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Distinct Differences in Striatal Dysmorphology Between Attention Deficit Hyperactivity Disorder Boys with and without a Comorbid Reading Disability

Dhruman D. Goradia^a, Sherry Vogel^b, Brianne Mohl^c, Dalal Khatib^b, Caroline Zajac-Benitez^b, Usha Rajan^b, Arthur Robin^b, David R. Rosenberg^b, and Jeffrey A. Stanley^{b,*}

^aBanner Alzheimer's Institute, Banner Health, Phoenix, AZ, USA

^bDepartment of Psychiatry and Behavioral Neurosciences, Wayne State University School of Medicine, Detroit, MI, USA

^cDepartment of Radiology and Department of Neurology, University of Colorado, Denver, CO, USA

Abstract

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

*Corresponding Author: Jeffrey A. Stanley, Ph.D. Wayne State University School of Medicine, Department of Psychiatry and Behavioral Neurosciences, Tolan Park Medical Building, Suite 5-B, 3901 Chrysler Service Drive, Detroit, MI 48201. Phone: (313) 577-9090; Fax: (313) 577-5900. jeffrey.stanley@wayne.edu.

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Contributors

Dr. Stanley was the principal investigator of the study and supervised data collection, analysis and manuscript preparation. Dr. Goradia conducted the analysis and prepared the first draft of the manuscript under the supervision of Dr. Stanley. Dr. Mohl and Dr. Rosenberg assisted with revising the manuscript. Ms. Vogel assisted with data preprocessing. Ms. Khatib and Ms. Zajac-Benitez assisted with participant recruitment and data collection. Ms. Rajan conducted psychiatric assessment and administered neurocognitive battery.

Conflict of Interest

None of the authors have any financial interests or potential conflicts of interest to disclose.

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implicated cortical areas projecting to the caudate that are associated with the greater neuropsychological impairments observed in ADHD/+RD.

Keywords

ADHD; Learning Disability; Caudate; Putamen; Magnetic Resonance Imaging; Shape Analysis

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 corticostriato-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 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 $p = 0.01$ 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 contraindications 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 T₁-weighted MRI images were collected using a magnetization prepared rapid gradient recalled echo (MPRAGE) sequence with a 12-channel volume head coil on a 3T Siemens Verio (Siemens Germany) whole body system. The acquisition parameters include: TR=2,200ms, TE=2.88ms, flip-angle=13°, FOV=200×256mm², 208 axial slices, slice thickness=0.8 mm, matrix=250×320, pixel resolution= 0.8×0.8×0.8mm³, GRAPPA=2 for parallel imaging, and scan-time=5:01min. 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 766ms to 808ms in order to reduce flow artifact. This protocol of collecting high-resolution T₁-weighted structural data has been shown to enhance contrast-to-noise ratio and boundary details (Kochunov et al., 2006).

2.3 Post-Processing and Generating Surface Maps

Figure 1 presents a schematic of the post-processing steps used to generate and analyze surface maps. The automated post-processing steps, which included non-uniform intensity correction, de-noising, skull stripping, subcortical segmentation, and 3D surface generation and coregistration, were performed using in-house developed Linux shell scripts, FSL (Jenkinson et al., 2012; Smith et al., 2004), Freesurfer (Dale et al., 1999; Fischl et al., 1999), non-uniform intensity correction developed by (Sled et al., 1998), spatially adaptive non-local means de-noising filter (SANLM) developed by (Manjon et al., 2010), and SPHARM-PDM (Styner et al., 2006). As a first step, the 3D T₁-weighted MRI volume segments were visually inspected and those with any excessive visible motion artifacts were removed and not included as part of the averaging of the multiple volumes. The MRI volume segments were then bias field corrected to correct for non-uniform intensity caused by radio frequency field inhomogeneity, eddy currents and brain anatomy (Sled et al., 1998). The bias field corrected volumes were de-noised using SANLM filter, which has been shown to improve SNR while preserving anatomical boundaries (Manjon et al., 2010). The de-noised MRI volume segments were co-registered to the first volume segment using 6 degrees-of-freedom (3 rotation and 3 translational) and then averaged to obtain a single 3D T₁-weighted MRI

volume (Kochunov et al., 2006), which was then down sampled to a 1 mm³ isotropic pixel resolution.

The tracing of the caudate and putamen structures were conducted on the averaged 3D T₁-weighted MRI volumes by generating binary masks outlining these structures separately (i.e., a binary mask for the caudate and putamen structure for each hemisphere). As a first approximation, binary masks of the caudate and putamen were estimated using the automated FSL-FIRST method (Patenaude et al., 2011) and the output was then manually corrected by inspecting slice-by-slice in the coronal view and editing pixels on the mask to ensure utmost accuracy in tracing the structural boundaries of the caudate and putamen structures. The guidelines for tracing the caudate and the putamen have been published before (Lacerda et al., 2003; Sanches et al., 2005). For caudate, the anterior boundary was the coronal slice where the caudate first appears; the posterior boundary was the coronal slice where the caudate is no longer visible; the medial boundary is the lateral ventricles; and the lateral boundary was the internal capsule. Special care was taken to exclude the nucleus accumbens. For putamen, the anterior boundary was the coronal slice where the putamen first appears; the posterior boundary was the coronal slice where the putamen is no longer visible; the medial boundaries are the internal capsule, the nucleus accumbens, and the globus pallidus as we progress from anterior to posterior; and the lateral boundary was the external capsule. Special care was taken to exclude the nucleus accumbens. Two trained raters who were blind to the diagnosis conducted manual editing. The inter-rater reliability was 0.96 for caudate and 0.94 for the putamen.

The manually corrected 3D volume binary masks of the caudate and putamen were then converted to individual 3D surface mesh using the shape analysis toolbox, SPHARM-PDM (<http://www.nitrc.org/projects/spharm-pdm>). This included transforming the volume masks to spherical harmonics based on shape descriptors and using 2,252 uniformly spaced surface points or vertices to define the surface mesh. The surface meshes were then aligned to a “standard” surface space using the Procrustes alignment approach (Styner et al., 2006) and a randomly selected surface mesh of a control subject as the standard surface space, followed by applying a 3mm FWHM smoothing kernel and averaging the surface meshes of each group in order to generate a study specific template surface mesh. Lastly, deformation surface maps were generated by computing at each vertex the signed normal distance difference between the subject’s surface and study specific template. To account for differences in head size, the intracranial volume (ICV) of each subject was also estimated using the output measurement from the Freesurfer’s processing pipeline (Buckner et al., 2004).

2.4 Statistical Analysis

Group differences in age, full scale, performance and verbal IQ, reading performance (word reading, pseudoword decoding, and spelling normed scores), and Conner’s ADHD symptom scores (inattention and hyperactivity scores) were assessed using one-way analysis of variance tests (ANOVA; SPSS version 22, IBM Corp.) with subject-group (ADHD/–RD, ADHD/+RD and TDC) as the main effect term followed by post-hoc analyses of planned contrast comparisons for those group terms reaching significance (i.e., $p < 0.05$). The right

and left caudate and putamen volumes were analyzed with age and ICV as covariates using a univariate analysis of covariance (ANCOVA) followed by post-hoc analyses with a Bonferroni correction to control for multiple comparisons (i.e., with a p-value of <0.004 for significance to control for 12 comparisons in total).

Statistical differences between groups on the surface deformation maps of the caudate and putamen structures were conducted using SurfStat (Worsley et al., 2009) and Matlab (The MathWorks Inc.). A multivariate generalized linear model (GLM) was used to assess group differences on the surface deformation maps on a vertex-by-vertex basis and covarying for age and ICV. ICV was included as a covariate to account for differences in head sizes as ICV was significantly correlated with the mean deformation of the caudate and putamen. The false discovery rate (FDR) multiple comparison correction implemented in SurfStat was employed and an FDR corrected p-value of 0.05 was deemed significant.

3. Results

3.1 Subject-group characteristics

There were no significant differences between subject groups in age ($F_{2,56} = 1.65$, $p = 0.20$), full scale IQ ($F_{2,56} = 0.58$, $p = 0.56$), verbal IQ ($F_{2,56} = 1.69$, $p = 0.19$) or performance IQ ($F_{2,56} = 0.03$, $p = 0.97$). For Conner's composite scores, there were no significant differences between ADHD/–RD and ADHD/+RD in inattention scores ($F_{1,32} = 0.01$, $p = 0.92$) or hyperactivity scores ($F_{1,32} = 1.65$, $p = 0.21$). As expected on the WIAT-III scores, there was a significant group effect on Word Reading normed scores ($F_{2,56} = 12.34$, $p < 0.001$), Pseudoword Decoding normed scores ($F_{2,56} = 18.32$, $p < 0.001$), and Spelling normed scores ($F_{2,56} = 10.69$, $p < 0.001$) with post-hoc analyses showing significantly poorer performance on these three reading scores in the ADHD/+RD group compared to both the ADHD/–RD and TDC groups ($p < 0.001$) and no significant differences between ADHD/–RD and TDC. Refer to Table 1 for complete results.

3.2 Conventional Volume Measurements

After controlling for age, the ICV was not significantly different between subject groups ($F_{2,55} = 1.22$, $p = 0.30$). Univariate analyses showed a significant group effect with the caudate volume bilaterally (right: $F_{2,54} = 6.36$, $p = 0.003$; left: $F_{2,54} = 8.64$, $p < 0.001$). Post-hoc comparisons showed a significantly reduced left ($p = 0.004$), but not right ($p = 0.09$) caudate volume in the ADHD/–RD boys relative to the TDC boys, and a significantly reduced caudate volume bilaterally (right: $p = 0.0008$; left: $p = 0.0004$) in the ADHD/+RD boys relative to the TDC boys (Figure 2a). There were no significant differences in caudate volume between ADHD/–RD and ADHD/+RD (Right: $p = 0.07$; Left: $p = 0.35$). Regarding the putamen volume, univariate analyses showed a significant group effect bilaterally (right: $F_{2,54} = 5.08$, $p = 0.01$; left: $F_{2,54} = 4.09$, $p = 0.022$, $\eta_p^2 = 0.14$). Planned contrast comparisons showed a significantly reduced right putamen volume in the ADHD/–RD boys compared to the TDC boys (Right: $p = 0.003$; non-significant Left: $p = 0.007$), and no significant differences in the putamen volume between the ADHD/+RD and TDC groups (Right: $p = 0.7$; Left: $p = 0.7$) (Figure 2b). There were no significant differences in the putamen volume between ADHD/–RD and ADHD/+RD (Right: $p = 0.03$; Left: $p = 0.04$).

3.3 Surface Deformation Measurements

GLM analysis comparing deformation at each vertex along the surface of the caudate structure of ADHD subgroups to TDC showed multiple significant clusters of vertices reflecting surface compression throughout the caudate structure (Figure 3; Table 2). Relative to TDC, ADHD/–RD showed significant, FDR-corrected clusters of vertices reflecting surface compression in the left anterior ($t = 4.09$; FDR $p = 0.021$; Area = 180.22 mm²) and left middle-posterior ($t = 2.80$; FDR $p = 0.039$; Area = 102.68 mm²) areas along the medial caudate surface (Figure 3a). In contrast, comparison of ADHD/+RD to TDC showed widespread significant, FDR-corrected clusters of vertices reflecting surface compression on the right anterior ($t = 4.56$; FDR $p = 0.003$; Area = 421.86 mm²), right middle-posterior ($t = 5.01$; FDR $p = 0.003$; Area = 310.84 mm²), and left anterior-posterior ($t = 4.56$; FDR $p = 0.003$; Area = 971.57 mm²) areas along the medial caudate surface (Figure 3b). There were no differences in the surface deformation between ADHD/–RD and ADHD/+RD after FDR correction.

GLM analysis comparing surface deformation in the putamen between ADHD subgroups and TDC showed multiple clusters reflecting surface compression along the putamen surface (Figure 4; Table 2). Specifically and relative to TDC, ADHD/–RD showed significant, FDR-corrected clusters of vertices reflecting surface compression bilaterally on the medial-lateral anterior (Right: $t = 4.56$; FDR $p < 0.001$; Area = 349.98 mm²; Left: $t = 5.96$; FDR $p < 0.001$; Area = 330.85 mm²) and dorsal-lateral posterior (Right: $t = 5.88$; FDR $p < 0.001$; Area = 222.31 mm²; Left: $t = 4.59$; FDR $p < 0.001$; Area = 208.76 mm²) surfaces (Figure 4a). In contrast, there were no significant differences in surface deformation between ADHD/+RD and TDC after FDR correction (Figure 4b).

4. Discussion

This study investigated differences not only in conventional volume but surface morphology of striatal substructures between ADHD boys with and without a RD relative to TDC boys. Within the ADHD sample, the proportion of boys with comorbid RD was 44% (i.e. 15 out of 34), which is at the upper end of reported prevalence values (Del'Homme et al., 2007; DuPaul et al., 2013; Willcutt and Pennington, 2000; Yoshimasu et al., 2010). This gave us the unique opportunity to investigate RD effects in ADHD. In line with numerous previous reports, reduced caudate volumes in both ADHD subgroups relative to TDC were observed. However, the effect was bilateral and to a greater degree in ADHD/+RD compared to TDC (Figure 2a). The reduced caudate volume in ADHD/–RD compared to TDC was only observed on the left side. Surprisingly, reduced right putamen volumes were specific to ADHD/–RD and not present in ADHD/+RD both compared to TDC (Figure 2b). A subsequent investigation of surface deformation showed unique significant clusters reflecting compression along the left anterior and left middle/posterior surface of the caudate (i.e., the head and tail portion) in ADHD/–RD compared to TDC (Figure 3a). As hypothesized, there were greater and more widespread significant clusters on both sides of the caudate (i.e., the head, body and tail portion) reflecting surface compression in ADHD/+RD compared to TDC (Figure 3b). However, surface analysis of the putamen showed significant clusters reflecting compressions along the anterior and posterior surfaces

only in ADHD/–RD (and not in ADHD/+RD) relative to TDC (Figure 4). To the best of our knowledge, this is the first study to demonstrate specific and unique morphological alterations in the caudate and putamen differentiating children and adolescents with ADHD/+RD from ADHD/–RD and TDC.

Consistent with our volume results, surface based analysis of the caudate of ADHD/–RD boys showed significant surface areas of compression along the left anterior (head) and left posterior (tail) surfaces. In the putamen, significant areas of compression were observed in the bilateral anterior and posterior surfaces, and in the left middle surface. Moreover, these results are consistent with previous finding of surface compression in the caudate and putamen in children with ADHD compared to TDC (Qiu et al., 2009; Shaw et al., 2014; Sobel et al., 2010). Given the highly organized nature of the striatum (Haber and Calzavara, 2009; Haber and Knutson, 2010), one may speculate that these clusters of surface compression in the head and tail portion of the caudate may implicate the prefrontal cortex (specifically ventral and orbital areas) and the cingulate cortex. This is supported by evidence of morphometric alterations observed in children with ADHD including reduced volume and cortical thinning of the prefrontal and cingulate cortex (Friedman and Rapoport, 2015; Krain and Castellanos, 2006; Nigg, 2013). These structural alterations in the cortex and striatum may underpin the impaired executive function, attention and cognitive control observed in ADHD.

To our surprise ADHD/+RD boys showed significant bilateral volume reduction in the caudate only, and not the putamen, relative to TDC. ADHD/+RD also showed a greater volume reduction or effect size when compared to TDC. Additionally, ADHD/+RD boys showed significant surface areas of compression that extended fully from the anterior to posterior surfaces (i.e., the head, body and tail portion), while the right caudate showed areas of surface compression along the anterior and posterior surfaces (i.e., the head and tail portion). Both ADHD/–RD and ADHD/+RD showed surface compression in the left anterior and posterior caudate surfaces; however, the areas of compression extended further to include the right anterior and bilateral middle caudate surfaces in the ADHD/+RD boys (Figure 3). Again, one may speculate that these more widespread areas of compression in the caudate of ADHD/+RD boys may implicate a greater extent of cortical projects from prefrontal and cingulate cortices. Though not directly assessed in this study, these widespread alterations ADHD/+RD boys are consistent with reports of greater severity of inattention symptoms, poorer performance in reading and greater impairments of cognitive domains observed in neuropsychological studies (Willcutt et al., 2010).

Regarding the putamen, distinct and unique morphological alterations were observed only in the ADHD/–RD boys relative to TDC, which included the anterior and posterior putamen surface areas bilaterally. However, uncorrected maps showed significant clusters of compression in the anterior and posterior putamen surfaces bilaterally of ADHD/+RD, which are similar to those observed in ADHD/–RD, suggesting a potential smaller effect size and subsequently, under powered statistically with the sample size of 15 individuals. This may suggest a similar morphological alteration in the putamen in both ADHD/+RD and ADHD/–RD boys, which may be associated to the hyperactive symptoms displayed by both

groups. Further investigation is required to determine whether the alterations in putamen of ADHD boys are also present in co-occurring RD.

As stated earlier, there are considerable inconsistencies in the reported structural alterations of the striatum in ADHD. This may be partly due to the heterogeneity in the sample with respect to symptomatology, comorbidities and variability in cognitive deficits. RD is one of the confounding factors that is rarely accounted for in neuroimaging studies of ADHD, but has proven to play an important factor in this study in differentiating unique patterns of striatal surface dysmorphology between the two ADHD subgroups. One may argue that the presence of co-occurring RD may partially explain for the inconsistencies observed in the neuroimaging literature, which emphasizes the importance of assessing for co-occurring RD in individuals with ADHD.

One of the limitations of the current study is the sample size (or statistical power), particularly after subdividing the ADHD sample into ADHD/–RD ($n = 19$) and ADHD/+RD ($n = 15$), which warrants further investigation. Another limitation is the lack of a RD only group in the study. That is, it is unclear whether the excessive morphological alterations in the caudate of ADHD/+RD are due to an additive effect of ADHD and RD. Though, RD and dyslexia are commonly used interchangeably, dyslexia was not specifically assessed in this study. However, a recent study reported a significant relationship between bilateral caudate volume and reading function in patients with dyslexia (Tamboer et al., 2015). Collectively, it is suggestive that the excessive morphological alterations in ADHD/+RD may be associated with the added impairment in reading ability observed in this group. Future studies involving four groups (HC, ADHD/–RD, ADHD/+RD and RD) are necessary to directly address the above question. To address potential effects due to ADHD subtypes, analyses were conducted (results not shown), which demonstrated no subgroup differences when comparing the combined type with the inattentive type regardless of RD status. Bear in mind that the sample size was too small to address any subtype by RD status interactions. Lastly, this study did not investigate any associations between behavioral or cognitive measures and the implicated morphological alterations, which limits the inference whether the ADHD/+RD subgroup with relatively greater striatal morphological alterations presented with greater cognitive deficits compared to ADHD/–RD.

In conclusion, this study provides for the first time evidence of greater and extensive structural and morphological alterations in the striatum of ADHD/+RD boys compared to ADHD/–RD. The greater compression or volume loss in ADHD/+RD may implicate widespread alterations in the cortical areas that project to the caudate and are involved in executive functions, attention and cognitive control. However, future studies with larger sample sizes and an additional RD without ADHD group are necessary to confirm and extend the findings of this study. Furthermore, future studies can investigate the potential implicated cortical projection structural alterations in cortex and white matter tracts respectively in children with ADHD with and without comorbid RD using cortical thickness and diffusion tensor imaging.

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Highlights

- Evidence of greater and extensive structural and morphological alterations in the Caudate of ADHD boys with RD compared to ADHD boys without RD.
- Structural and morphological alterations in the Putamen were observed only in ADHD boys without RD.
- The distinct striatal dysmorphology observed in ADHD boys with RD may implicate widespread alterations in the cortico-striatal networks involved in executive functions, attention and cognitive control

Figure 1.

Schematic of the post-processing steps of the T1-weighted images to generate the intracranial volume (ICV), caudate and putamen volume, and the deformation surface maps of the caudate and putamen using a combination of software packages (FSL, Freesurfer, SPHARM and SURFSTAT). Abbreviations: FSL= FMRI, MRI and DTI software library; Freesurfer= Software suite for brain MRI processing and analysis; NU = MNI Non-uniformity correction; SANLM = Spatially adaptive non-local means filter; SPHARM-PDM= Shape analysis toolbox; SURFSTAT= Surface Statistics toolbox.

Figure 2.

A) With the group term being significant, post hoc analyses show significant volume reduction bilaterally in the caudate of ADHD/+RD boys on the left side of ADHD/-RD boys, both compared to TDC. B) Likewise, there is a significant group effect with the putamen volume with post hoc analyses showing reduced right putamen volumes in ADHD/-RD compared to TDC.

Figure 3.

Compared to TDC, results show significant clusters of compressions (inward deformations) in A) the left medial/dorsal portion of the anterior and bilateral posterior surfaces of ADHD/-RD boys and B) the left medial/dorsal portion of the caudate surface from the anterior to posterior edges and the right medial/dorsal portion of the anterior and posterior surfaces of ADHD/+RD. Abbreviation: A= anterior, P= posterior, R= right, L= left.

Figure 4.

GLM analysis for putamen surface deformation controlling for age and ICV showed significant clusters of compressions (inward deformations) relative to TDC in A) ADHD/-RD in the anterior and posterior surface bilaterally only; B) ADHD/+RD did not show any significant clusters of deformation. Abbreviation: A= anterior, P= posterior, R= right, L= left.

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	-	11	14	-
Combined	-	-	-	-
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

^aPost-hoc results show significant differences compared to both ADHD/-RD and TDC (p 0.001)

Table 2

Results of surface deformation analysis of the striatum in boys with ADHD with and without RD relative to TDC.

Comparison	Region Of Interest	Location	Side	Surface Area (mm ²)	t	FDR <i>p</i>
ADHD/-RD < TDC	Caudate	Medial Anterior	Left	180.22	4.09	0.021
		Medial Middle-Posterior	Left	102.68	2.80	0.039
	Putamen	Medial to Lateral Anterior	Right	349.98	4.56	<0.001
		Dorsal Lateral Posterior	Right	222.31	5.88	<0.001
ADHD/+RD < TDC	Caudate	Medial to Lateral Anterior	Left	330.85	5.96	<0.001
		Dorsal Lateral Posterior	Left	208.76	4.59	<0.001
	Caudate	Medial Anterior	Right	421.86	4.56	0.003
		Medial Middle-Posterior	Right	310.84	5.01	0.003
		Medial Anterior-Posterior	Left	971.57	4.56	0.003