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Anomalous subcortical morphology in boys, but not girls, with ADHD compared to typically developing controls and correlates with emotion dysregulation

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Abstract

There has been limited investigation of volume and shape difference in subcortical structures in children with ADHD and a paucity of examination of the influence of sex on these findings. The objective of this study was to examine morphology (volume and shape) of subcortical structures and their association with emotion dysregulation (ED) in girls and boys with ADHD as compared to their typically-developing (TD) counterparts. Participants included 218 children ages 8-12 years old with and without DSM-IV ADHD. Structural magnetic resonance images were obtained, and

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Contributors

KES, XT and KSR wrote the manuscript and carried out the statistical analysis and interpretation. XT conducted segmentation of subcortical structures. DC collected the data, assisted in data preparation, and provided critical feedback on the manuscript. SHM and MIM contributed to the conceptualization and design of the study and provided critical feedback on the manuscript. All the authors read and contributed to the manuscript and the ideas presented in it. KES and XT are joint first authors.

Conflict of Interest

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shape analyses were conducted using large deformation diffeomorphic metric mapping (LDDMM). Compared to TD boys, boys with ADHD showed reduced volumes in the bilateral globus pallidus and amygdala. There were no volumetric differences in any structure between ADHD and TD girls. Shape analysis revealed localized compressions within the globus pallidus, putamen and amygdala in ADHD boys relative to TD boys, as well as significant correlations between increased ED and unique subregion expansion in right globus pallidus, putamen, and right amygdala. Our findings suggest a sexually dimorphic pattern of differences in subcortical structures in children with ADHD compared to TD children, and a possible neurobiological mechanism by which boys with ADHD demonstrate increased difficulties with ED.

Keywords

attention-deficit/hyperactivity disorder; limbic; emotion; emotion regulation; subcortical

1. Introduction

Attention-deficit/hyperactivity disorder (ADHD) is a neurodevelopmental disorder characterized by developmentally inappropriate levels of inattention, hyperactivity and impulsivity.(American Psychiatric Association, 2013) While fronto-striatal regions have been extensively examined and implicated in the pathophysiology of ADHD(Cubillo et al., 2012; Sagvolden et al., 2005; Sonuga-Barke, 2005), less attention has been paid to subcortical structures such as the globus pallidus, amygdala, hippocampus and thalamus. Morphological differences in these structures may be particularly important in the pathophysiology of ADHD as they may contribute to deficient motor control(Gaddis et al., 2015; Mostofsky et al., 2003a), atypical response to reward(Luman et al., 2010), and problems with emotional processing and regulation(Shaw et al., 2014b) in individuals with ADHD

To date, the extant literature examining subcortical structures in individuals with ADHD has largely focused on examination of basal ganglia morphology. Results have shown that compared to typically developing (TD) children, children with ADHD demonstrate reductions in volume (Ellison-Wright et al., 2008; Frodl and Skokauskas, 2012b; Qiu et al., 2009b; Valera et al., 2007) and significant localized inward deformation (compression) in selective subregions of the caudate, putamen, and globus pallidus in children with ADHD. (Shaw et al., 2014a; Sobel et al., 2010) Only one study to date has reported evidence of sex differences such that boys with ADHD show significantly smaller basal ganglia volumes and differences in the shape of the left caudate, right and left putamen and globus pallidus compared to TD boys, while no differences were observed between ADHD and TD girls. (Qiu et al., 2009a) However, whether these abnormalities in basal ganglia are similar for girls and boys with ADHD relative to TD same-sex peers has not been comprehensively investigated due to the examination of primarily male samples. Furthermore, ADHD-related sex differences in the morphology of the amygdala, hippocampus, and thalamus have not yet been reported.

Significantly less research has examined limbic regions such as the amygdala, hippocampus and thalamus in children with ADHD compared to TD children, and results have been mixed. Some volume-based analysis of the amygdala have observed no volume differences in children with ADHD compared to TD children (Castellanos et al., 1996; Greven et al., 2015a; Plessen et al., 2006), whereas others have reported smaller amygdalar volumes among children with ADHD compared to TD children. (Lopez-Larson et al., 2009a; Sasayama et al., 2010) Contrasting results have also been demonstrated for the hippocampus, with studies reporting no volume differences (Castellanos et al., 1996; Greven et al., 2015a; Lopez-Larson et al., 2009b) as well as volumetric reductions (Brieber et al., 2007) and enlargements (Plessen et al., 2006) in children with ADHD relative to TD children. Results from thalamus studies in children with ADHD show some evidence of significant volumetric reductions in children with ADHD, (Batty et al., 2015) while other studies suggest no group differences in volume. (Greven et al., 2015b; Ivanov et al., 2010) Significantly less research has employed shape-based analysis of limbic regions. One study suggested an enlarged head of the hippocampus in children with ADHD relative to TD children, which marginally correlated with more severe ADHD symptoms. (Plessen et al., 2006) Shape analysis of the thalamus has shown that ADHD-related reductions may be localized to the pulvinar, a region involved in supporting attentional processing which also has connections with limbic structures such as the amygdala. (Ivanov et al., 2010; Wester et al., 2001)

Taken together, the extant research examining subcortical structures in children with ADHD has a number of limitations. First, studies have primarily relied on volumetric analysis with few studies on shape morphometry which provide detailed information about localized deformations within a structure (e.g., expansions or compressions). This allows for detection of subtle changes in neuroanatomy that may guide identification of specific fronto-subcortical circuits. This is particularly relevant for subcortical structures such as the amygdala which contains multiple functionally-distinct nuclei with different afferent and efferent connections to cortical regions (LeDoux and Schiller, 2009) and the basal ganglia in which specific anatomical locations are associated with different functional roles (e.g., reward processing, motor and cognitive control, etc). (Haber, 2003) A second limitation of the existing literature is that subcortical analyses have been examined mostly in boys therefore limiting the examination of sex differences in children with ADHD. Finally, no studies have examined volume and shape abnormalities in children with ADHD in relation to emotion dysregulation (ED) or affective problems in this population, despite co-occurring difficulties with ED in approximately 24-50% of individuals with ADHD (Sjowall et al., 2013; Spencer et al., 2011) and longitudinal associations of ED with increased psychiatric comorbidity, greater social impairments, poorer quality of life, and greater academic and occupational difficulties in children with ADHD. (Althoff et al., 2010c; Barkley and Fischer, 2010; Biederman et al., 2012; Seymour et al., 2013)

As such, the purpose of the current study was to clarify the existing literature examining the volume and shape of subcortical structures in a large sample of children with ADHD oversampled for girls relative to same-sex TD children. Our study not only expands upon previous work on volumetric analyses, but is also one of the first to examine differences in multiple subcortical structures in children with ADHD via a sophisticated surface mapping

technique, large deformation diffeomorphic metric mapping (LDDMM). LDDMM has been successfully applied to group-comparison based subcortical shape analysis (Tang et al., 2014) as well as correlation to function scores (Tang et al., 2015b). Brain-behavior correlations between subcortical morphology and parent-reported ADHD symptoms and ED were also examined.

2. Methods

2.1 Participants

Participants included 109 children with ADHD (male n=71; female n=38) and 109 TD children (male n=70; female n=39) between the ages of 8-12 years. Participants were recruited via local schools, community-wide advertising, volunteer organizations, medical institutions, and word-of-mouth. This study was approved by the Johns Hopkins Institutional Review Board. Written informed consent from a parent/guardian and assent from the child were obtained prior to study participation.

Parents completed a telephone screen, and children with a history of intellectual disability, seizures, traumatic brain injury or other neurological illnesses were excluded from participation. Intellectual ability was assessed using the Wechsler Intelligence Scale for Children, Fourth Edition (WISC-IV; Wechsler, 2003) and participants with full scale intelligence quotient (FSIQ) scores below 80 were excluded. Children were also administered the Word Reading subtest from the Wechsler Individual Achievement Test, Second Edition (WIAT-II; Wechsler, 2002) to screen for a reading disorder and were excluded for a significant discrepancy between FSIQ and WIAT-II scores.

ADHD diagnostic status was established using the Diagnostic Interview for Children and Adolescents, Fourth Edition (DICA-IV) (Reich et al., 1997). Children were excluded for the presence of comorbidity aside from oppositional defiant disorder (ODD). Parents and teachers (when available) completed either the Conners' Parent and Teacher Rating Scales-Revised Long Version or the Conners-3 (CPRS and CTRS; Conners, 2002, 2008), and the ADHD Rating Scale-IV home and school versions (ADHD-RS) (DuPaul et al., 1998).

An ADHD diagnosis was confirmed or established based on the following criteria: (1) T-score of 60 or higher on either the DSM-IV Inattentive or Hyperactivity/Impulsivity subscales on the CPRS or CTRS, when available, or a score of 2 or 3 on at least 6/9 items on the Inattentive or Hyperactivity/Impulsivity scales of the ADHD-RS and (2) an ADHD diagnosis on the DICA-IV. ADHD diagnosis was confirmed by a child neurologist (S.H.M.). Children taking psychotropic medications other than stimulants were excluded from participation. Children taking stimulants were asked to withhold medication the day prior to and day of testing, and parents were asked to complete the rating forms and diagnostic interview about their child's symptoms off medication.

Inclusion in the TD group required scores below clinical cutoffs on the parent and teacher ADHD rating scales. TD participants could not meet diagnostic criteria for any psychiatric disorder nor could they have history of neurological disorder, be taking psychotropic

medication or meet criteria for diagnosis of learning disability, and were required to have an FSIQ above 80.

2.2 Measures

2.2.1 ADHD symptoms—Dimensional ratings of ADHD symptoms (Inattention; Hyperactivity/Impulsivity) were assessed using either the CPRS or Conners 3 Parent Rating Scale.

2.2.2 Emotion Dysregulation—The CBCL Dysregulation Index (Althoff et al., 2010a; Althoff et al., 2010b), an overall measure of self-regulation derived from the Attention Problems, Aggressive Behaviors and Anxious/Depressed subscales was used to measure ED. The Dysregulation Index has been associated with severe childhood psychopathologies (Faraone et al., 2005; Holtmann et al., 2007) and has been shown to predict negative adult outcomes (Meyer et al., 2009).

2.3 MRI Dataset and Processing

High resolution T1-weighted 3D MPRAGE images covering the whole brain were acquired for each participant on a Philips 3T 'Achieva' MRI scanner (Best, the Netherlands) using an 8-channel head coil (TR=7.99ms, TE=3.76ms, Flip angle=8°, voxel size=1mm isotropic). Details regarding the automated structural segmentation and statistical shape analysis are provided in the **Supplement (S1)** and previous publications (Tang et al., 2015a; Tang et al., 2013).

2.4 Data Analysis

2.4.1 Examination of Group Differences—Group differences in subcortical structures were examined using Analysis of Covariance (ANCOVA) in which the Diagnosis×Sex interaction and main effects of diagnosis and sex were tested with age as a covariate. The interaction and main effect of diagnosis are reported. All analyses were also conducted with both age and total cerebral volume (TCV) as covariates, the latter being automatically computed in FreeSurfer (version 4.5) (Fischl et al., 2002) to determine whether diagnostic group differences existed irrespective of TCV, which tends to be reduced in ADHD (see **Supplement S2b**). (Durstun et al., 2004; Mostofsky et al., 2002) Diagnostic differences in volume and shape of each subcortical structure were examined in the entire group and then separately in boys and girls given our specific hypotheses regarding sex differences. A false discovery rate (FDR) correction of .05 was applied for volumetric diagnostic group difference analyses (Benjamin and Hochberg, 1995). For shape analyses, multiple comparison correction was performed at the vertex level by controlling the family-wise error rate (FWER) at .05 (see **Supplement S1d**). Cohen's *d* is reported as a measure of effect size for diagnostic group differences in volume (Cohen, 1988) and is also reported for the shape analysis by averaging the effect size across all surface vertices. Supplemental analyses were also conducted to examine the effect of (a) comorbid ODD and (b) stimulant medication on subcortical volumes and shapes (**Supplement S2c-d**).

2.4.2 Partial correlation analysis—Partial correlational analyses (with age and TCV as covariates) between subcortical structure volumes and shapes and dimensional measures of

ADHD symptoms and ED were conducted. In the shape correlation analysis, multiple correlation correction was performed by adjusting the p -values at the vertex level to control the FWER of .05.

3. Results

3.1 Demographics

The demographic characteristics of the sample are summarized in **Supplement Table S1**. See **Supplement S2a** for details about group differences on demographic and symptoms measures.²

3.2 Volume analysis

3.2.1 Diagnostic group differences—Within the whole group, there were no significant effects of diagnosis or Diagnosis×Sex interaction after correcting for multiple comparisons (**Supplement Table S2**). However, within-sex comparisons showed that diagnostic group differences were only observed in boys such that ADHD boys showed reduced volume compared to TD boys in the globus pallidus, [left: $F(1,138)=10.64$, $p=.001$, $d=0.54$; right: $F(1,138)=9.68$, $p=.002$, $d=0.51$] and amygdala [left: $F(1,138)=10.64$, $p=.001$, $d=0.54$; right: $F(1,138)=9.68$, $p=.002$, $d=0.51$]. There was no significant effect of diagnosis in ADHD girls compared to TD girls for any structure (**Supplement Table S2**). These results remained consistent when TCv was added as a covariate (**Supplement S2b**) and there were no discernible effects of comorbid ODD or stimulant medication history within the ADHD group (**Supplement S2c-d**).

3.2.2 Partial Correlations with ADHD Symptoms and ED—Partial correlations were conducted for the globus pallidus and amygdala, the only structures in which there were significant group differences, and among boys only, as there were no diagnostic differences in volume among girls. Partial correlations were performed within the full sample of boys and then within the sample of boys with ADHD.

Within all boys, greater inattention symptom severity significantly correlated with reduced globus pallidus volumes, (left: $r=-.255$, $p=.003$; right: $r=-.234$, $p=.006$), and amygdalar volumes, (left: $r=-.209$, $p=.015$; right: $r=-.266$, $p=.002$). Similarly, within all boys, greater hyperactivity/impulsivity symptom severity significantly correlated with reduced globus pallidus (left: $r=-.274$, $p=.001$; right: $r=-.246$, $p=.004$), and amygdalar volumes (left, $r=-.201$, $p=.020$; right: $r=-.219$, $p=.011$).

Within all boys, greater ED significantly correlated with reduced left globus pallidus volume ($r=-.223$, $p=.021$). None of the remaining correlations were significant ($ps>.07$, $rs<-.14$).

²Outliers were examined using SPSS and within group outliers (subcortical volumes greater than $1.5 \times$ interquartile range) were removed, including 7 ADHD participants (1 female) and 7 TD participants (all males). Outliers did not differ from other participants in terms of age $F(1,230)=0.002$, $p=.965$, or race, $\chi^2(1, 231)=.000$, $p=1.00$, although they were more likely to be male, $\chi^2(1, 232)=4.680$, $p=.031$. ADHD outliers did not differ from ADHD participants included in the analyses in terms of inattention, $F(1,112)=0.13$, $p=0.72$, or hyperactivity/impulsivity, $F(1,112)=0.34$, $p=0.56$.

Within the sample of ADHD boys, no significant correlations between subcortical volumes and ADHD symptoms or ED (all $ps > .06$, all $rs < .27$) were observed.

3.3 Shape analysis

3.3.1 Diagnostic Group Differences—Within the whole group, there were no significant Diagnosis $\times$ Sex interactions after correcting for multiple comparisons for any of the structures. However, a main diagnostic effect was observed for the left putamen ($p = .003$, $d = .19$), such that children with ADHD showed shape compression relative to TD children. There were no significant effects of diagnosis for any other structures after the FDR correction was applied (**Supplement Table S3**).

Within-sex shape comparisons showed that diagnostic group differences were only observed in boys such that ADHD boys showed compression of the globus pallidus, (left: $p = .003$, $d = 0.44$; right: $p = .001$, $d = 0.40$), putamen, (left: $p = .003$, $d = 0.28$; right: $p = .005$, $d = 0.29$), and amygdala (left: $p = .002$, $d = 0.38$; right: $p = .005$, $d = 0.44$) compared to TD boys (**Figure 1**). In the left and right globus pallidus, these diagnostic effects were localized to the anterior dorsolateral surface. In the left putamen, compressions were observed on the medial central surface, and for the right putamen compressions were along the lateral ventral surface. Compressions in the amygdala were observed on the dorsal surface of the left amygdala (spanning the lateral and basolateral nuclei), and primarily the centromedial nuclei of the right amygdala with some involvement of the lateral and basomedial nuclei. There were no significant diagnostic effects for any other structures (e.g., thalamus, caudate, hippocampus) within boys or for any of the subcortical structures within girls (**Supplement Table S3**). These results remained consistent when TCv was added as another covariate and no discernible effects of comorbid ODD or stimulant medication history within the ADHD group were observed (**Supplement S2b**).

3.3.2 Correlations with ADHD Symptoms and ED—Partial correlations were conducted for the globus pallidus, putamen, and amygdala and among boys only.

Within all boys, greater inattention significantly correlated with compression of the globus pallidus, (left: $r = -.282$, $p = .032$; right: $r = -.282$, $p = .029$), putamen, (left: $r = -.317$, $p = .018$; right: $r = -.315$, $p = .021$), and amygdala, (left: $r = -.281$, $p = .027$; right: $r = -.273$, $p = .034$). Similarly, within all boys, greater hyperactivity/impulsivity significantly correlated with compression of the globus pallidus, (left: $r = -.280$, $p = .033$; right: $r = -.274$, $p = .039$), left putamen, ($r = -.320$, $p = .019$), and right amygdala, ($r = -.267$, $p = .039$).

Within all boys, greater ED significantly correlated with compression in the right globus pallidus ($r = -.334$, $p = .018$), left putamen ($r = -.351$, $p = .019$), and right amygdala ($r = -.298$, $p = .043$).

However, within the sample of boys with ADHD, localized expansion, not compression, was associated with ED (**Figure 2**). ED correlated with expansion of the ventral posterior surface of the right globus pallidus ($r = .441$, $p = .041$), the ventral surface of the right putamen, ($r = .497$, $p = .023$), and the basolateral, basomedial and centromedial nuclei of the right amygdala, ($r = .456$, $p = .027$).

4. Discussion

The current study sought to clarify and extend the extant literature examining the volume and shape of subcortical structures in children with ADHD compared to TD children. This is one of the first studies to examine sex differences in subcortical structures using a sophisticated morphometric shape analyses of these structures. Further, it is the first to examine the relationship between subcortical morphology and ED in children with ADHD. In line with our hypotheses, results revealed a sexually dimorphic pattern such that boys, but not girls, with ADHD showed reduced globus pallidus and amygdala volumes compared to same-sex TD children. Shape analyses revealed that boys with ADHD showed localized compression of the globus pallidus, putamen and amygdala relative to TD boys. Further, correlational analyses showed that in ADHD boys, localized expansion in the globus pallidus, putamen, and amygdala was significantly related to ED.

Our findings of reduced volume of the globus pallidus and amygdala in boys with ADHD relative to TD boys, but not in girls, complement and extend the existing literature.(Ellison-Wright et al., 2008; Frodl and Skokauskas, 2012a; Lopez-Larson et al., 2009a; Sasayama et al., 2010) The lack of difference in subcortical morphology between ADHD girls and TD girls is consistent with some previous studies,(Castellanos et al., 2001; Qiu et al., 2009b) although most studies have not included a large enough sample of girls to adequately test for these effects. Our effect size estimates indicated that the effects seen in boys were 2-3 times as large as those seen in girls, suggesting that the lack of significant effects among girls was not due to a smaller sample size. Further, we did not observe significant volumetric reductions in the caudate or putamen in either girls or boys with ADHD. This result was unexpected given the critical role of the ventral striatum (specifically the nucleus accumbens) in motivational deficits implicated in ADHD (Volkow et al., 2011) and previous studies reporting reduced accumbal or striatal volumes in ADHD (e.g., Carmona et al., 2009; Cha et al., 2015). However, localized expansion of the ventral surface of the right putamen correlated with ED among boys with ADHD (discussed below), suggesting that the ventral striatum may be implicated in particular motivational or emotional problems associated with ADHD.

Our findings are particularly interesting given work showing sex differences in the, developmental trajectories of the basal ganglia. Specifically, the volume of the striatum peaks earlier in girls (12.1 years) than boys (14.7 years), whereas the peak globus pallidus volume occurs earlier in boys (7.7 years) than girls (9.5 years).(Raznahan et al., 2014) Regarding the amygdala, left amygdalar volume has been shown to increase with age for boys (ages 4-18), but not for girls,(1996) perhaps related to the predominance of androgen receptors in the amygdala.(Clark et al., 1988) Interestingly, research has shown that for TD boys, but not TD girls, attenuation of the normative pattern of change (i.e., static or reductions in volume) of the amygdala from ages 12-16 is associated with the onset of a depressive disorder.(Whittle et al., 2014) Together with our results, this literature may suggest that limbic abnormalities increase risk for the development of affective problems among boys with ADHD. Our results in conjunction with prior work also suggest the importance of prospective longitudinal research examining subcortical morphology among girls with ADHD as we may be missing a critical window for detecting differences in girls.

Our shape analyses revealed localized compression in the globus pallidus and putamen in boys with ADHD compared to TD boys. Specifically, compression of the anterior dorsolateral and dorsomedial surfaces of the globus pallidus was observed, suggesting involvement of both the internal segment with projections to the thalamus and then the cortex,(Middleton and Strick, 2001) and the external segment, thought to modulate signals received from the striatum. Compression of the medial central surface of the left putamen and the lateral ventral surface of the right putamen was also observed in boys with ADHD. These regions receive inputs from the supplementary motor area and primary motor cortex, which are involved in motor planning and execution, and project to the globus pallidus. (Leisman and Melillo, 2013; Middleton and Strick, 2001) This pattern of localized compression may suggest that the impact of abnormal reward and motivation signaling in the basal ganglia in boys with ADHD is most apparent within circuits involved in basic response selection complementing findings of abnormalities in motor and premotor cortical regions in children with ADHD.(Dirlikov et al., 2015; Gaddis et al., 2015; Jacobson et al., 2015; Mostofsky et al., 2002; Mostofsky et al., 2006; Suskauer et al., 2008)

Shape analyses also revealed compression in the left and right amygdala in boys with ADHD relative to TD boys. In the left amygdala, compressions were noted along the dorsal surface of the lateral and basolateral nuclei whereas in the right amygdala compressions were more diffuse spanning the lateral, basomedial and centromedial nuclei. Prior research on the unique functions of amygdala subnuclei has highlighted the importance of the lateral nucleus in emotional processing and regulation, including updating current stimulus value associations through connections with the OFC and perception and regulation of emotionally significant events via interactions with sensory/perceptual systems, limbic-paralimbic affective systems, fronto-parietal attention networks and the medial prefrontal emotion regulation system.(Baxter and Murray, 2002; LeDoux, 2007) As such, localized compression in the amygdala of boys with ADHD corresponds with hubs of emotional processing, which may be related to the ED often noted in children with ADHD.(Shaw et al., 2014b) In fact, prior work has shown altered amygdala-cortical intrinsic functional connectivity in children with ADHD and deficits in emotion regulation (Hulvershorn et al., 2014). Moreover, functional MRI studies have shown increased amygdala activation in response to emotionally salient stimuli in children with ADHD compared to controls, and greater connectivity between the amygdala and lateral PFC in children with ADHD compared to controls. Taken together with our results, these studies suggest abnormalities in amygdala-cortical function and connectivity may underlie emotion regulation deficits in children with ADHD. While the implication of inward deformations is not completely understood in animal studies that examine the effects of chronic stress on limbic structures, reductions in limbic structure volume (presumably associated with inward deformations) were associated with increased packing density of glia and neurons (Stockmeier et al., 2004) and with reduced arborization of neuronal processes (McLaughlin et al., 2009) suggesting possible mechanisms by which shape changes might influence behavioral manifestations.

Brain-behavior correlations conducted in all boys paralleled the diagnostic group differences with evidence of reduced volume and greater compression being associated with greater ADHD symptom severity and ED. In contrast, shape correlations conducted within ADHD boys showed that localized expansion in different regions from where the compression was

observed was associated with greater problems with ED. Specifically, ED correlated with expansion of the ventral posterior surface of the right globus pallidus, the ventral surface of the right putamen, and the centromedial and basolateral nuclei of the right amygdala. This localized expansion among boys with ADHD, who generally show reduced subcortical volume, may represent a biomarker for ED in boys with ADHD. Such expansion may be related to heightened reactivity to emotional stimuli resulting in greater ED. In particular, expansion of the ventral putamen suggest involvement of the nucleus accumbens in ED, adding to previous studies showing reduced right accumbal volumes in children with ADHD are correlated with increased aggression (Cha et al., 2015). However, such a hypothesis requires additional research support. Further, given that comorbidity aside from ODD was not permitted in our sample of ADHD children, future studies should examine whether this pattern of expansion correlates with affective symptoms in children with ADHD and comorbid mood and/or anxiety disorders.

Like all research studies, our study has some limitation. First, it is difficult to characterize a complex construct such as emotion dysregulation using a rating scale. While the CBCL Dysregulation Index has been shown to relate to increased rates of pediatric bipolar disorder, suicidality, comorbid psychiatric disorders and rates of adult psychopathology, it is possible that it reflects greater overall impairment rather than a specific problem in emotion regulation. Future studies of ED in children with ADHD should rely on multi-dimensional assessment of ED including both questionnaires and behavioral task assessments of emotion regulation to more thoroughly characterize this construct. A second limitation is that our sample, while large and oversampled for female participants, may be skewed towards participants with above average cognitive abilities. While there were no group differences in the General Ability Index (GAI) between ADHD and control participants, both groups were above average in this metric.

In sum, our findings suggest sexually dimorphic volumetric reductions and shape compressions in the basal ganglia and amygdala in boys with ADHD compared to TD boys. No group differences were observed between ADHD and TD girls. Localized expansion of the right globus pallidus, putamen, and amygdala correlated with greater ED among ADHD boys. Overall, these findings inform the growing literature reporting sex differences in neuroanatomy in children with ADHD. Moreover, this study is the first to report correlations between subcortical morphology and ED in boys with ADHD. Our findings add to the evolving literature suggesting the importance of the globus pallidus, putamen, and amygdala in the pathophysiology of ADHD especially in respect to the difficulties with ED observed in this population. Specifically, there may be a subset of boys with ADHD who are at greater risk for ED due to expansion within certain subcortical structures. Moving forward, replication of these findings will be critical in longitudinal studies of children with ADHD oversampled for girls. Further, it will be important to examine how subcortical abnormalities relate to subsequent affective and behavioral outcomes for children with ADHD.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

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Highlights

- Compared to typically-developing boys, boys with ADHD showed reduced volumes in the bilateral globus pallidus and amygdala.
- No differences in subcortical structure volumes were seen in girls with ADHD vs. typically-developing girls.
- Shape analysis revealed localized compressions within the globus pallidus, putamen and amygdala in ADHD boys relative to typically-developing boys.
- In boys with ADHD, there were significant correlations between increased emotion dysregulation and unique subregion expansion in right globus pallidus, putamen, and right amygdala.

Figure 1.
Group Shape Differences in ADHD Boys Compared to TD Boys Controlling for Age

Figure 2.
Correlation between CBCL Dysregulation and Subcortical Structures in Boys with ADHD

Demographic and clinical characteristics of ADHD and TD groups overall and within sex

Table 1

	TD						ADHD						ADHD vs. TD		
	Girls (n=39)		Boys (n=70)		All (n=109)		Girls (n=38)		Boys (n=71)		All (n=109)		Girls	Boys	All
	Mean	SD	Mean	SD	Mean	SD	Mean	SD	Mean	SD	Mean	SD	<i>p</i> -values		
Age (years)	10.09	1.10	10.12	1.70	10.02	1.41	10.11	1.46	9.99	1.38	10.11	1.14	.944	.527	.638
% Minority	33%		25%		28%		26%		30%		28%		.501	.572	.996
SES	50.87	9.56	51.04	10.09	50.98	9.85	49.85	10.32	49.88	11.26	49.87	10.90	.657	.523	.435
Handedness R:L:M (count)	35:0:3		53:9:8		88:9:11		32:3:3		57:8:3		89:11:6		.209	.294	.437
FSIQ	110.31	9.36	111.16	9.76	110.85	9.56	107.08	13.90	106.14	11.84	106.47	12.54	.234	.007	.004
GAI	109.79	9.58	113.61	9.86	112.25	9.89	108.68	13.43	111.48	13.53	110.50	13.50	.677	.287	.278
VCI	112.33	11.52	115.96	11.36	114.66	11.49	109.66	14.05	111.82	14.30	111.06	14.19	.363	.059	.041
PRI	104.31	9.94	107.34	11.02	106.26	10.70	106.82	13.90	108.18	12.37	107.71	12.88	.364	.671	.367
WMI	106.26	11.44	106.33	11.58	106.30	11.48	102.92	15.58	101.00	13.21	101.67	14.04	.287	.012	.008
PSI	107.23	12.75	100.51	12.06	102.92	12.67	99.82	13.12	91.93	10.04	94.68	11.77	.014	<.001	<.001
ADHD Boys vs. ADHD Girls <i>p</i> -values															
Conners IA T	46.66	5.67	44.01	4.40	44.96	5.03	80.24	9.40	68.78	8.40	72.85	10.31	n/a	n/a	<.001
Conners HI T	46.08	4.32	46.63	5.03	46.43	4.77	75.16	13.86	70.43	12.37	72.11	13.05	n/a	n/a	.073
Dysreg. T	51.27	1.85	51.13	1.87	51.19	1.85	63.70	6.64	61.09	5.89	62.11	6.29	n/a	n/a	.059
ADHD Subtype, CO:IA:HI (count)	n/a		n/a		n/a		28:9:1		54:15:2		82:24:3		n/a	n/a	.954
% Stimulant Medication	0		0		0		66%		67%		67%		n/a	n/a	.848
ODD	0		0		0		42%		35%		38%		n/a	n/a	.479

Note. % Minority=Percentage of subjects with a self-reported race of African American, Asian, Hispanic, or Biracial; SES=Hollingshead Four-Factor Index of Socioeconomic Status*missing for 2 kids; Handedness=Edinburgh Handedness Inventory*missing for 4 kids; FSIQ=Wechsler Intelligence Scale for Children Fourth Edition (WISC-IV) Full-scale IQ; GAI=WISC-IV General Ability Index; VCI=WISC-IV Verbal Comprehension Index; PRI=WISC-IV Perceptual Reasoning Index; WMI=WISC-IV Working Memory Index; PSI=WISC-IV Processing Speed Index; Conners IA T=Conners' Parent Rating Scales DSM Inattention Scale T-score; Conners HI T=Conners' Parent Rating Scale DSM Hyperactivity/Impulsivity Scale T-score; Dysreg. T = CBCL Dysregulation Index T-score; CO=Combined subtype; IA=Inattentive subtype; HI=Hyperactive/Impulsive subtype; % Stimulant Medication = Percentage of subjects taking stimulant medication; ODD=Oppositional Defiant Disorder.

Table 2

Subcortical volumes for ADHD and TD groups.

	TD				ADHD				ADHD vs. TD							
	Girls (n=39)		Boys (n=70)		All (n=109)		Girls (n=38)		Boys (n=71)		All (n=109)		Girls		Boys * $q=.016$	
	Mean	SD	Mean	SD	Mean	SD	Mean	SD	Mean	SD	Mean	SD	p	d	p	d
L-Cau	3946	432	4348	466	4204	492	3978	410	4326	453	4205	468	.747	.12	.789	.07
R-Cau	3989	469	4433	485	4274	523	4019	411	4359	498	4241	495	.766	.12	.374	.06
L-GP	1665	142	1802	130	1753	149	1635	143	1724	150	1693	153	.288	.23	.001*	.54
R-GP	1552	131	1668	123	1627	137	1534	144	1600	137	1577	143	.513	.12	.002*	.51
L-Put	4580	375	5026	411	4866	451	4565	431	4878	440	4769	460	.846	.02	.043	.29
R-Put	4483	365	4936	378	4774	431	4483	415	4788	408	4682	434	.985	.06	.030	.32
L-Tha	6942	543	7535	571	7323	627	7046	628	7429	574	7295	618	.423	.34	.319	.06
R-Tha	6788	563	7377	553	7166	622	6898	585	7242	586	7122	605	.388	.36	.192	.13
L-Amy	999	108	1108	103	1069	117	985	99	1052	86	1029	95	.465	.14	.001*	.60
R-Amy	933	98	1053	113	1010	122	943	98	991	89	974	94	.634	.19	<.001*	.61
L-Hip	2823	263	3062	254	2976	281	2799	240	3017	235	2941	258	.635	.07	.301	.06
R-Hip	2946	277	3225	280	3125	308	2947	254	3160	251	3085	271	.998	.08	.170	.14

Notes. L = left; R = right; Cau = caudate; GP = globus pallidus; Put = putamen; Tha = thalamus; Amy = amygdala; Hip = hippocampus.

* q = FDR-corrected significance level

p = p-value for the univariate ANCOVA

* p -value is below the FDR-corrected significance level

Table 3

Differences between ADHD and TD in the shape of subcortical structures.

	ADHD vs. TD								
	Girls (n=77)			Boys (n=141) * <i>q</i> =.025			All (n=218) * <i>q</i> =.004		
	% SA	p	d	% SA	p	d	% SA	p	d
L-Cau	n/a	.878	0.14	n/a	.478	0.13	n/a	.558	0.10
R-Cau	n/a	.852	0.13	n/a	.410	0.16	n/a	.555	0.10
L-GP	n/a	.358	0.20	33.48%	.003 *	0.44	10.93%	.019	0.32
R-GP	n/a	.525	0.14	31.32%	.001 *	0.40	3.87%	.016	0.27
L-Put	n/a	.855	0.14	3.88%	.003 *	0.28	2.77%	.003 *	0.19
R-Put	n/a	.637	0.13	3.05%	.005 *	0.29	n/a	.084	0.19
L-Tha	n/a	.159	0.16	n/a	.152	0.19	n/a	.163	0.13
R-Tha	n/a	.821	0.13	n/a	.269	0.18	n/a	.759	0.10
L-Amy	n/a	.253	0.09	8.62%	.002 *	0.38	5.94%	.015	0.23
R-Amy	n/a	.417	0.14	13.61%	.005 *	0.44	0.44%	.049	0.22
L-Hip	n/a	.426	0.17	n/a	.315	0.13	n/a	.607	0.09
R-Hip	n/a	.875	0.12	n/a	.057	0.20	n/a	.122	0.13

Notes. L = left; R = right; Cau = caudate; GP = globus pallidus; Put = putamen; Tha = thalamus; Amy = amygdala; Hip = hippocampus.

**q* = FDR-corrected significance level

%SA = the percentage of surface area that significantly differs between ADHD and TD groups; p = p-value obtained from the statistical shape analysis pipeline with multiple comparison correction performed with age as a covariate; *d* = average Cohen's *d* effect size estimate for the magnitude of the diagnostic group difference at each vertex.

*
p-value is below the FDR-corrected significance level