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Response control correlates of anomalous basal ganglia morphology in boys, but not girls, with attention-deficit/ hyperactivity disorder

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Abstract

Anomalous basal ganglia morphology may contribute to deficient motor response control in children with attention-deficit/hyperactivity disorder (ADHD). This study expands upon recent evidence of sex differences in subcortical morphology and motor response control deficits among children with ADHD to examine basal ganglia volume and shape in relation to motor response control. Participants included 8–12 year-old children with ADHD (n = 52, 21 girls) and typically developing (TD) controls (n = 45, 19 girls). High resolution T1-weighted 3D MPRAGE images covering the whole brain were acquired for all participants on a 3 T scanner. Participants performed two computer-based go/no-go tasks that differed in the extent to which working memory was necessary to guide response selection. Shape-based morphometric analyses were performed in addition to traditional volumetric comparisons and correlations with measures of motor response control were examined. Boys with ADHD consistently demonstrated increased commission error rate and response variability, regardless of task demands, suggesting broad response control deficits. In contrast, response control deficits among girls with ADHD varied depending on task demands and performance measures. Volumetric reductions and inward

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deformation (compression) on the dorsal surface of the globus pallidus and within subregions of the putamen receiving projections from limbic, executive and motor cortices were observed in boys, but not girls, with ADHD relative to TD children. Mediation analyses revealed that putamen and globus pallidus volumes mediated the relationship between diagnosis and commission error rate. Furthermore, reduced volumes of these structures and localized inward deformation within executive and motor circuits correlated with poorer response control, particularly under conditions of increased cognitive load. These findings suggest that anomalous basal ganglia morphology is related to impaired motor response control among boys with ADHD.

Keywords

ADHD; Basal ganglia; Response control; Sex differences; MRI; Inhibition

1. Introduction

Attention-Deficit/Hyperactivity Disorder (ADHD) is a neurodevelopmental disorder characterized by developmentally inappropriate symptoms of inattention, hyperactivity, and impulsivity [1]. The behavioral symptoms of ADHD are thought to be related to executive dysfunction, [2,3] atypical motivation [4,5], and impaired motor response control, broadly defined as consistent and accurate execution of a motor response [6–8]. The neurobiological basis for these behavioral symptoms is thought to involve disruptions in fronto-subcortical circuitry [5,9,10,11]. In particular, anomalous basal ganglia structure and function in ADHD may contribute to ADHD-associated impairments in response control. However, there is a paucity of research demonstrating that anomalous basal ganglia morphology (i.e. shape) in children with ADHD relates to impaired response control. Understanding how anomalous basal ganglia development contributes to the behavioral expression of ADHD is an important area in need of further research [12].

The basal ganglia, including the caudate, putamen, and globus pallidus, are core components of richly interconnected cortico-striatal loops supporting many cognitive and motor processes implicated in ADHD, including motor response control [13]. It is well-established that through these cortico-striatal loops, the basal ganglia mediate a wide range of goal-directed behavior ranging from simple motor actions to complex cognitive functions [14]. There is also strong evidence form human and animal studies for a transitional modularity in cortical-striatal projections, with the putamen primarily involved in motor functions, the dorsal caudate involved in cognition, and the ventral caudate involved in motivation [13,14]. Furthermore, various factors shown to influence motor response control in individuals with ADHD, including stimulant medication [4,15,16], event rate [15,17], reward [4,15], and cognitive demands [18,19], may also be mediated by the basal ganglia. Thus, impaired response control characteristic of ADHD and changes in response control with cognitive and motivational factors may be related to a dysfunction within the basal ganglia and/or its reciprocal cortical connections which mediate these processes and provide an interface between motivation and action [13].

Volumetric reductions of the basal ganglia structures have been observed in children with ADHD compared to typically developing (TD) children [20–26]. In fact, in a mega-analysis of 1713 participants with ADHD and 1529 controls, results showed that participants with ADHD had significant volumetric reductions in the nucleus accumbens (Co-hen's $d = -0.15$), caudate ($d = -0.11$) and putamen ($d = -0.14$) [25], although the effect sizes were small. These effect sizes increased when the sample was limited to children (age < 15 years-old). However, few published ADHD studies have moved beyond the traditional volume-based analysis and employed shape-based approaches [24,26–28] which have some important advantages. The advent of sophisticated brain warping techniques, such as the large deformation diffeomorphic metric mapping (LDDMM) that has been successfully applied to ADHD shape analysis in our previous work [26], has enabled shape-based analyses providing detailed information about the specific target sub-regions in the neuropathology of ADHD. This allows for detection of subtle changes in neuroanatomy that may guide localization of specific fronto-subcortical circuits implicated in the pathophysiology of ADHD. Furthermore, if compression and expansion are observed in different subregions within the same structure, the overall volumetric differences may not be apparent, whereas shape-based analyses are capable of detecting localized changes. Prior shape-based analyses of the basal ganglia have shown significant localized inward deformation (compression) in children and adolescents with ADHD in ventral, anterior, and posterior regions of all three nuclei and specifically in the dorsal striatum [27,28], with evidence that morphological differences may be specific to boys with ADHD [24,26].

Whether these abnormalities in basal ganglia structures are similar for girls and boys with ADHD relative to TD same-sex peers has not been comprehensively investigated due in large part to the examination of primarily male samples. Of the studies that have included a greater proportion of females with ADHD, some have reported that the diagnosis by sex interactions in basal ganglia structures did not emerge [29–31], although other studies suggest that diagnostic differences in basal ganglia morphology are specific to boys (in studies that included girls and boys) [24,26] or not observed in girls (in a study that included girls only) [32], and that accounting for sex eliminates evidence of diagnostic group differences [20]. We recently published findings from 109 children with ADHD and 109 TD children [26] showing that compared to TD boys, boys with ADHD had reduced volume in the bilateral globus pallidus and putamen, but no differences were observed between girls with ADHD and TD girls, suggesting a sexually dimorphic pattern of results. Moreover, shape analysis using LDDMM showed that, compared to TD boys, boys with ADHD exhibited region-specific shape compressions of the globus pallidus and putamen. Taken together, these results underscore the importance of comparing girls and boys with ADHD to same-sex TD children. Inconsistencies in the ADHD literature with regard to sex differences may be partially due to the age range of samples in these studies and the sexually dimorphic developmental course of the basal ganglia [33], in which boys attain peak striatal volume significantly later than girls. Evidence of sex-related differences in ADHD has also emerged from behavioral studies; pre-pubescent school-age boys with ADHD tend to display greater motor impairment [8,34–36], whereas girls with ADHD tend to show greater higher order cognitive deficits during childhood [35] and impaired response control only under conditions of high cognitive load [18]. Moreover, girls and boys with ADHD have been shown to

respond differently to reward [37,38]. Collectively, these findings suggest that motor control and executive dysfunction may differ between girls and boys with ADHD and this may be related to the different morphological abnormality patterns in the basal ganglia.

The relationship between cognitive and motor performance and basal ganglia morphology in either TD controls or children with ADHD has been examined in two previous studies to our knowledge. Sandman et al. [39] reported that increased gray matter volume in the putamen was significantly associated with worse performance on measures of non-verbal intellectual reasoning ability, visual-spatial construction skills, motor response speed, and declarative memory among 6–10 year-old TD children (n = 50). Although this study included a response inhibition task (go/no-go), they did not examine or report basal ganglia volume or shape associations with commission errors (i.e., failures to inhibit), instead focusing on response speed. Furthermore, bilateral outward deformation of the head and tail of the putamen and inward deformation of dorsal and ventral areas of the putamen were associated with poor performance on measures of perceptual reasoning ability, supporting the importance of considering localized differences in shape as well as overall volume of subcortical structures. Casey et al. [40] examined this relationship among 5–12 year-old boys with and without ADHD, revealing a positive correlation between left globus pallidus volume and mean reaction time during response execution and between caudate asymmetry (right greater than left) and response inhibition. However, this study did not conduct shape-based analyses and did not include girls with ADHD. These findings are difficult to reconcile with the studies discussed above suggesting that children with ADHD tend to show reduced basal ganglia volume and more localized compression or inward deformation as well as poorer motor response control (i.e., slower response speed, weaker response inhibition, etc.). Thus, one might expect reduced basal ganglia volume and localized compression, rather than expansion, to relate to weaker response control. Although these studies may guide our hypotheses about the contribution of the basal ganglia to efficient motor response control, there is a need for research examining sex differences in the neuroanatomical correlates of impaired response control among children with and without ADHD given evidence of differential response control deficits and basal ganglia abnormalities among girls and boys with ADHD relative to same-sex TD children.

The current study extends previous findings of sex differences in anomalous basal ganglia morphology (volume and shape) and impaired motor response control among 8–12 year-old children with ADHD through examination of brain-behavior correlations. Based on prior research reporting ADHD-related sex differences in subcortical structures [18,26], we also examined whether similar brain-behavior associations are observed for girls and boys with and without ADHD. A key strength of this study is the utilization of a sophisticated brain warping technique, LDDMM, to characterize region-specific abnormalities in the shape of all three basal ganglia structures, in addition to traditional volumetric analyses. Further, we sub-divided the striatum into multiple functionally-distinct subregions using an approach described and validated elsewhere to better characterize the functional significance of the localized shape effects [41]. We hypothesized that boys, but not girls, with ADHD would show reduced volumes and inward shape deformation (compression) in basal ganglia structures relative to TD controls based on previous studies [24,26]. Of primary interest for the current study, we hypothesized that these differences would be associated with

dimensional measures of motor response control across tasks with differing cognitive demands. Specifically, we predicted that among boys with ADHD, reduced basal ganglia volume and inward putamen and globus pallidus deformation would correlate with weaker motor response control regardless of cognitive demand. In contrast, among girls with ADHD, we predicted that basal ganglia volume and shape would be unrelated to impaired motor response control during high cognitive demand, possibly due to reliance on prefrontal rather than subcortical brain regions.

2. Materials and methods

2.1. Participants

Analyses were conducted on 52 children with ADHD (21 girls) and 45 TD children (19 girls), ages 8–12 years with 3 T MPRAGE data and behavioral data on two go/no-go (GNG) tasks (described below). Participants included in the current analyses are drawn from samples reported in two previously published papers comparing diagnostic groups in terms of subcortical morphology and go/no-go task performance [18,26] to allow for examination of brain-behavior relationships. Therefore, we only included participants with good quality anatomical MRI data who completed two GNG tasks that differed in the extent to which cognitive load guides response selection, permitting examination of the association between basal ganglia morphology and motor response control among girls and boys with ADHD and TD children.

Participants were primarily recruited through local schools, with additional resources including community-wide advertisement, volunteer organizations, medical institutions, and word of mouth. This study was approved by the Johns Hopkins Institutional Review Board. After participants were provided with detailed information about the study, written informed consent was obtained from a parent/guardian and assent was obtained from the child.

An initial screening was conducted through a telephone interview with a parent. 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 [42] 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 [43] to screen for a reading disorder and were excluded in the case of a significant discrepancy between FSIQ and WIAT-II.

Diagnostic status was established through the Diagnostic Interview for Children and Adolescents, Fourth Edition (DICA-IV) [44]. Parents and teachers (when available) also completed the Conners' Parent and Teacher Rating Scales-Revised Long Version or the Conners-3 (CPRS and CTRS) [45,46] and the ADHD Rating Scale-IV, home and school versions (ADHD-RS) [47]. An ADHD diagnosis was confirmed or established based on the following criteria: (1) a T-score of 65 or higher on scale L (DSM-IV: Inattentive) or M (DSM-IV: Hyperactivity/Impulsivity) 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 (parent or teacher report) and (2) an ADHD diagnosis on the DICA-IV. Within

the ADHD group, comorbid diagnoses aside from oppositional defiant disorder (ODD) and simple phobia were not permitted. This information was then reviewed and the diagnosis was confirmed by a child neurologist or licensed clinical psychologist. Children taking psychotropic medications other than stimulants were excluded from participation and all children taking stimulants were asked to withhold medication the day of and prior to testing/scanning.

Inclusion in the TD group required scores below clinical cutoffs (i.e., T-scores below 60 and fewer than 4 symptoms endorsed) on the parent and teacher (when available) rating scales (CPRS, CTRS, and ADHD-RS). TD participants could not meet diagnostic criteria for any psychiatric disorder based on DICA-IV, have a history of neurological disorder, be taking psychotropic medication, or fail the screening for a reading disability based on WIAT-II word reading scores below 85. All participants were also required to have an FSIQ above 80.

2.2. Go/no-go tasks

Participants completed simple and complex GNG paradigms described in previous studies [18,48,49].

2.2.1. Simple GNG paradigm—

The task stimuli consisted of green spaceships for "Go" trials (80% of trials) and red spaceships for "No-Go" trials (20% of trials), presented one at a time. Participants were instructed to push the spacebar with their index finger as quickly as possible in response to green spaceships only. The use of familiar stimulus-response associations (green for "go"; red for "no-go") minimized the perceptual and cognitive demands of the tests. Presentation cues were weighted towards green spaceships at a ratio of 4:1, intensifying the need to inhibit a habituated motor response. Go and no-go trials appeared in pseudorandom order with the restrictions that there were never fewer than 3 go trials before a no-go cue and never more than 2 no-go trials in a row. There were 11 practice trials (8 go cues; 3 no-go cues) followed by 217 experimental trials (173 go cues; 44 no-go cues). Stimuli were present on-screen for 300 ms with an interstimulus interval of 2000 ms (trial length = 2300 ms) during which a fixation cross was present on-screen. Responses and reaction times (RTs) were recorded for the entire trial duration. The task duration was 8 min and 19 s.

2.2.2. Complex GNG paradigm—

The trial structure of the complex GNG task was nearly identical to that of the simple GNG task but there were additional cognitive demands. The stimuli were identical to those in the standard GNG task, consisting of red or green spaceships presented for 300 ms, followed by a blank screen for 2000 ms (trial length = 2300 ms). Children were instructed to push the button as quickly as possible in response to a green spaceship and in response to a red spaceship preceded by an even number of green spaceships. They were to refrain from responding to red spaceships preceded by an odd number of green spaceships. There were 5 practice trials to demonstrate an even sequence, 6 practice trials to demonstrate an odd sequence, and 11 practice trials with each type of sequence. The task consisted of 207 experimental trials including 163 green go cues, 21 red go cues (i.e., preceded by an even number of green spaceships) and 23 red no-go cues (i.e.,

preceded by an odd number of green spaceships). Responses and RTs were recorded for the entire trial duration. The total time of this task was 7 min and 56 s.

The primary dependent variables for each of the GNG tasks were commission error rate and the ex-Gaussian parameter, tau. Ex-Gaussian modeling may be more advantageous for examining response variability in relation to ADHD than the standard deviation as it separates the RT distribution into the normal (Gaussian) component which includes the mean (mu) and standard deviation (sigma) as well as the exponential component of the RT distribution and its mean (tau), reflecting a subset of abnormally slow responses [50,51]. The use of exGaussian parameters has shown that ADHD-related ISV appears to principally be the result of a subset of abnormally slow responses (tau) rather than variable responding during the entire task (sigma) [48,50–52]. Responses faster than 200 ms were excluded from all RT analyses and tau was calculated for correct go trials. Ex-Gaussian RT estimates and a goodness-of-fit value, with lower values indicating better fit to the ex-Gaussian model, were computed in Matlab version R2016a using the DISTRIB toolbox [53], during which data converged for all participants. Commission error rate was defined as the proportion of no-go trials (red spaceship for simple GNG and red spaceship preceded by an even number of green spaceships for complex GNG) on which the participant responded. Exclusion criteria were > 50% omission error rate, > 30% anticipatory response rate (i.e., trials with RT < 200 ms), failure to inhibit to all no-go trials (i.e., commission rate = 1.0). No participants were excluded based on these criteria. Outliers were defined as individuals with scores > 2 SD above the sample mean for commission error rate and tau during either task. One TD boy was identified as an outlier for simple GNG tau. Analyses were conducted with and without this participant and results were similar, so they were retained in all analyses.

2.2.3. Statistical analysis of GNG performance—Diagnostic group differences in performance of each GNG task was examined using separate 2 Diagnosis (ADHD vs. TD) × 2 Sex (girls vs. boys) × 2 Task (simple GNG vs. complex GNG) repeated measures analysis of variance (RM-ANOVA), with commission error rate (proportion of no-go trials on which the participant responded), and the ex-Gaussian parameter tau based on go trial RTs as dependent variables. Cohen's *d* is reported as a measure of effect size [54].

2.3. MRI dataset and processing

2.3.1. MRI acquisition—High resolution T1-weighted 3D MPRAGE image covering the whole brain was acquired for each participant on a Philips 3 T 'Achieva' MRI scanner (Best, the Netherlands) using an 8-channel head coil (repetition time = 7.99 ms, echo time = 3.76 ms, Flip angle = 8°, voxel size = 1 mm being isotropic).

2.3.2. Automated structural segmentation—The three basal ganglia structures, namely the caudate, putamen, and globus pallidus, were automatically obtained from MR images using a validated hierarchical segmentation pipeline [55] which is built upon a two-level multi-atlas likelihood-fusion algorithm in the frame-work of the random deformable template model [56]. The pipeline's reliability and accuracy in segmenting the basal ganglia structures from MR images used in this study was already established in our previous study [55].

2.3.3. Shape processing—For each structure of interest, we created a 2D triangulated surface contouring the boundary of each 3D volumetric segmentation using an approach detailed and validated elsewhere [41,57]. The vertex-wise surface areas of each target shape were quantified by a diffeomorphism connecting a common template shape to that target shape. The common template shape was generated from all target surfaces using a LDDMM-based Bayesian template estimation algorithm [58]. The LDDMM-surface mapping algorithm [59] was then used to map the common template surface to each individual target surface, from which a scalar field was subsequently calculated as the log-determinant of the Jacobian of the diffeomorphism. This scalar field is indexed at each vertex of the common template surface, quantifying the factor by which the diffeomorphism expands or contracts the vertex-based localized surface area in the target, relative to the template, using a logarithmic scale; i.e. a positive value corresponds to a localized surface area expansion of the target relative to the template while a negative value suggests a localized surface area contraction. We refer to this scalar field as the deformation marker.

2.3.4. Statistical analysis of basal ganglia volumes and shapes—To determine whether diagnostic groups differed in basal ganglia volume, we conducted a 2 Diagnosis × 2 Sex multivariate analysis of covariance (MANCOVA) with age and total cerebral volume (TCV) as covariates and all six basal ganglia structures as dependent variables. TCV was computed using FreeSurfer (version 4.5) [60] and included total cerebral (including subcortical structures) gray matter and white matter volume and excluded the ventricles and cerebellum. For inter-group comparisons of shapes, we employed the linear model as described in [41] $y_k(s) = \beta_{k,0} + \beta_{k,1}\, g(s) + \Sigma_{\mathrm{cov}}\, \alpha_{\mathrm{cov}}\, X_{\mathrm{cov}}(s) + \varepsilon_k(s)$, where $y_k(s)$ is the deformation marker for subject s at vertex k on the template surface, $g(s)$ is a binary group variable, and X_{cov} (s) denotes the covariate information of subject s included in the analysis (TCV and age were included). We tested the null hypothesis $H_k^0 : \beta_{k,1} = 0$ against the general hypothesis $H_k^1 : \beta_{k,1} \neq 0$ and, as such, the complete null hypothesis is $H_k^0 : \beta_{k,1} = 0$ simultaneously for all k. This form of testing necessitates a correction for multiple comparisons which we performed by controlling the familywise error rate (FWER) at a level of 0.05 using the maximum statistic approach [61]. The statistical significance of a group difference is quantified by a p-value obtained from Fisher's method of randomization and non-parametric permutation tests.

We included TCV to determine whether proportionate diagnostic group differences were observed relative to TCV, which tends to be reduced in ADHD [30,62,63]. Diagnostic differences in basal ganglia volume and shape were examined separately in boys and girls. Cohen's d is reported as a measure of effect size for diagnostic group differences in volume [54].

2.3.5. Correlation analysis—We examined partial correlations between the basal ganglia volumes and shapes with commission error rate and tau for each of the GNG tasks. We included age and TCV as covariates to determine whether brain-behavior correlations were observed after controlling for these variables, particularly given the strong correlation between TCV and basal ganglia morphology. Brain-behavior partial correlations were conducted in the overall group and then separately for boys and girls. Significant

correlations were followed-up by (1) moderation analyses testing whether diagnosis moderates significant brain-behavior correlations examined across and within sex and (2) mediation analyses testing whether diagnostic group differences in response control are mediated by brain structure. For the volume analyses, we applied a false discovery rate (FDR) correction for the 24 correlation tests (4 task variables × 6 brain volumes). In the shape correlation analysis, analyses were conducted separately for right and left structures among girls and boys. For each structure of interest, all vertices (549 for the left caudate, 544 for the right caudate, 242 for the left globus pallidus, 240 for the right globus pallidus, 532 for the left putamen, and 516 for the right putamen) were included in the shape-behavior correlation analysis. Statistical significance was measured using a *p*-value obtained from nonparametric permutation tests. Multiple correlation correction was then performed by adjusting the *p*-values at each voxel to control the FWER at a level of 0.05.

2.3.6. Template surface partition—Our template surfaces for the striatum were sub-divided into multiple functionally-distinct subregions using the approach described and validated elsewhere [41]. It was accomplished by projecting the boundary definitions of subregions defined in pre-created atlases to our common study-specific template surfaces. For the pre-created atlases, each of them was divided into seven subregions respectively based on connections to the limbic cortex, the executive cortex, the rostral-motor cortex, the caudal-motor cortex, the parietal cortex, the occipital cortex, and the temporal cortex, according to the most likely diffusion tensor imaging (DTI) tractography [64]. However, it is important to note that there are not clear boundaries between the identified subregions; rather, there is a gradual change in cortical inputs from anterior to posterior [13,14]. Further, there may be inaccuracies in the boundary definitions resulting from the original atlas creation procedure (DTI tractography) or the boundary transferring process (from the DTI defined atlas to our study-specific population atlas), or both. Despite these limitations, the functional striatal atlas applied here assists with interpretation of our localized shape deformation findings. Please note such a template for the globus pallidus that had been divided into multiple subregions is not available. As such, we did not conduct template surface partition of the globus pallidus.

3. Results

3.1. Demographics

The demographic characteristics and inferential statistics are summarized in Table 1. The ADHD and TD children did not differ significantly in age, socioeconomic status, percent minority, or hand dominance either within sex or at the whole group level. In addition, neither FSIQ nor the General Ability Index (GAI), a measure of broad intellectual ability based on verbal and perceptual reasoning abilities, differed significantly between the two groups at the whole group level or within sex. Among children with ADHD, boys and girls did not significantly differ in the percentage of children currently being treated with stimulant medication, diagnosed with comorbid ODD, or ADHD subtype. However, girls with ADHD were rated by their parents as displaying greater inattention symptoms.

3.2. Go/No-Go task performance

The performance of the ADHD and TD groups (compared both across and within sex) on the simple and complex GNG tasks along with inferential statistics and effect size estimates are summarized in Table 2. The results of the 2 Diagnosis × 2 Sex × 2 Task ANOVAs for commission error rate indicated a main effect of diagnosis, $F(1,93) = 14.9$, $p < .001$, a main effect of task, $F(1,93) = 12.2$, $p = .001$, but no significant interactions. Specifically, children with ADHD made more commission errors than TD children across both tasks, and participants made more errors during the complex GNG compared to the simple GNG, regardless of diagnosis.

The results of the 2 Diagnosis × 2 Sex × 2 Task mixed ANOVAs for tau indicated a main effect of diagnosis, $F(1,93) = 19.5$, $p < .001$, a main effect of task, $F(1,93) = 6.3$, $p = .001$, that were qualified by a Diagnosis × Task interaction, $F(1,93) = 5.3$, $p = .024$, but no other significant interactions. Specifically, children with ADHD displayed higher tau during the complex GNG tasks relative to the simple GNG task ($p = .001$) whereas response control did not significantly differ between the GNG tasks among TD controls ($p = .880$).

Although there was no Diagnosis × Sex interaction for commission error rate or tau within-sex, diagnostic comparisons were examined given a priori hypotheses of ADHD-related sex differences in response control based on previous findings [18]. Results indicated that boys with ADHD made more commission errors and displayed higher tau during the simple ($p = .004$, $d = 0.80$; $p = .002$, $d = .98$, respectively) and complex ($p = .004$, $d = 0.77$; $p = .001$, $d = 1.09$, respectively) GNG tasks. In contrast, girls with ADHD showed a higher commission error rate compared to TD girls primarily under conditions of increased cognitive demand (complex GNG $p = .017$, $d = .80$), with a smaller, non-significant difference during the simple GNG task ($p = .396$, $d = .27$). In contrast to our previous findings, tau was elevated among girls with ADHD compared to TD girls regardless of task demands (simple GNG $p = .014$, $d = .85$; complex GNG $p = .030$, $d = .85$).

3.3. Volume analysis

3.3.1. Diagnostic group differences—Table 3 lists the mean and standard deviations of the basal ganglia volumetric measures (raw values) and the diagnostic group differences with age and TCV as covariates along with effect size estimates (Cohen's d). Analyses conducted in the full sample suggested a significant multivariate Diagnosis × Sex interaction, $F(6,86) = 2.9$, $p = .013$, whereas the main effect of diagnosis was not significant, $F(6,86) = 0.65$, $p = .694$. Examination of univariate tests indicated significant or trend-level Diagnosis × Sex interactions for all six basal ganglia structures (ps ranging from .001 to .063; see Table 3). Post-hoc comparisons probing these interactions indicated significant volume reductions among boys, but not girls, with ADHD compared to TD same-sex peers in the right caudate ($p = .022$), left and right globus pallidus (ps = .004, .017, respectively), and left and right putamen (ps = .002, .001, respectively). Comparison of effect size estimates suggestes volumetric reductions among children with ADHD relative to same-sex TD peers for the left and right putamen are almost twice as large among boys (ds = .86, .89, respectively) than among girls (ds = .37, .55, respectively) and three times as large for the

left and right globus pallidus among boys (*d*s = .79, .66, respectively) than among girls (*d*s = .14, .17, respectively).

3.3.2. Relationship between basal ganglia volumes and response control—

We conducted partial correlations (controlling for age and TCV) to examine whether bilateral basal ganglia volumes were associated with response control in the full sample and then within sex. The correlation results between the basal ganglia volumes and GNG performance are reported in Table 4 and illustrated in Fig. 1. There were no significant correlations between basal ganglia volume and commission error rate or tau across the full sample after applying the FDR correction. Examination of correlations separately among girls and boys suggest strong negative correlations among boys only between putamen volumes and commission error rate during both GNG tasks and between globus pallidus volumes and commission error rate during the complex GNG task. However, basal ganglia volumes were not significantly correlated with response variability (tau) during either GNG task across the full sample or when examined within sex. Furthermore, there were no significant correlations among girls between basal ganglia volumes with either commission error rate or tau for both GNG tasks (see Table 4).

Next, we tested whether diagnosis moderated the significant relationships between the putamen and globus pallidus and commission errors on each of the GNG tasks among boys. There was no evidence of moderation for the relationships observed between putamen volume and commission error rate during the simple ($p = .985$) or complex ($p = .241$) GNG tasks or for globus pallidus volume and commission errors during the simple ($p = .935$) or complex ($p = .209$) GNG tasks. Therefore, shape correlations were conducted on the full sample of boys in the regions with observed volumetric differences and significant associations with commission error rate for each GNG task.

Finally, we tested whether diagnostic group differences in response control (i.e., commission error rate) are mediated by brain structure among boys. Results suggest that bilateral putamen volume mediates the effect of diagnosis on commission errors during the simple GNG task [$b = .026$; 95% CI (.001, .056)] and the complex GNG task [$b = .036$; 95% CI (.010, .072)]. In addition globus pallidus volume mediates the effect of diagnosis on commission errors during the complex GNG task [$b = .024$; 95% CI (.002, .053)], but not for the simple GNG task [$b = .014$; 95% CI (−.006, .037)].

3.4. Shape analysis

3.4.1. Diagnostic group differences—

Significant inward deformations (compressions) were observed among ADHD boys relative to TD boys for both the putamen and globus pallidus in both hemispheres (left putamen: $p = 0.049$; right putamen: $p = 0.014$; left globus pallidus: $p = 0.015$; right globus pallidus: $p = 0.024$), after FWER correction (see Figs. 2–3). The inward deformation in both the left and right globus pallidus was most prominent on the dorsolateral and dorsomedial surfaces. For the putamen, compression was observed on the ventral lateral surface of the left putamen (subregion connecting primarily to the limbic cortex) and the central lateral surface of the right putamen (subregions connecting at the interface of projections to the executive and rostral motor cortices). No significant

shape differences were detected in the caudate between ADHD boys and TD boys and no significant shape differences were detected for any of the basal ganglia structures between ADHD girls and TD girls.

3.4.2. Relationship between basal ganglia shape and response control—

Partial correlations (controlling for age and TCV) between shape deformations of the putamen and the globus pallidus and GNG performance measures among boys are respectively shown in Figs. 2 and 3. In boys, we observed significant negative correlations between the complex GNG commission error rate and certain vertices of the left and right putamen and the right globus pallidus. These negative correlations indicated that greater commission error rate during the complex GNG was associated with greater inward deformation of the right globus pallidus and right and left putamen. These correlations were localized to the central medial surface of the left putamen, the dorsolateral and central surface of the right putamen, and the dorso-lateral surface of the right globus pallidus. According to sub-divisions of the putamen (see Fig. 2), the correlations were mainly concentrated on subregions connecting to the executive and rostral motor cortices. Commission error rate during the simple GNG task did not correlate significantly with the shape deformations of the putamen or globus pallidus among boys. Response variability (tau) was uncorrelated with the four structures of interest (left and right putamen and globus pallidus) during both GNG tasks among boys. No significant correlations between basal ganglia shape and GNG performance were observed among girls for either task.

4. Discussion

The current study expands upon previous investigations of basal ganglia morphology in ADHD through examination of correlations with response control across two go/no-go tasks that differ in the extent to which working memory is required to guide response selection. Our findings of basal ganglia anomalies among boys, but not girls, with ADHD, and weaker motor response control among boys with ADHD, regardless of task demands (whereas it varied depending on task demands among girls with ADHD) are consistent with prior research [18,26]. To our knowledge, this is the first study to move beyond the diagnostic group comparisons of basal ganglia morphology and behavioral measures of response control to examine whether anomalous brain structure relates to motor response control among children with and without ADHD. These analyses indicated that reduced globus pallidus and putamen volumes correlated with weaker motor response control across both GNG tasks exclusively among boys. Moreover, putamen and globus pallidus volumes mediated the relationship between diagnosis and commission error rate. Finally, shape analyses identified localized changes in surface morphology of the globus pallidus and putamen that were associated with motor response control, particularly during the complex GNG task.

Our findings of greater impairments in motor response control, regardless of cognitive demand, and reduced volumes of the globus pallidus and putamen in ADHD boys compared to TD boys, with no evidence of diagnostic differences among girls, are generally consistent with previously published results in the larger sample [26] and in some previous studies [24,32]. Of importance, these results were not due to less power to detect these effects

among our smaller sample of girls as the means were in the opposite direction for girls and boys with ADHD, with non-significantly larger basal ganglia volumes among ADHD girls compared to TD girls and smaller basal ganglia volumes among ADHD boys compared to TD boys. This pattern of results indicated significant diagnosis by sex interactions in this sample, which were not observed in the larger sample from which they were drawn, although within-sex comparisons indicated that reduced basal ganglia volumes were also only observed among boys in that study [26]. The significant diagnosis × sex interactions observed for basal ganglia volumes in this smaller sample may be due to the greater volume reductions in the putamen and globus pallidus among this subset of boys with ADHD compared to TD boys. Given the well-established neuropsychological heterogeneity in children with ADHD [65–67] one would expect similar heterogeneity in anomalous brain structure across individuals diagnosed with ADHD. Thus, findings at the group level are influenced by individual variability in neurocognitive and motor deficits and anomalous brain structure that is generally associated with ADHD, but not necessarily observed in every individual diagnosed with ADHD. This reiterates the importance of examining brain-behavior relationships to better understand how variability in brain structure relates to the expression of neurocognitive and motor deficits typically associated with ADHD, moving beyond diagnostic group comparisons.

An important extension of this study beyond most prior work is the identification of local shape differences using LDDMM may help to specify the contributions of frontal-subcortical circuits to the pathophysiology of ADHD. Diagnostic group shape comparisons for the putamen show inward compressions of the ventral medial and central lateral surfaces in boys with ADHD, suggesting atypical structure in areas receiving input from ventromedial prefrontal regions involved in motivation and affect, dorsolateral prefrontal regions involved in executive function, and rostral motor regions involved in motor planning. Due to the lack of clear boundaries between the striatal subregions, the localized deformation at the very posterior aspect of the executive subregion of the putamen (with some extension into the rostral and caudal motor subregions) very likely contains a mixture of inputs from both prefrontal and premotor/motor cortices. Inward deformation of this putamen region may therefore impact integration of executive and motor signals at the level of the striatum. The localized compression in this central lateral surface of the putamen is consistent with findings in the larger sample from which this subset of participants was drawn [26] whereas the compression on the ventral medial surface was not previously observed. In addition, greater inward deformation of the globus pallidus was also observed in boys with ADHD, localized to the dorsolateral and dorsomedial surfaces, consistent with the results in the larger sample [26], suggesting involvement of both the internal and external segment of the globus pallidus. The external segment of the globus pallidus is thought to modulate signal received from the striatum whereas the internal segment comprises efferent projections to the thalamus, which then project to regions of the cortex involved in executive functions and motor control [68].

These localized shape differences suggest that among boys with ADHD, anomalous basal ganglia morphology is most apparent within circuits involved in motor control and executive function. Therefore, basic control of motor responses in children with ADHD may be influenced by greater demands on executive function, such as increased cognitive load. Our

current behavioral findings provide partial support for this hypothesis, such that increased cognitive load had a greater negative impact on response variability among boys with ADHD. In addition, greater compression of the ventral medial surface of the putamen among boys with ADHD implicates neural circuitry involved in motivation and emotion. This may suggest that response control may be differentially impacted by the motivational or emotional context in which the behavior occurs among boys with ADHD. Consistent with this idea, previous studies have shown improvement in response control among boys with ADHD in the context of performance-based rewards [37] with some evidence of differential improvement among children with ADHD, although this is less consistent [4]. It may also be that negative emotion or non-reward results in greater impairments in response control among boys with ADHD. One limitation of these findings is the confluence of motor and cognitive demands during the go/no-go task, preventing examination of whether cognition and motor performance differentially relate to basal ganglia morphology. This will be an interesting question to examine in future studies.

Importantly, the current study moved beyond diagnostic group comparisons to examine whether and how basal ganglia morphology relates to neurocognitive deficits implicated in ADHD. In particular, response disinhibition is central to etiological theories of ADHD [69] and among the most consistent findings in the ADHD neurocognitive literature [49,70]. However, deficient response control is not observed in all individuals with ADHD due to neurocognitive heterogeneity as discussed above [67] suggesting that examination of individual variability in brain structure and function is critical to elucidate the patho-physiology of ADHD. Our novel findings suggest that reduced globus pallidus and putamen volumes were associated with greater commission errors during both GNG tasks, regardless of cognitive demands. Furthermore, diagnosis did not moderate this relationship, suggesting similar associations among boys with and without ADHD. However, mediation analyses indicated that putamen and globus pallidus volumes significantly mediated the relationship between diagnosis and response inhibition, providing further support for the important relationship between basal ganglia volumes and motor response control. Shape-based analyses indicated that greater compression of the central lateral surface of the right putamen, a region containing projections from prefrontal regions, was associated with weaker response control during the complex GNG task, but not during the simple GNG task, among boys. This pattern of findings might suggest diffuse involvement of the globus pallidus and putamen in response control during a motor task and localized morphological changes in relation to response control under conditions of greater cognitive load. Collectively, these findings indicate anomalous morphology of the globus pallidus and putamen in boys with ADHD that relates to response control. These findings are only partially consistent with a previous study reporting larger putamen volume correlated with poorer performance on measures of non-verbal intellectual reasoning ability, visual-spatial construction skills, motor response speed, and declarative memory [39]. In addition, localized expansion and compression within the putamen correlated with poorer performance on a perceptual reasoning task [39]. We did not find any evidence of localized expansion or increased volume correlating with our response control measures. However, the participant characteristics (inclusion of TD children only spanning a younger age range) and the methods used to quantify subcortical morphology differed between studies, possibly

contributing to the inconsistent findings. Furthermore, Sandman et al. did not examine associations with response inhibition or variability during the Go/No-Go task, instead focusing on measures of response speed. Thus, it will be important to reconcile these inconsistent results in future studies with larger samples to better understand the association between basal ganglia morphology and cognitive performance in the context of typical and atypical development and sex differences.

The results of this study considered in combination with prior reports of greater prefrontal abnormalities among girls with ADHD in this age range [71,72] should be considered within a developmental framework given the delay in cortical maturation associated with ADHD [73]. Furthermore, the sexually dimorphic developmental course of the basal ganglia suggests that whether girls and boys with ADHD display basal ganglia anomalies may depend on their age [33]. Specifically, Raznahan et al. [33] suggests that the estimated peak volume of the globus pallidus is earlier in boys (age 7.7) than girls (age 9.5) whereas the estimated peak volume of the striatum and thalamus is earlier in girls (ages 12 and 13.8, respectively) than boys (ages 14.7 and 17.4, respectively). Thus, it may be that motor deficits and the associated anomalies in basal ganglia morphology may be more apparent among boys with ADHD during this developmental period whereas girls with ADHD may show similar anomalies compared to TD girls at a younger or older age depending on the brain region. This pattern is supported by findings from our recent study of preschoolers with and without ADHD, showing reduced volume of the caudate, globus pallidus, and thalamus among girls with ADHD compared to TD girls whereas no significant diagnostic differences were observed among boys [74].

5. Conclusions

In sum, our findings suggest that reduced volume and shape abnormalities of the putamen and globus pallidus relate to motor response control, particularly with regard to cognitive control over motor responses. Among girls with ADHD, basal ganglia morphology was similar to that of TD girls and impaired response control was only observed when working memory was necessary to guide response selection. Overall, these findings add to the growing literature reporting ADHD-related sex differences in neuroanatomy and neurocognitive functioning. It will be important to replicate and extend these findings in longitudinal studies of children with ADHD oversampled for girls and to include children with affective comorbidities along with additional behavioral measures of reward and emotional processing to better characterize the role of basal ganglia dysfunction in ADHD.

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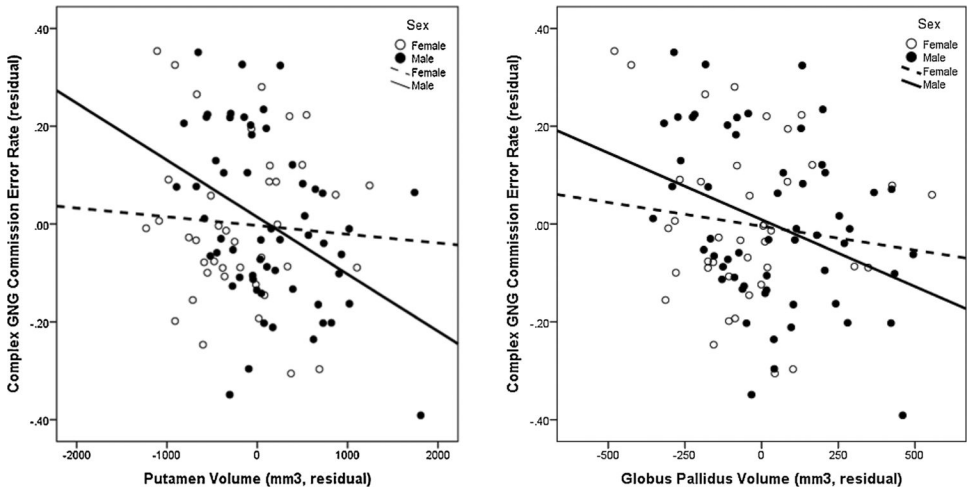

Fig. 1.

Scatterplots of partial correlation (covarying for age and TCV) between putamen and globus pallidus volumes with complex GNG commission error rate among boys and girls regardless of diagnostic group.

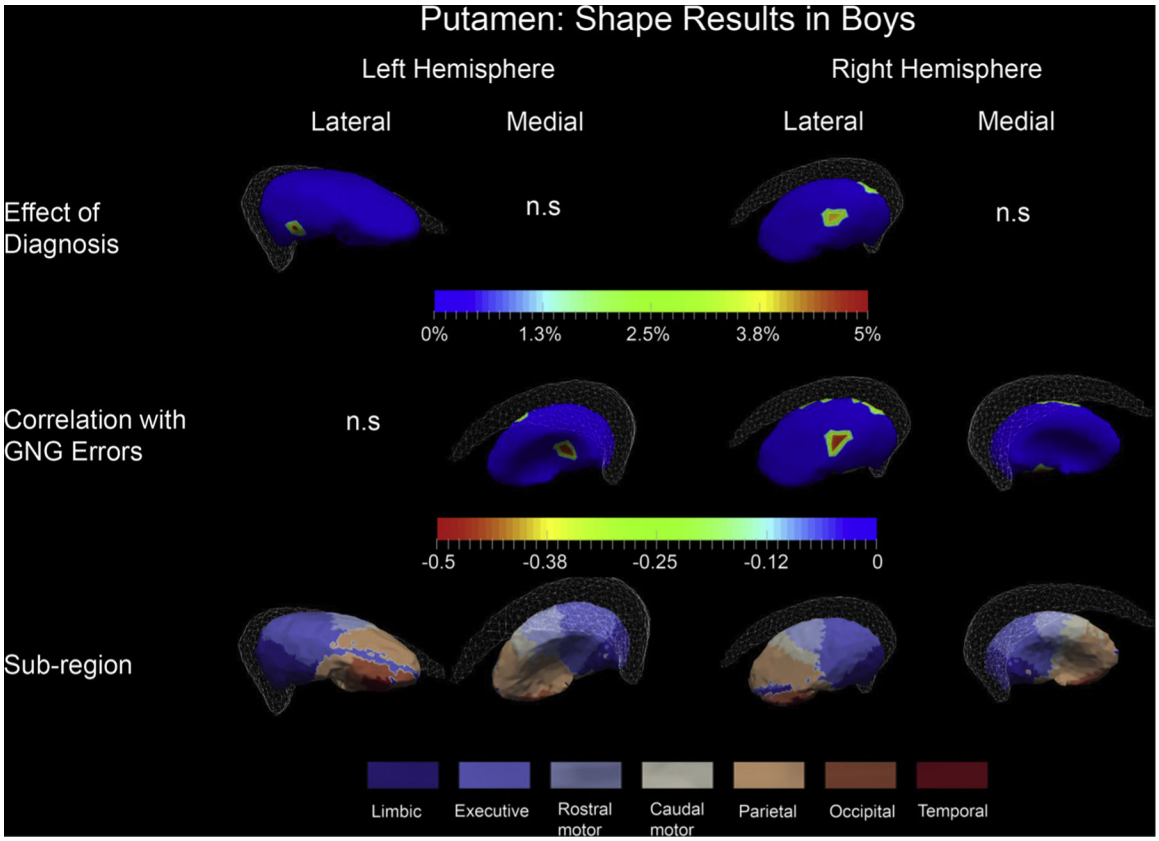

Fig. 2.

Shape analysis results for the putamen. The upper portion represents the vertex-wise shape group differences between ADHD boys and TD boys (controlling for age and TCV), wherein the color bar denotes the proportion of compression in ADHD boys when compared to TD boys. The middle portion represents the Pearson's partial correlation coefficient (controlling for age and TCV) between shape deformation markers and the commission error rate during the complex GNG in all boys, wherein the color bar denotes the specific PCC value. The lower portion represents the subregion definition of the bilateral putamen. In all figures except those displaying the sub-regions, only regions with statistical significance at a level of 0.05 after FWER-controlling are highlighted.

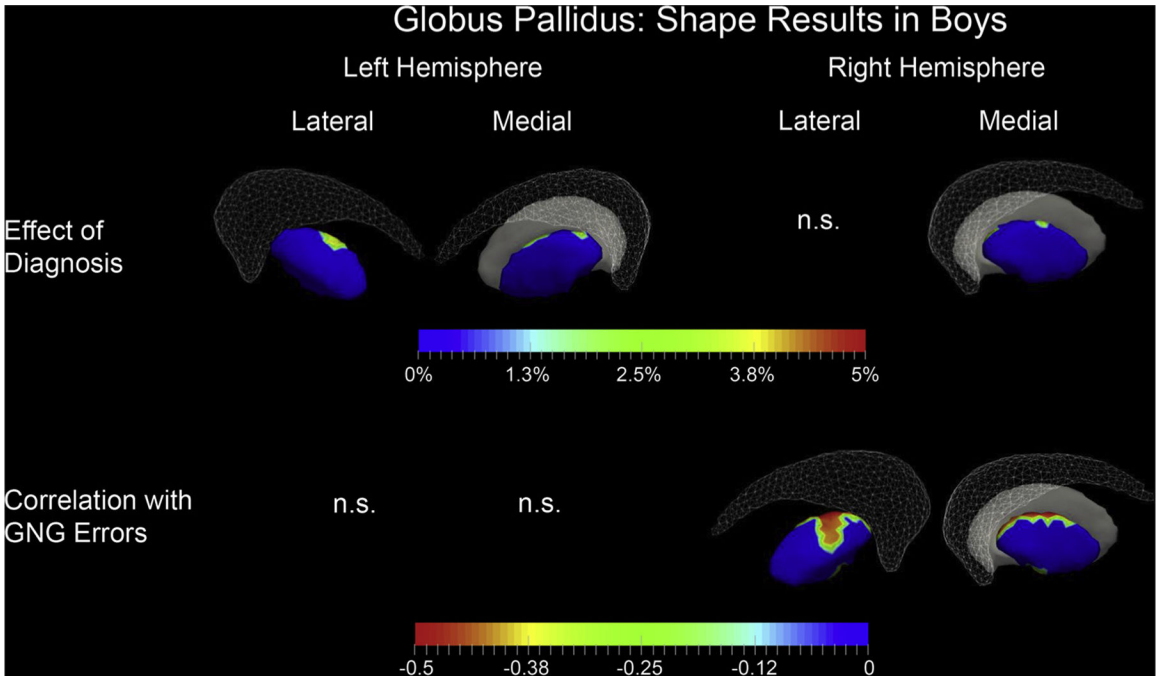

Fig. 3.

Shape analysis results for the globus pallidus. The upper portion represents the vertex-wise shape group differences between ADHD boys and TD boys (controlling for age and TCV), wherein the color bar denotes the proportion of compression in ADHD boys when compared to TD boys. The lower portion represents the Pearson's partial correlation coefficient (controlling for age and TCV) between shape deformation markers and the commission error rate during the complex GNG in all boys, wherein the color bar denotes the specific PCC value. In all figures, only regions with statistical significance at a level of 0.05 after FWER-controlling are highlighted.

Table 1

Demographic and clinical characteristics of girls and boys with ADHD and typically developing (TD) controls.

	TD						ADHD						Group Comparisons			
	Girls (n = 19)		Boys (n = 26)		All (n = 45)		Girls (n = 21)		Boys (n = 31)		All (n = 52)		Girls TD vs. ADHD	Boys TD vs. ADHD	All TD vs. ADHD	ADHD Boys vs. Girls
	Mean	SD	Mean	SD	Mean	SD	Mean	SD	Mean	SD	Mean	SD	*p*-values			
Age (years)	10.0	0.9	9.9	0.8	9.9	0.9	10.1	1.5	9.5	1.0	9.8	1.2	.773	.142	.457	.085
% Minority	21%		31%		27%		19%		32%		27%		.874	.904	.977	
SES	50.8	9.2	50.1	10.8	50.4	10.0	51.5	11.1	49.6	11.3	50.3	11.2	.821	.853	.981	.545
Handedness Integer	0.8	0.2	0.6	0.6	0.7	0.5	0.6	0.6	0.7	0.5	0.6	0.5	.093	.396	.810	.561
FSIQ	109.9	10.3	113.0	9.7	111.7	9.9	107.4	15.0	107.5	13.4	107.5	13.9	.536	.089	.093	.967
GAI	109.1	10.6	116.3	10.0	113.2	10.7	107.5	13.5	112.4	13.8	110.4	13.8	.675	.234	.262	.213
VCI	112.7	12.3	117.5	11.4	115.5	11.9	108.6	15.5	113.1	13.0	111.3	14.1	.361	.184	.119	.265
PRI	102.3	10.7	110.2	10.1	106.9	11.0	107.6	13.0	108.0	13.6	107.8	13.3	.166	.487	.701	.927
WMI	106.0	11.0	106.4	12.4	106.2	11.7	102.9	17.2	103.4	13.6	103.2	15.0	.507	.387	.273	.917
PSI	108.5	13.8	99.8	12.3	103.5	13.5	102.0	13.3	93.5	11.9	97.0	13.0	.141	.053	.017	.019
Conners IA T	47.9	5.4	43.7	4.7	45.4	5.4	79.5	10.4	68.6	10.4	73.1	10.6	< .001	< .001	< .001	< .001
Conners HI T	47.2	4.8	46.1	3.7	46.5	4.2	74.4	14.2	69.2	14.2	71.4	14.1	< .001	< .001	< .001	.197
ADHD-RS IA Raw	2.4	2.4	2.7	3.0	2.6	2.8	20.4	4.3	17.9	4.3	18.9	4.3	< .001	< .001	< .001	.038
ADHD-RS HI Raw	1.3	1.6	1.8	2.0	1.6	1.9	13.6	7.2	13.7	7.2	13.7	7.0	< .001	< .001	< .001	.955
ADHD Subtype, CO:IA:HI (count)	n/a		n/a		n/a		15:6:0		23:7:1		38:13:1		n/a	n/a	n/a	.647
% Stimulant Medication	0		0		0		81%		61%		69%		n/a	n/a	n/a	.132
ODD	0		0		0		38%		32%		34%		n/a	n/a	n/a	.664

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; Handedness=Edinburgh Handedness Inventory; 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; CO=Combined subtype; IA=Inattentive subtype; HI=Hyperactive/Impulsive subtype; % Stimulant Medication=Percentage of subjects taking stimulant medication at the time of the study (all subjects discontinued medication the day prior to and day of study participation); ODD=Oppositional Defiant Disorder.

Table 2

GNG task performance for the ADHD and TD groups overall and within sex.

	TD						ADHD						ADHD vs. TD					
	Girls (n = 19)		Boys (n = 26)		All (n = 45)		Girls (n = 21)		Boys (n = 31)		All (n = 52)		Girls		Boys		All	
	Mean	SD	Mean	SD	Mean	SD	Mean	SD	Mean	SD	Mean	SD	*p*	*d*	*P*	*d*	*p*	*d*
S-GNG Com	0.35	0.2	0.41	0.2	0.38	0.2	0.40	0.2	0.56	0.2	0.49	0.2	.396	.27	.004	.80	.012	.57
C-GNG Com	0.41	0.1	0.45	0.2	0.44	0.2	0.56	0.2	0.60	0.2	0.58	0.2	.017	.80	.004	.77	< .001	.79
S-GNG Tau	105.9	33.3	89.0	27.2	96.1	30.8	149.9	70.3	136.5	69.9	141.9	69.7	.014	.85	.002	.98	< .001	.91
C-GNG Tau	114.6	49.8	84.0	34.6	96.9	43.9	186.0	117.3	182.1	144.6	183.7	133.0	.030	.85	.001	1.09	< .001	.98

Note. S-GNG = Simple Go/No-Go Task; C-GNG = Complex Go/No-Go Task; Com = commission error rate (proportion of no-go trials on which the participant incorrectly responded); Tau = ex-Gaussian parameter for the skewed tail of the reaction time distribution.

Table 3

Basal ganglia volumes (raw) in mm^3 and differences between ADHD and TD overall and within sex.

	TD						ADHD						ADHD vs. TD					
	Girls (n=19)		Boys (n=26)		All (n=45)		Girls (n=21)		Boys (n=31)		All (n=52)		Girls		Boys		All Dx × Sex	
	Mean	SD	Mean	SD	Mean	SD	Mean	SD	Mean	SD	Mean	SD	*p*	*d*	*p*	*d*	*p*	*d*
L-Caudate	3905	374	4522	643	4261	622	4010	348	4305	387	4186	396	.204	.41	.163	.38	.063	.38
R-Caudate	3906	374	4604	639	4309	641	4051	326	4288	417	4192	397	.141	.48	.022	.63	.010	.54
L-Putamen	4506	373	5172	566	4891	591	4555	353	4846	405	4729	408	.255	.37	.002	.86	.004	.60
R-Putamen	4397	341	5077	529	4790	567	4498	367	4750	394	4648	400	.093	.55	.001	.89	.001	.70
L-GlobPal	1632	137	1850	199	1758	205	1627	133	1731	170	1689	163	.671	.14	.004	.79	.029	.46
R-GlobPal	1524	127	1709	179	1631	183	1526	138	1610	153	1576	152	.600	.17	.017	.66	.053	.40

Note. L = left, R = right, GlobPal = globus pallidus. P-value and effect size estimate (cohen's d) for the univariate analysis of covariance in which age and TCV are included as covariates.

Table 4

Partial correlations (controlling for age and TCV) between basal ganglia volumes and Go/No-Go performance among boys and girls with and without ADHD.

		Simple GNG Com	Complex GNG Com	Simple GNG Tau	Complex GNG Tau
Boys	L Caudate	−.152	−.218	−.234	−.099
	R Caudate	−.280	−.273	−.208	−.195
	L Putamen	−.420*	−.490*	−.109	−.153
	R Putamen	−.368*	−.525*	−.185	−.189
	L GlobPal	−.315	−.421*	−.135	−.224
	R GlobPal	−.268	−.440*	−.128	−.245
Girls	L Caudate	.059	−.058	.167	.128
	R Caudate	.075	.057	.164	.054
	L Putamen	.117	.150	.040	−.047
	R Putamen	.119	.117	.079	.002
	L GlobPal	−.099	.111	−.178	−.183
	R GlobPal	−.106	−.005	−.225	−.193

Note. GNG = Go/No-Go Task; Com = Commission Error Rate.

*Significant after FDR correction within each group (24 tests).