dorsomedial prefrontal, bilateral parietal and bilateral orbitofrontal cortices while ADHD+RD showed thicker cortex only in the right parietal and right postcentral cortices.

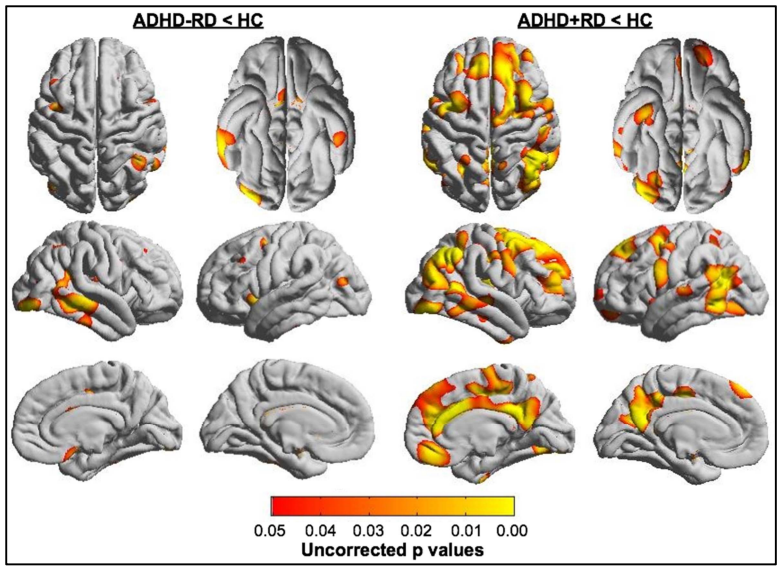

Fig 1: Cortical thickness analysis showing significant clusters of cortical thinning in ADHD-RD and ADHD+RD relative to HC with ADHD+RD showing widespread cortical thinning than ADHD-RD. Note: The top row shows dorsal and ventral views respectively, middle row shows lateral view and bottom row shows medial view.

Discussion: Consistent with other studies, cortical thickness analysis showed significant cortical thinning in dorsal prefrontal, parietal and cingulate cortices in ADHD groups compared to HC. The ADHD+RD group, however, showed more widespread cortical thinning than ADHD-RD when compared to HC. The dorsal prefrontal, parietal and cingulate cortices are critical components of the networks that subserve executive function, attention and cognitive control, which are often impaired in children with ADHD or RD. These results suggest that ADHD+RD boys present a greater extent of cortical alterations relative to ADHD-RD boys, which may underpin the greater cognitive impairments observed in ADHD+RD compared to ADHD alone[2].

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