Mapping the Development of the Basal Ganglia in Children With Attention-Deficit/Hyperactivity Disorder

Philip Shaw, MD, PhD, Pietro De Rossi, MD, Bethany Watson, BA, Amy Wharton, BA, Deanna Greenstein, PhD, Armin Raznahan, MD, PhD, Wendy Sharp, MSW, Jason P. Lerch, PhD, M. Mallar Chakravarty, PhD

Objective: The basal ganglia are implicated in the pathophysiology of attention-deficit/hyperactivity disorder (ADHD), but little is known of their development in the disorder. Here, we mapped basal ganglia development from childhood into late adolescence using methods that define surface morphology with an exquisite level of spatial resolution. **Method:** Surface morphology of the basal ganglia was defined from neuroanatomic magnetic resonance images acquired in 270 youth with *DSM-IV*–defined ADHD and 270 age- and sex-matched typically developing controls; 220 individuals were scanned at least twice. Using linear mixed model regression, we mapped developmental trajectories from age 4 through 19 years at approximately 7,500 surface vertices in the striatum and globus pallidus. **Results:** In the ventral striatal surfaces, there was a diagnostic difference in developmental trajectories ($t = 5.6$, $p < .0001$). Here, the typically developing group showed surface area expansion with age (estimated rate of increase of 0.54 mm^2 per year, standard error [SE] 0.29 mm^2 per year), whereas the ADHD group showed progressive contraction (decrease of 1.75 mm^2 per year, SE 0.28 mm^2 per year). The ADHD group also showed significant, fixed surface area reductions in dorsal striatal regions, which were detected in childhood at study entry and persisted into adolescence. There was no significant association between history of psychostimulant treatment and developmental trajectories. **Conclusions:** Progressive, atypical contraction of the ventral striatal surfaces characterizes ADHD, localizing to regions pivotal in reward processing. This contrasts with fixed, nonprogressive contraction of dorsal striatal surfaces in regions that support executive function and motor planning. J. Am. Acad. Child Adolesc. Psychiatry, 2014;53(7):780–789. **Key Words:** attention-deficit/hyperactivity disorder, basal ganglia, ventral striatum, development, neuroimaging

Pathology of the basal ganglia has been consistently implicated in the pathogenesis of attention-deficit/hyperactivity disorder (ADHD). The basal ganglia are core components of richly interconnected "loops" that connect the cortex and thalamus, supporting many cognitive processes that are impaired in ADHD.[1] Dysfunction in the circuit spanning the ventral striatum (nucleus accumbens, ventral caudate, and putamen) and limbic cortex is linked primarily with the abnormal processing of rewards found in ADHD[2-3]. Problems with executive functions, such as cognitive control and working memory, have been tied to anomalies in the circuit linking the lateral prefrontal cortex with the head of caudate and anterior putamen.[4-7] Finally, problems in motor planning and control, another hallmark of ADHD, may be underpinned by disruptions in the links between the posterior/caudal regions of the basal ganglia and sensorimotor cortex.[8-12]

Consonant with these functional deficits are findings of structural compromise. Reduced total striatal volumes have often, but not always, been reported, with meta-analyses of voxel-based morphometric studies localizing this loss to the putamen and head of caudate.[13-15] Two recent studies have mapped changes in the surface morphology of the striatum and found predominantly


Supplemental material cited in this article is available online.

highly localized, multifocal surface contractions, undetectable by traditional volumetric techniques. In both studies, surface area contractions were found in the tail of caudate, the mid-body of the putamen, and medial, anterior globus pallidus, with less prominent expansion in the posterior putamen[16] and head of caudate.[17]

Despite these advances, there are several major gaps in our knowledge. Foremost is the need to map the trajectory of basal ganglia development in ADHD, as all but 1 previous study[18] have been cross-sectional and confined to a relatively narrow age range. This developmental mapping requires methods that afford a high level of spatial resolution, given the recent evidence that ADHD is characterized by highly localized alterations to surface morphology.[14,16,17]

A second question surrounds the possible effects of psychostimulant treatment on basal ganglia structure. A recent meta-analysis of cross-sectional studies suggested that treatment is associated with more normative dimensions, and 1 surface morphology study found that diagnostic differences were confined to medication-naive participants with ADHD.[14,17] However, no study has used longitudinal data to test for associations between the duration of psychostimulant treatment and basal ganglia development.

We thus mapped the development of the basal ganglia over childhood and adolescence, combining both longitudinal and cross-sectional neuroanatomic magnetic resonance data collected on a large cohort of participants.

METHOD

Study Participants and Procedures

A total of 270 children and adolescents with ADHD participated. Details of this cohort can be found elsewhere,[18] but in brief, diagnosis was based on the Parent Diagnostic Interview for Children and Adolescents,[19] and Conners' Teacher Rating Scales.[20] Exclusion criteria were a full-scale IQ of less than 80, evidence of medical or neurological disorders on examination or by clinical history, Tourette disorder, or any other axis I psychiatric disorder requiring treatment with medication at study entry. At study entry, 238 participants (88.2%) had combined-type ADHD, 17 (6.2%) had inattentive subtype, and 15 (5.6%) had hyperactive/impulsive subtype. Numbers and age of participants at each wave of scanning and their sex and IQ are given in Table 1. All participants with ADHD retained the diagnosis at each assessment. The focus of the study was childhood and adolescence, and the age range was between age 4 and 18.9 years. The proportion of time that participants were taking psychostimulant medication during the study was obtained from parental history. Conventional volumetric change in the caudate has previously been reported upon in 291 individuals in this study, with a total of 544 scans.[18] This study includes new data on 249 participants, with a total of 325 new neuroanatomic images and reports on surface morphological change for the first time. Socioeconomic status was defined using the Hollingshead Four-Factor Index of Socioeconomic Status, and IQ was estimated using an age-appropriate version of the Wechsler intelligence scales.

The typically developing participants were part of the National Institutes of Health (NIH) intramural project on typical brain development.[21] The group was matched with the ADHD group on sex, IQ, and number of scans. A parent of each child completed the Childhood Behavior Checklist (CBCL) as a screening tool and underwent a structured diagnostic interview to rule out other neuropsychiatric diagnoses. Both the participants with ADHD and those typically developing were recruited through advertisement and community contacts and were predominately from the geographic area surrounding the study center. The institutional review board of the NIH approved the research protocol for both the typically developing children and adolescents and those with ADHD, and written informed consent and assent to participate in the study were obtained from parents and children, respectively.

Both the participants with ADHD and the typically developing participants had neuroanatomic magnetic resonance imaging (MRI) on the same 1.5-T General Electric (Milwaukee, WI) Signa scanner throughout the study. T1-weighted images with contiguous 1.5-mm slices in the axial plane were obtained using 3-dimensional spoiled gradient-recalled echo in the steady state. Imaging parameters were as follows: echo time = 5 milliseconds, repetition time = 24 milliseconds, flip angle = 45°, acquisition matrix = 256 × 192, number of excitations = 1, and field of view = 24 cm.

The basal ganglia were automatically identified using a recently developed segmentation method known as the MAGeT Brain algorithm.[22] Here we define the basal ganglia as comprising the striatum (the caudate and putamen) and globus pallidus. To summarize the technique, a single atlas for the striatum and an atlas for the globus pallidus that were previously defined using a 3-dimensional reconstruction of serial histological data[23] were warped to an MRI-based template. The atlases were then customized to a subset of the dataset (30 randomly selected participants between the ages of 5 and 18 years) using a nonlinear transformation estimated in a region-of-interest defined around the subcortical structures.[23,24] This set of participants now acts as a set of templates, and all other participants are now warped to these templates. This provides 30 candidate segmentations for each participant's striata and globus pallidi. The final segmentation is decided upon using a voxelwise majority vote, that

TABLE 1 Demographic and Clinical Characteristics of the Attention-Deficit/Hyperactive Disorder (ADHD) and Typically Developing Groups

	ADHD Group	Typically Developing Group	Group Difference
Age, y, mean (SD)			
Time 1	n = 270 9.8 (3.1)	n = 270 10.3 (3.3)	$t_{538} = 1.69$, $p = .09$
Time 2	n = 110 11.9 (2.9)	n = 110 12.6 (2.9)	$t_{218} = 1.73$, $p = .08$
Time 3	n = 43 13.9 (2.9)	n = 45 14.4 (2.3)	$t_{86} = 1.06$, $p = .29$
Time 4	n = 9 16.3 (2.1)	n = 12 16.0 (1.5)	$t_{19} = 037$, $p = .72$
Sex, n (%)	Male 184 (68) Female 86 (32)	Male 184 (68) Female 86 (32)	N/A
IQ, mean (SD)	108 (15)	108 (11)	t(500)=0.39, $p = .7$
SES, mean (SD)	47 (24)	45 (20)	t(512)=1.15, $p = .25$
On psychostimulant medication at study entry (yes/no)	168/99 (data missing on 3 participants)		
Ethnicity, n (%)			White, non-Hispanic vs. others
White, non-Hispanic	207 (77)	219 (81)	X(1)2=1.6, $p = .21$
White Hispanic	17 (6)	8 (3)	
African American	36 (13)	29 (11)	
Other	10 (4)	14 (5)	
CBCL attention problems, mean (SD)	72 (9)	N/A	
CBCL externalizing problems	65 (11)	N/A	
DSM-IV–diagnosed disorders, n (%)			
ODD	91 (32)	N/A	
Any mood disorder	15 (5)	N/A	
Any anxiety disorder	17 (6)	N/A	
Any tics	16 (6)	N/A	
Any learning disability	28 (10)	N/A	

Note: Missing data are reflected in the degrees of freedom. CBCL = Child Behavior Checklist; N/A = not applicable; ODD = oppositional defiant disorder; SES = socioeconomic status.

is, the label occurring most frequently at a specific location is retained. These methods are reliable in comparisons to "gold standard" manual definitions ($\kappa = 0.86$).[22]

To determine shape, first surface-based representations of the basal ganglia defined on the input atlas were estimated using the marching cubes algorithm[25] and were morphologically smoothed using the AMIRA software package (Visage Imaging; San Diego, CA). The resulting surfaces have about 6,300 vertices per striatum and 1,300 per globus pallidus. The nonlinear portions of the 30 transformations that map each participant to the input template were concatenated and then averaged across the template library to limit the effects of noise and error and to increase precision and accuracy.[26] These surface-based representations were warped to fit each template, and, as in the case of the segmentation, each of these surfaces was warped to match each participant. This yields 30 possible surface representations per participant, which are then merged by creating a new surface representation of the striatum or pallidum by estimating the median coordinate representation at each location. At this point, one-third of the surface of each triangle is assigned to each vertex within the triangle. The surface area value stored at each vertex is the sum of all such assignments from all connected triangles.[27] Finally, surface area values were blurred with a surface-based diffusion smoothing kernel (5 mm and 3 mm for the striatum and pallidum, respectively).

Data Analysis

Morphometric group differences at study entry were determined using t tests. In the longitudinal analyses, we determined developmental trajectories for total volumes and the surface area at every vertex using mixed-model regression analysis.[28] This approach allows the inclusion of participants with a single observation and participants with multiple observations measured at different and irregular time periods. Although most data were from individuals with repeated observations (549 observations, comprising 63% of all data), in the primary analysis we included data from individuals who had only a single scan, as these provide additional information about between-participant variation and overall curve shape. The inclusion of a random intercept per person accounts for the nonindependence of the subcortical measures in participants with multiple observations. To determine the fit for each morphometric index of interest, a likelihood ratio test was used to determine whether a model

including a quadratic age terms accounted for significantly more variance at $p < .05$ than a model including only a linear age term. For striatal volumes, a quadratic model was appropriate; for pallidal volumes and for surface area change at the vertex level, a linear model provided the best overall fit. In the linear model, the jth surface area of the ith individual in the kth group was modeled as follows:

$$\text{Metric}_{ij} = \text{intercept} + d_i + \beta_1\,\text{age} + \beta_2\,\text{group} + \beta_3\,(\text{age} \times \text{group}) + e_{ijk}$$

where d_i is a random effect modeling within-person dependence, the intercept and β terms are fixed effects, and e_{ijk} represents the residual error (for further details, see Supplemental Methods). Group differences in the slopes (or linear trajectory) at each vertex is given by the β_3 term. We used t tests to test the significance of each parameter in the mixed-model regression, and projected the results onto a brain template. To control for multiple comparisons, we used the false discovery rate procedure, which controls the expected proportion of incorrectly rejected null hypotheses.[29] We set this proportion at 5% ($q = 0.05$). We also repeated all analyses including only participants with repeated observations.

To examine associations with psychostimulant treatment, we compared medication-naive participants against those on psychostimulants at study entry. We also tested for an interaction between the proportion of time during the study on psychostimulants and trajectories using only those individuals with longitudinal data.

RESULTS

Baseline Differences

At study entry, basal ganglia volume and total surface areas were significantly reduced in individuals with ADHD (Table S1, available online). Vertex-level analyses showed that this reduction was most prominent in the lateral surface of the caudate bilaterally, extending from the head through the body of the caudate to the anterior regions of the tail (Figure 1). Surface area reduction in the putamen was confined to a small region of the anterior–superior putamen, the mid-body, and posterior–inferior regions. In the globus pallidus, there was surface area reduction predominantly in posterior–inferior regions (Figure S1, available online). There was relative sparing at baseline of the ventral regions of the globus pallidus and striatum, with no significant group difference.

Trajectory Differences

In both groups, the striatal volumes increased with age, peaking around mid-adolescence and then beginning to decrease. Trajectories are given in Figure 2. The growth trajectories did not differ significantly by diagnosis, although there was a trend toward convergence between the ADHD and typical groups on the right (right $F = 2.9$, $p = .053$; left $F = 0.74$, $p = .48$). For the total striatal surface areas, there was also no diagnostic difference in trajectories (right $F = 1.9$, $p = .15$; left $F = 0.18$, $p = .83$). For the volumes and total surface areas of the globus pallidus, there were no group differences in trajectories (right volumes $t = 0.89$, $p = .37$; left volumes $t = 0.45$, $p = .65$; right total surface area $t = 1.1$, $p = .29$; left total surface area $t = 0.77$, $p = .44$). Adjustment for total brain volume did not alter

FIGURE 1 Regions where the group with attention-deficit/hyperactivity disorder (ADHD) showed a significant reduction in surface area at study entry, after adjustment for multiple comparisons. Note: (A) right lateral view; (B) left lateral view; (c) inferior (ventral) view.

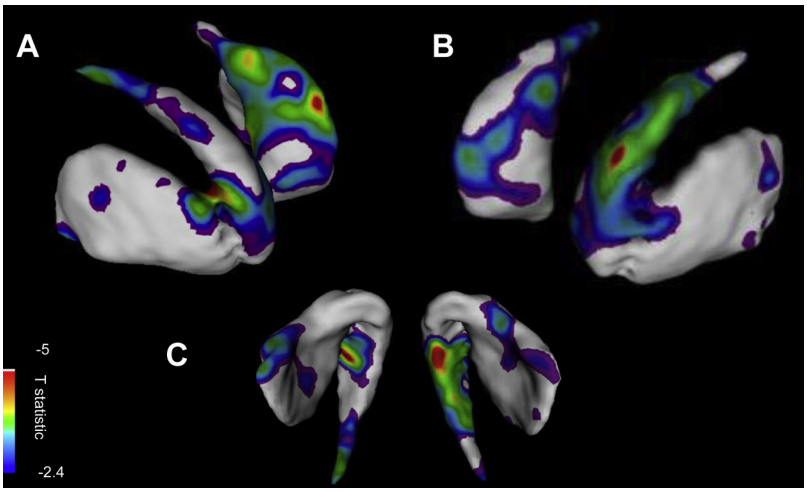
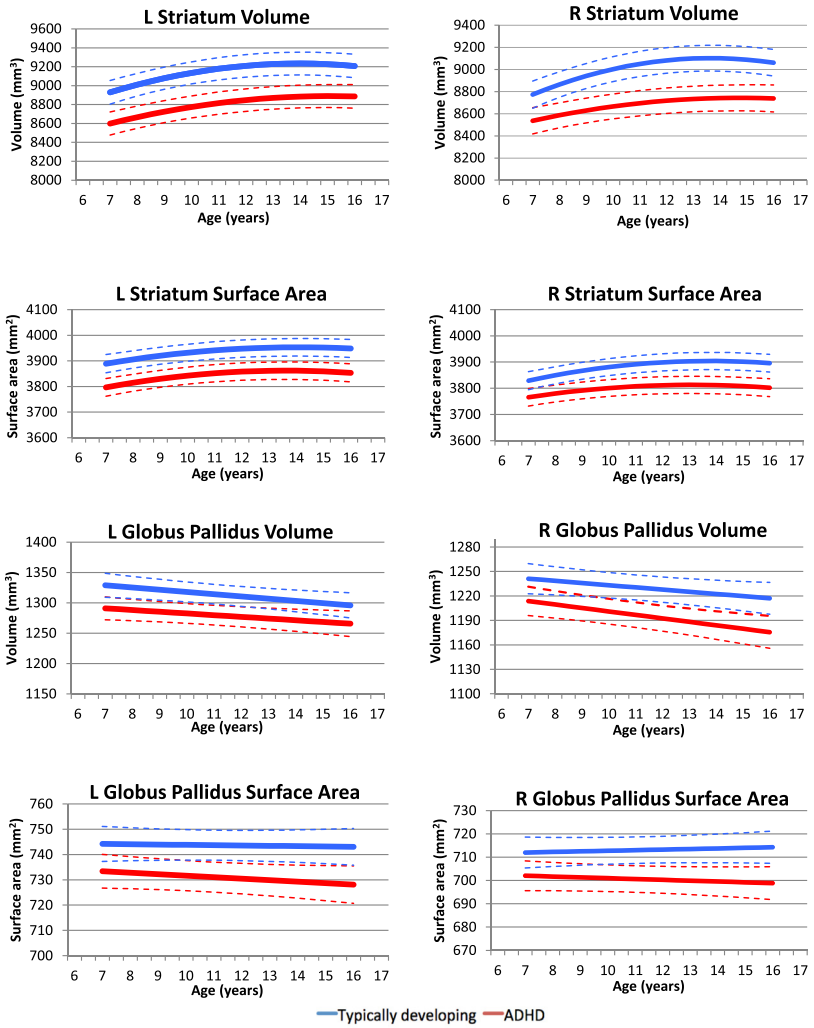


FIGURE 2 Developmental trajectories (estimates with 95% CI) for the striatal and globus pallidus volumes and total surface areas. Note: There were no significant differences in the shapes of the curves. The group with attention-deficit/hyperactivity disorder (ADHD) is shown in red, and the typically developing group is shown in blue.

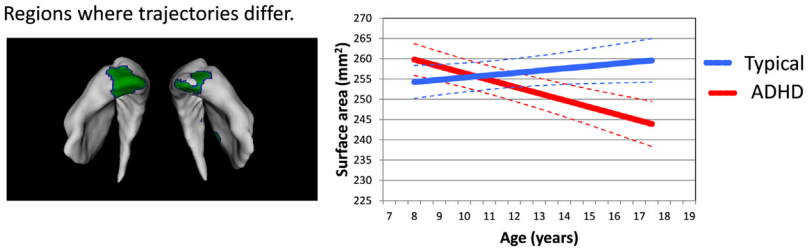


the longitudinal results but did render nonsignificant the baseline differences in volume and surface area for the globus pallidus and the surface area of the right striatum (Table S1, available online).

Vertex-level surface analyses showed a significant group difference in the trajectory of a region centered on the ventral striatum bilaterally (overall slope difference in this region, $t = 5.6$, $p < .00001$). Here, the typically developing group showed expansion of the surface area with age (increase of 0.54 mm^2 per year, standard error [SE] 0.29 mm^2 per year). By contrast, the group with ADHD showed marked, progressive contraction of the ventral striatal surface (decrease of 1.75 mm^2 per year, SE 0.28 mm^2 per year), as shown in Figure 3. This diagnostic difference in ventral striatal development is illustrated in a time-lapse sequence that shows the progression of significant group differences in this region with age (Movie S1, available online) and in a series of still images in Figure 4. A similar group difference was also seen in a small region of the right posterior putamen. Throughout the remainder of the putamen and caudate, there were no trajectory differences, as can be seen in Figure S2 (available online), which illustrates trajectories at points throughout the striatum. Thus, the dorsal striatal surface area reductions noted at study entry persisted into adolescence.

The pattern of results was almost identical when only those individuals with 2 or more observations were included, when analyses were

FIGURE 3 Regions where there was a significant difference in trajectories after adjustment for multiple comparison (overall slope difference in this region, $t = 5.6$, $p < .0001$) and a graph showing the trajectories of surface area change for this region, with 95% CI). Note: ADHD = attention-deficit/hyperactivity disorder.



confined to the subgroup of participants with ADHD but without any comorbid disorders, and when analyses were confined to those with combined-type ADHD only (Figures S3 and S4, available online). Male participants had greater striatal surface areas in both groups, although this sex effect was accentuated in the group with ADHD in a small region in the head of caudate, resulting in a significant sex × group interaction in this region (Figure S5, available online). In the longitudinal analyses, there were no regions that showed a significant interaction between diagnosis and sex after adjustment for multiple comparisons.

In the globus pallidus, there was a group difference at a nominal level of significance in trajectories in ventral regions bilaterally (Figure S6, available online). These group differences in trajectories did not survive adjustment for multiple comparisons.

There were no significant differences following adjustment for multiple comparisons between those on or off psychostimulants (treating medication status as a dichotomous variable) at study entry (Table S2 and Figure S7, available online). Likewise there were no regions of significant interaction between the proportion of time on psychostimulants and the trajectories of surface area change, following adjustment for multiple comparisons (full results are given in Figure S8, available online).

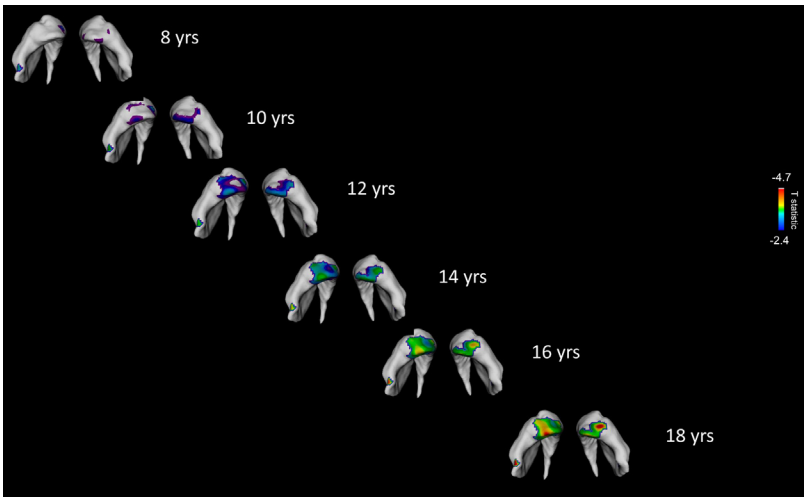
DISCUSSION

Three novel findings emerge from this study, which is the first to map basal ganglia development at a high level of spatial resolution in individuals with ADHD. First, we find a diagnostic difference in developmental trajectories of the ventral striatum throughout childhood and adolescence; this region shows progressive surface contraction in individuals with ADHD but not in those with typical development. Second, multiple areas show surface area reductions in individuals with ADHD that are fixed and do not progress with age, including the head and tail of the caudate and inferior–posterior putamen. Third, we found no significant association between duration of treatment with psychostimulants during the study and the developmental morphology of basal ganglia surfaces.

The diagnostic difference in ventral striatal development is consonant with its dysfunction in patients with ADHD, particularly in abnormal reward processing. Many, but not all, studies find a preference for immediate over delayed rewards—even when this strategy is ultimately disadvantageous[30-32]—in patients with ADHD. Decreased activity within the ventral striatum during the anticipation and receipt of rewards is 1 of the more consistent functional imaging findings in patients with ADHD.[33,34] Atypical connectivity between the ventral striatum, the amygdala, and orbitofrontal cortex has been found in both the patterns of spontaneous resting brain activity and during tasks of reward processing.[34-36] This delineates dysfunction in a network that may contribute to motivational deficits in ADHD. Given the implication of ventral striatal dysfunction in risk for drug dependence, the hypothesis emerges that this progressive ventral striatal surface loss could contribute to the vulnerability to substance misuse found among young adults with ADHD.[37,38]

We found that the dorsal striatum showed fixed surface area reduction in individuals with ADHD, detected in childhood and persisting into adolescence. This reduction was present in the so-called "associative" regions of the striatum (head/body of caudate and anterior putamen) that receive input from and project via the thalamus to predominately lateral prefrontal cortical

FIGURE 4 The emergence of significant group differences in surface area in the ventral striatal region from ages 8 to 18 years. Note: This is derived from the linear mixed model regression by re-centering age from age 8 to 18 years and illustrates the progression of ventral striatal contraction in attention-deficit/hyperactivity disorder (ADHD).



regions, supporting executive functions.[39,40] Dysfunction within this circuit in ADHD has been demonstrated by fMRI during tasks of attention and working memory.[6,7] The mid-body/tail of the caudate and posterior–inferior regions of the putamen also showed fixed surface area reduction in individuals with ADHD. These regions receive rich inputs from motor and premotor areas and parietal somatosensory areas.[12,39] Structural anomalies in this area could contribute to problems in the planning, control, and execution of motor behavior that are a hallmark feature of ADHD.[8,9] Hypoactivation in this circuit, specifically in the left putamen and supplementary motor area, was confirmed in a meta-analysis of fMRI studies of motor inhibitory control.[6] The 2 other surface morphology studies found surface anomalies in similar regions, a notable convergence in results, given the different approaches to mapping surface morphology.[16,17] It is important to note that these fronto-striato-thalamic circuits interact richly with one another, allowing flexible and adaptive behavior.[41] Thus, disruption in 1 striatal region is unlikely to be tied to a single neuropsychological deficit but instead may have an impact on many cognitive functions.

Why do ventral striatal regions alone show diagnostically different trajectories? Nested within each cortico-striato-thalamic circuit is a direct pathway (monosynaptically linking striatal neurons with the internal globus pallidus and substantia nigra) and an indirect pathway (linking the striatum and internal globus pallidus through the external globus pallidus and subthalamic nucleus). Dopamine is thought to activate the direct pathway through D1 receptors and to inhibit the indirect pathway through D2 receptors.[42,43] Different densities of these receptors throughout the striatum with high levels of D1 receptor in the medial caudate and limbic regions could be an important factor in contributing to the regional differences in growth that we report.[44] Interestingly, the effects of action at these receptors on behaviors relevant to the symptoms of ADHD (such as behavioral inhibition) vary with striatal region. For example, in rats, antagonists of D1 and D2 receptors in the dorsal but not ventral striatum have different effects on behavioral inhibition.[45] Other factors altering dopaminergic tone may also be important, such as the relatively low levels of dopamine transporters in the ventral striatum.[46] Animal studies link cytoarchitectural change with local perturbation in dopamine concentrations, and regional differences in dopamine transporter density might contribute to regional differences in growth. However, any trophic effects of psychostimulants are likely to be complex, varying by the mode of administration (chronic versus intermittent versus acute[47-49]) and by brain region.[48,50]

Striatal projections to the globus pallidus are topographically organized, and thus we would expect and indeed found congruence between changes seen at the striatal and pallidal levels. At baseline, both the striatum and globus pallidus

showed multifocal surface area reductions primarily in dorsal regions, with relative sparing of the ventral regions. In the longitudinal analyses, the diagnostic differences in the trajectories of ventral striatal surface morphology were mirrored by similar trajectory differences in ventral pallidal areas. In the ventral pallidum, whereas the typically developing group showed a clear increase in surface area with age, the ADHD group showed either progressive surface contraction or minimal change, as was found in the ventral striatum.

We did not find any association between psychostimulant medication and the structural development of the basal ganglia using our longitudinal data, nor did we find any medication-related differences at study entry. Although a meta-analysis of cross-sectional voxel-based morphometric studies reported more normative striatal volumes with psychostimulant treatment,[14] studies using manual delineations and surface mapping techniques yield more inconsistent findings.[16,51,52] One limitation of our study is that we treated medication use as a dichotomous variable at study entry and did not take into account the amount of time on psychostimulants before study entry as a variable. We also did not consider the possible effects of nonpharmacological interventions.

How do these findings relate to other anomalies of developmental trajectories found in the prefrontal cortex? This study confirms regional heterogeneity for developmental trajectories in typical development: the prefrontal cortex and striatum appear to follow somewhat different growth patterns.[53] Given such regional heterogeneity in typical growth patterns, we might expect to find regional heterogeneity in the altered trajectories associated with ADHD, which complicates the integration of cortical and subcortical trajectories. Nonetheless, a unifying theme emerges in ADHD of disruption to developmental trajectories in interconnected prefrontal cortical and striatal regions. For example, we recently found that, among children with ADHD persisting into adulthood, there was a fixed, nonprogressive thinning during adolescence of the medial prefrontal cortex/cingulate regions that projected heavily to the ventral striatum.[54] There is thus disruption at both the cortical and subcortical levels in a network supporting functions frequently implicated in ADHD, including reward processing. It has also been hypothesized that the primary neuroanatomic anomaly in ADHD lies in deep structures such as the striatum, with the prefrontal cortical anomalies reflecting symptom severity.[55] This model might predict that the subcortex shows relatively fixed or even progressive anomalies, whereas trajectories of the prefrontal cortex may be more reflective of current symptom status, which is consonant with some of our findings. It is also possible that other methods for modeling growth, beyond the mixed-model regression that we used, could reveal a common, underlying anomaly in both cortical and subcortical growth in ADHD.

The "multi-atlas" segmentation method that we used has several possible advantages over methods using a single template, defined and labeled by an expert neuroanatomist. In the single-template approach, the "labels" for each structure are customized to a specific participant's unique neuroanatomy by first estimating a participant-to-template nonlinear transformation and then applying the inverse transformation to the labels. These segmentations are prone to errors in the transformation estimation, irreconcilable neuroanatomical differences between the neuroanatomy of the template and the participant, and resampling errors after the application of the transformation to the labels. An approach incorporating multiple templates can mitigate these errors. For example, the use of 30 surface representations of the same structure may attenuate the impact on registration of any highly atypical features that might occur in a single template.

The inclusion criteria for the study resulted in a homogenous, severely affected phenotype at baseline; nearly all participants had combined-type ADHD and were relatively free of other major psychiatric comorbidities beyond oppositional defiant disorder. Although this enhances the applicability of the results to the "pure" syndrome, it limits the generalizability of the findings to children with either inattentive or hyperactive-impulsive subtype ADHD. Our participants were also drawn from a relatively socioeconomically affluent area, and a priority for future work is the inclusion of a more diverse sample. Although there is evidence of sexual dimorphism in the development of subcortical structures,[56,57] we did not find an interaction between sex and diagnosis, although we may have been underpowered because of the preponderance of male participants. We did not measure reward sensitivity in our participants, although the interpretation of our ventral striatal finding benefits from the large behavioral and neuroimaging literature demonstrating its role in reward processing in

individuals with ADHD. The study also used a mix of cross-sectional and longitudinal data, although the results held when analyses were confined to the longitudinal data only.

In this study, we demonstrate a highly atypical progressive surface area contraction in the ventral striatum in ADHD that contrasts with a fixed, nonprogressive surface area loss in the dorsal striatum. The finding of both fixed and progressive surface alterations throughout the basal ganglia is in keeping with the concept of multiple neurocognitive deficits contributing to ADHD, and of multiple pathways to the disorder.[2,58,59] &

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Drs. Shaw and De Rossi contributed equally to this study.

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Correspondence to Philip Shaw, MD, PhD, Section on Neurobehavioral Clinical Research, Social and Behavioral Research Branch, National Human Genome Research Institute, Building 31, B1 B37, Bethesda, 20892, MD; e-mail: shawp@mail.nih.gov

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SUPPLEMENT 1

Method

In the model reported, the variance of y is given by ZGZ′ + R, where Z is the design matrix for the random effects, G is the variance/covariance matrix for the random effects, and R is the covariance matrix for the within-participant random errors. R and G are block diagonal and assumed to have no correlation. In the model, $R = \sigma^2$ times the identity matrix (In). More complex covariance structures for within-person residuals that are appropriate for our data, such as the first-order autoregressive, returned an almost identical pattern of results.

Movie S1

Ventral striatal contraction in attention-deficit/hyperactivity disorder (ADHD). Movie S1 shows the difference in surface area between the group with ADHD and the typically developing group from age 8 through 19 years. The value of the group difference is expressed as a t statistic. Areas in blue indicate a group difference at t = 2.4, and areas in red, a difference of t = 4.8. The movie captures the progression of ventral striatal surface area contraction in ADHD. At age 8 years, few ventral regions are significantly reduced in ADHD; by age 19 years, most of the ventral striatum shows highly significant surface area contraction.

FIGURE S1 Areas of significant surface area reduction in the globus pallidus in attention-deficit/hyperactivity disorder (ADHD) at baseline, after adjustment for multiple comparisons. Note: The striata are overlaid in red to help with orientation. (A) Posterior view, showing surface loss in inferior/posterior globus pallidus; (B) ventral view, showing relative sparing at baseline in the ventral pallidal regions.

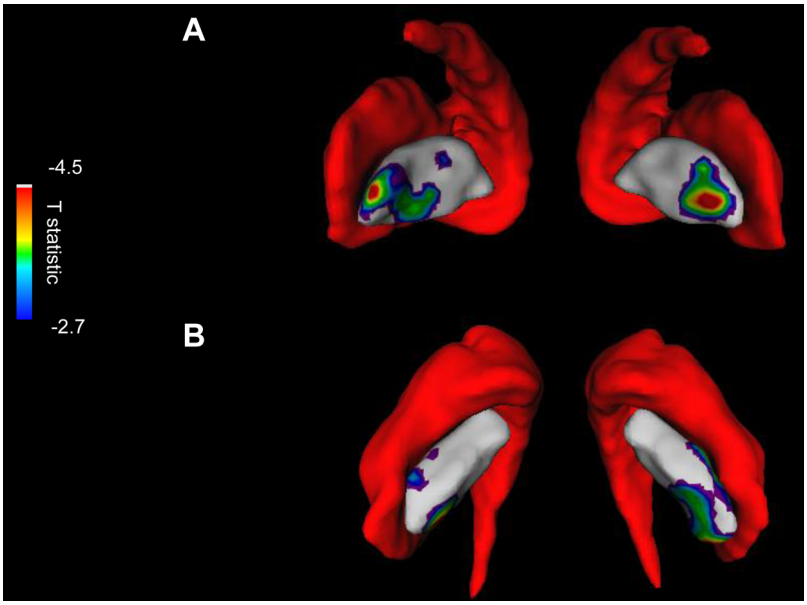


FIGURE S2 Trajectories of surface area at multiple vertices throughout the striatum. Note: Regions where there was significant reduction in surface area at study entry are colored (and are shown in Figure 1). There were no significant group differences in trajectories for all of the dorsal striatal points indicated. Group differences in trajectories were confined to ventral striatal regions. ADHD = attention-deficit/hyperactivity disorder.

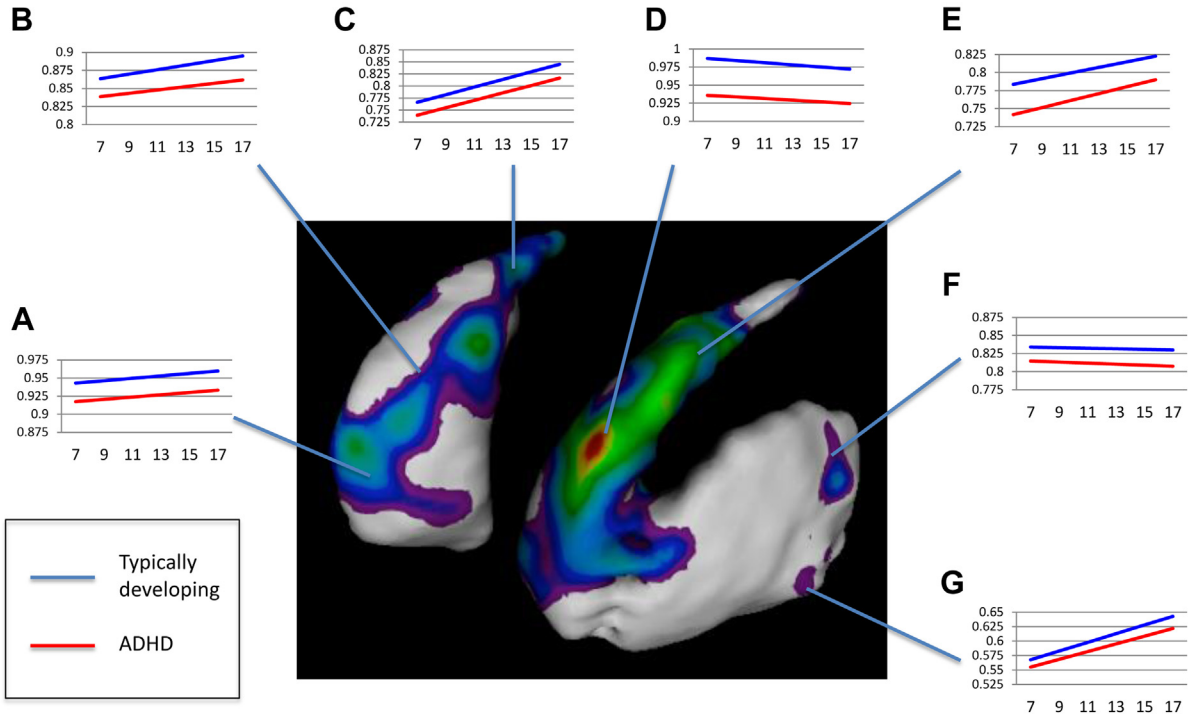
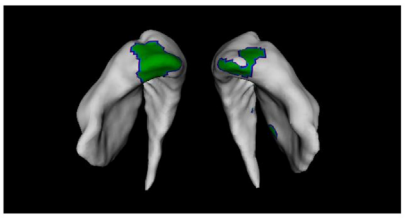
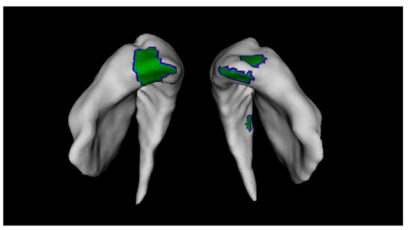


FIGURE S3 Top panel (A) shows the regions where there was a significant group difference in surface area trajectories (false discovery rate corrected, $p < 0.05$) (from Figure 2). Lower panel (B) shows the same analyses but is confined to individuals who had 2 or more scans.



A Regions where there was a group difference in trajectories for the entire cohort



B Regions where there was a group difference in trajectories confining analyses to individuals with two or more observations

FIGURE S4 Regions where there was a significant difference in trajectories for the participants with attention-deficit/hyperactivity disorder (ADHD) with no comorbid disorders (n = 150, 56% of the ADHD cohort).

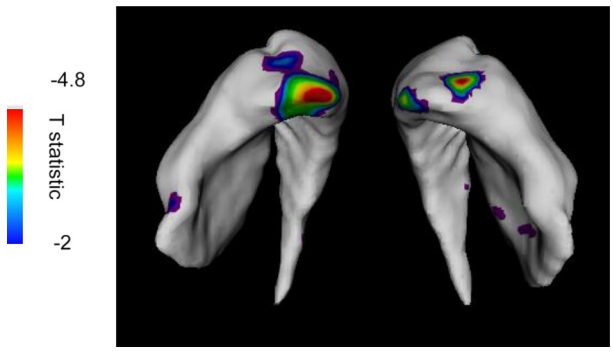


FIGURE S5 Panels show regions where there was a significant interaction between diagnosis and sex in the baseline surface areas. Note: (A) Right lateral view; (B) left lateral view. Male participants had larger surface areas in both groups, although this sex effect was accentuated in the group with attention-deficit/hyperactivity disorder (ADHD) in a small region in the head of caudate. In the longitudinal analyses, there were no regions that showed a significant interaction between diagnosis and sex after adjustment for multiple comparisons.

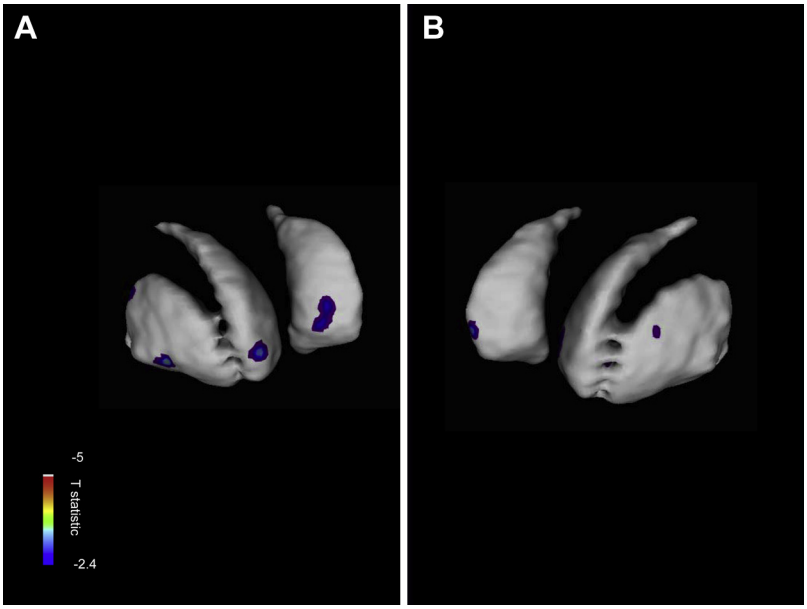


FIGURE S6 Group differences in trajectories in surface area changes in the globus pallidus. Note: These were predominately found in the ventral globus pallidus and at a nominal level of significance only. This trajectory difference did not survive adjustment for multiple comparisons. ADHD = attention-deficit/hyperactivity disorder.

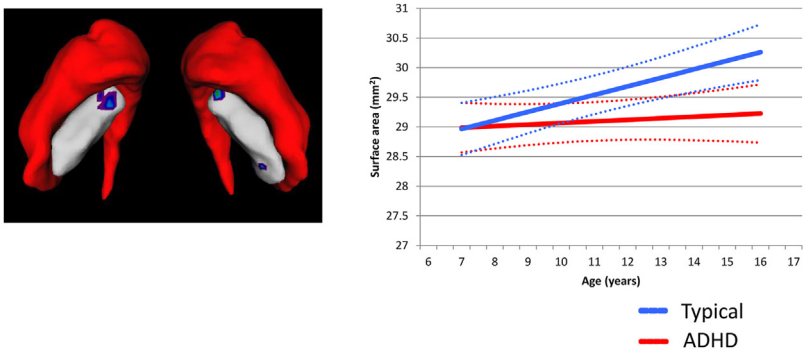


FIGURE S7 Pairwise contrasts of surface area at study entry between (A) participants with attention-deficit/hyperactivity disorder (ADHD) on psychostimulant treatment at study entry and those who were in the unmedicated groups at study entry. Note: Adjustment was made for age at scan, which differed significantly between these groups. (B) Participants with ADHD on psychostimulants versus typical controls and (C) unmedicated participants with ADHD versus typical controls. The level of significance is the same as the false discovery rate adjusted as shown in Figure 1. At a nominal level of significance, there were some small regions in the body of the putamen where the medication-naive participants showed surface reduction at baseline compared to those on psychostimulants, but these did not survive adjustment for multiple comparisons.

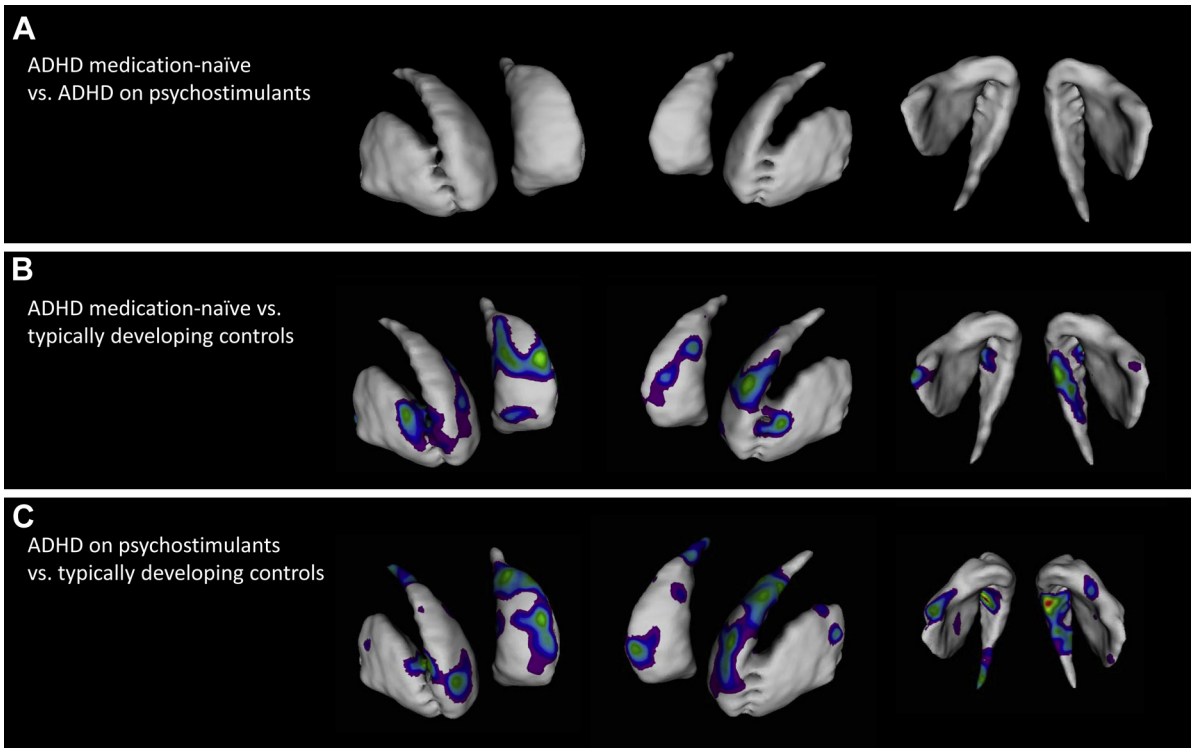


FIGURE S8 Regions are shown where there was a significant interaction between the proportion of time on psychostimulants and the trajectories of surface area change. Note: There were no group differences that survived adjustment for multiple comparisons. At a nominal level of significance ($p < .05$), there was a significant interaction between the proportion of time on psychostimulants and the trajectories of surface area change in small areas of the anterior caudate bilaterally and the posterior putamen.

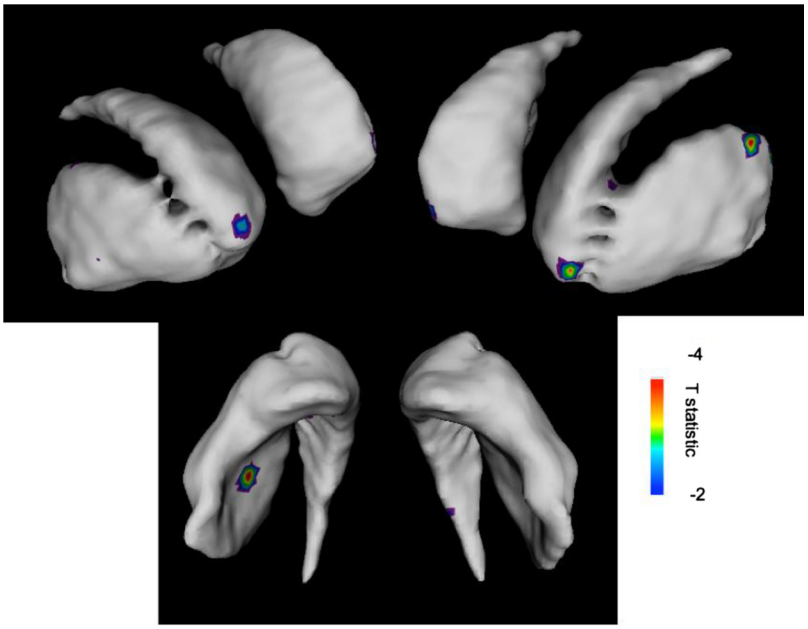


TABLE S1 Comparison of the Dimensions at Study Entry of the Striatum and Globus Pallidus in the Group With Attention-Deficit/Hyperactivity Disorder (ADHD) Versus the Typically Developing Groups

	Unadjusted			Adjusted for Brain Volume		
	ADHD Group (n = 270)	Typically Developing (N = 270)	t_{538}, p	ADHD Group (n = 270)	Typically Developing Group (n = 270)	$F_{1,537}$
Volumes (mm^3)[a]						
Right striatum	8,640 (941)	8,937 (918)	$t = 3.7$, $p < .0001$	8,734 (39)	8,843 (39)	$F = 4.0$, $p = .05$
Left striatum	8,729 (988)	9,081 (951)	$t = 4.22$, $p < .0001$	8,829 (41)	8,9981 (41)	$F = 6.9$, $p = .008$
Right globus pallidus	1,202 (138)	1,282 (124)	$t = 2.65$, $p = .008$	1,212 (7)	1,222 (7)	$F = 1.05$, $p = .31$
Left globus pallidus	1,282 (141)	1,316 (133)	$t = 2.81$, $p = .005$	1,293 (7)	1,305 (7)	$F = 1.38$, $p = .24$
Total surface area (mm^2)						
Right striatum	3,789 (268)	3,867 (266)	$t = 3.36$, $p = .001$	3,818 (11)	3,837 (11)	$F = 0.16$, $p = .19$
Left Striatum	3,921 (281)	3,838 (271)	$t = 3.92$, $p < .0001$	3,858 (11)	3,891 (11)	$F = 4.68$, $p = .03$
Right globus pallidus	701 (50)	713 (45)	$t = 2.92$, $p = .004$	705 (2)	709 (2)	$F = 1.49$, $p = .22$
Left globus pallidus	731 (51)	743 (48)	$t = 2.76$, $p = .006$	736 (2)	739 (2)	$F = 1.02$, $p = .32$

Note: SE = standard error.

[a]*Mean and SD for unadjusted and mean and SE for adjusted.*

TABLE S2 Unadjusted Volumes and Surface Area at Study Entry for Participants on Psychostimulants (n = 168) and Those Who Were Medication-Naive (n = 99)

	ADHD Group, Medication Naive, Mean (SD)	ADHD Group on Stimulants, Mean (SD)	t Test (*df* = 265) (Unadjusted Values)		F test (*df* = 1,263) (Adjusted for Age and Total Brain Volumes)
Volumes (mm^3)					
Right striatum	8,568 (942)	8,689 (945)	t = 1.0,	$p = .31$	F = 0.79, $p = .38$
Left striatum	8,657 (1,000)	8,784 (985)	t = 1.0,	$p = .31$	F = 1.12, $p = .29$
Right globus pallidus	1,212 (134)	1,197 (141)	t = .82,	$p = .41$	F = 0.83, $p = .41$
Left globus pallidus	1,291 (143)	1,278 (142)	t = 0.71,	$p = .48$	F = 0.89, $p = .34$
Total Surface Area (mm^2)					
Right striatum	3,756 (261)	3,810 (273)	t = 1.59,	$p = .11$	F = 0.05, $p = .81$
Left striatum	3,796 (277)	3,848 (284)	t = 1.46,	$p = .15$	F = 0.02, $p = .87$
Right globus pallidus	700 (49)	702 (51)	t = 0.31,	$p = .76$	F = 0.01, $p = .92$
Left globus pallidus	732 (52)	732 (52)	t = 0.07,	$p = .95$	F = 0.14, $p = .71$

Note: Data were missing for 3 participants with attention-deficit/hyperactivity disorder (ADHD). The medication-naive participants were younger at baseline (8.4 years, SD 2.9 years; medicated 10.7 years, SD 3 years, t = 5.9, p < .001), and analyses were repeated, adjusting for age and total brain volume. No significant differences emerged in either the unadjusted or adjusted comparisons.