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Distinct differences in striatal dysmorphology between attention deficit hyperactivity disorder boys with and without a comorbid reading disability

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A B S T R A C T

There is evidence of greater cognitive deficits in attention deficit hyperactivity disorder with a comorbid reading disability (ADHD/+RD) compared to ADHD alone (ADHD/−RD). Additionally, the striatum has been consistently implicated in ADHD. However, the extent of morphological alterations in the striatum of ADHD/+RD is poorly understood, which is the main purpose of this study. Based on structural MRI images, the surface deformation of the caudate and putamen was assessed in 59 boys matching in age and IQ [19 ADHD/−RD, 15 ADHD/+RD and 25 typically developing controls (TDC)]. A vertex based analysis with multiple comparison correction was conducted to compare ADHD/−RD and ADHD/+RD to TDC. Compared to TDC, ADHD/+RD showed multiple bilateral significant clusters of surface compression. In contrast, ADHD/−RD showed fewer significant clusters of surface compression and restricted to the left side. Regarding the putamen, only ADHD/−RD showed significant clusters of surface compression. Results demonstrate for the first time a greater extent of morphological alterations in the caudate of ADHD/+RD than ADHD/−RD compared to TDC, which may suggest greater implicated cortical areas projecting to the caudate that are associated with the greater neuropsychological impairments observed in ADHD/+RD.

1. Introduction

Attention deficit hyperactivity disorder (ADHD), which is marked by atypical levels of inattention, hyperactivity and impulsivity (American Psychiatric Association, 2000), is one of the most commonly diagnosed psychiatric disorders in children with a prevalence of approximately 4–8% worldwide (American Psychiatric Association, 2000; Faraone et al., 2003; Polanczyk et al., 2014; Thomas et al., 2015). The etiology of ADHD or the extent of neuro-morphological alterations in ADHD is not fully understood. Of particular interest is the basal ganglia or specifically the striatum (caudate and putamen) because of its critical role as a hub in receiving inputs from various cortical areas. These corticostriatal projections are part of larger cortico-striato-thalamo-cortical networks such as the limbic, associative and sensorimotor pathways (Haber and Calzavara, 2009; Haber and Knutson, 2010), which have all been implicated in ADHD. Additionally, the mapping of these cortical projections to the striatum is highly organized topographically with the ventral portion of the striatum associated to reward/motivation processing, the head and body of the caudate subserving executive functions, attention and cognitive control, and the putamen primarily related to planning, control and execution of motor functions (Draganski et al., 2008; Haber and Calzavara, 2009; Haber and Knutson, 2010; Leh et al., 2007; Lehericy et al., 2004). Therefore, investigating where along the structural surface of the striatum deviations occur in ADHD compared with typically developing controls (TDC) provides greater insight over conventional volume studies with respect to identifying which corticostriatal projections and related functional role may be implicated in ADHD.

To date, there have only been three studies investigating surface deformation of the striatum in ADHD children. In general, all three studies show surprisingly consistent results of areas of surface compression in the left head and body portion of the caudate and compressed surface areas in the right body and tail portion of the caudate in ADHD children and adolescents compared with TDC (Qiu et al., 2009; Shaw et al., 2014; Sobel et al., 2010). The putamen is implicated in all three studies with compressed deformation along the anterior, middle and posterior portions with greatest effects on the left

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side of ADHD children and adolescents compared to TDC (Qiu et al., 2009; Shaw et al., 2014; Sobel et al., 2010). Additionally, though not noted in all studies, there is evidence of gender effects with greater deformation in ADHD boys compared to ADHD girls (Qiu et al., 2009), age effects with the ventral striatum showing a lack of a progressive expansion with age in ADHD (Shaw et al., 2014), effects of psychostimulant medication status (Sobel et al., 2010), and correlations of symptom severity with surface compression (Sobel et al., 2010). In all, these findings show morphological specificity to surface deformation in the striatum of ADHD children and adolescents but with evidence of variability due to multiple factors.

Another factor to consider is the effect of having a comorbid reading disability (RD) in children with ADHD. The estimated prevalence of co-occurring RD in ADHD is quite high, ranging between 25% and 45% (Del'Homme et al., 2007; DuPaul et al., 2013; Willcutt and Pennington, 2000; Yoshimasu et al., 2010). The etiology of ADHD comorbid with RD is not fully understood; however, it is hypothesized that the common genetic risk factors resulting in the shared pathophysiological endophenotypes may play a key role (Willcutt et al., 2007). ADHD individuals with RD (ADHD/+RD) typically present with deficits in phonological processing (i.e. sounding words) and, to a lesser degree, deficits in orthographic processing (i.e. recognizing words) (de Jong et al., 2009; Willcutt et al., 2010). Also, deficits in multiple cognitive domains including executive functions (working memory and inhibitory control) and processing speed are more pronounced in ADHD/+RD children compared to children with ADHD but without a comorbid RD diagnose (ADHD/−RD) (Willcutt et al., 2010). Collectively, the compelling evidence suggests greater neuropathology in ADHD/+RD compared to ADHD/−RD, but has yet to be investigated specifically from the perspective of structural neuroimaging. Additionally, the inclusion/exclusion criteria of comorbid RD across neuroimaging studies are mixed (i.e., either RD is not assessed, RD is assessed but not included or included in the ADHD sample), which may add greater variance and inconsistencies between studies.

The purpose of this study was to investigate whether unique patterns of surface deformation of striatal structures differentiate ADHD/+RD from ADHD/−RD and TDC. In line with the evidence as noted above from neuropsychological studies showing relatively greater impairments of multiple domains in ADHD/+RD relative to ADHD/−RD and the topographic organization of cortical projections in the striatum, we hypothesize that ADHD/+RD children and adolescents will demonstrate a greater extent of surface compression in the striatum as well as a reduction in conventional caudate volume compared to ADHD/−RD and TDC individuals.

2. Methods

2.1. Participants

Thirty-four ADHD boys and 25 TDC boys from the Detroit (Michigan) metropolitan area and its neighboring border city, Windsor (Ontario), participated in this study. All participants were assessed using the Schedule for Affective Disorders and Schizophrenia for School-Age Children–Present and Lifetime version (K-SADS-PL) (Kaufman et al., 1997) administered by a trained psychologist. Moreover, the parent/guardian and the participant's teacher completed the Disruptive Behavior Disorders Scale (DBD) (Pelham et al., 1992) and the Iowa Connors Hyperactivity/Impulsivity Scale (Loney and Milich, 1982) questionnaires, which was also used as part of determining the ADHD status. The Wechsler Abbreviated Scale of Intelligence (WASI) (Wechsler, 1999) was administered to measure verbal, performance and full scale IQ (FSIQ). The normalized discrepancy scores from the WIAT-III (Psychological Corporation, 2009), based on WIAT-III achievement scores compared to FSIQ, were used to determine if the participant has RD. Participants were considered RD if two out of the three subtest scores eclipsed a discrepancy that is significant at

Table 1
Sample characteristics.

		TDC	ADHD/−RD	ADHD/+RD	*Main Term p-value*
Sample Size		25	19	15	
Age (SD)		10.1 (2.2)	11.0 (2.5)	9.6 (2.4)	n.s.
Full Scale IQ (SD)		105 (13)	109 (18)	104 (16)	n.s.
Verbal IQ (SD)		105 (13)	112 (20)	102 (17)	n.s.
Performance IQ (SD)		104 (13)	104 (15)	104 (13)	n.s.
ADHD Subtype	Combined	–	11	14	–
	Inattentive	–	8	1	–
Oppositional Defiance Disorder		–	7	6	–
Conner's Inattention (SD)		–	60 (12)	60 (9)	n.s.
Conner's Hyperactivity (SD)		–	66 (13)	72 (13)	n.s.
Word Reading Norm (SD)		103 (10)	103 (12)	84 (16)[a]	< 0.001
Pseudoword Decode Norm (SD)		103 (9)	106 (12)	82 (17)[a]	< 0.001
Spelling Norm (SD)		103 (15)	102 (10)	84 (13)[a]	< 0.001

[a] Post-hoc results show significant differences compared to both ADHD/−RD and TDC ($p \le 0.001$).

$p=0.01$ based on the WIAT-III discrepancy score norms (Psychological Corporation, 2009). In case of uncertainty, RD diagnosis was confirmed using consensus from two independent clinical psychologists.

ADHD participants were excluded from the study if they also met criteria for a DSM-IV Axis-I diagnosis of any psychiatric disorder other than oppositional defiance disorder (ODD), conduct disorder (CD) and/or anxiety disorder. The exclusion criteria included individuals who had: (1) a DSM-IV diagnosis of substance abuse in the past 3 months; (2) a significant neurological illness in his medical history; (3) a full scale IQ less than 80; (4) a Children's Global Assessment Scores (CGAS) (Shaffer et al., 1983) score less than 60; or (5) any contra-indications to MRI. A parent/guardian of the participant provided written informed consent and the participant provided verbal assent, as approved by the Wayne State University Institutional Review Board. The subject-group characteristics are summarized in Table 1.

2.2. MRI acquisition

High-spatial resolution 3D T_1-weighted MRI images were collected using a magnetization prepared rapid gradient recalled echo (MPRAGE) sequence with a 12-channel volume head coil on a 3 T Siemens Verio (Siemens Germany) whole body system. The acquisition parameters include: TR=2,200 ms, TE=2.88 ms, flip-angle=13°, FOV=200×256 mm^2, 208 axial slices, slice thickness=0.8 mm, matrix=250×320, pixel resolution=0.8×0.8×0.8 mm^3, GRAPPA=2 for parallel imaging, and scan-time=5:01 min. To improve signal-to-noise ratio and reduce susceptibility to head motion due to long scanning times, seven individual measurements were collected and averaged offline. Furthermore, each measurement was collected at a different inversion time ranging from 766 ms to 808 ms in order to reduce flow artifact. This protocol of collecting high-resolution T_1-weighted structural data has been shown to enhance contrast-to-noise ratio and boundary details (Kochunov et al., 2006).