Supplemental Materials

Supplemental Methods

Participants and Recruitment

We acquired magnetic resonance images in 47 children with ADHD and 57 healthy controls, aged 7-18 years. Subjects with a primary diagnosis of ADHD were recruited either through the Yale outpatient clinic or through a local chapter of Children and Adults With Attention Deficit Disorder. All control participants were randomly selected from a purchased telemarketing list of 10,000 individuals who were comparable in age and lived in similar zip codes as the patients with ADHD. We matched control participants to the ADHD group on age, sex, socioeconomic status(1), and intelligence(2-4).

Clinical Diagnosis and Behavioral Assessment

The sources of information to establish a clinical diagnosis of ADHD or other comorbid diagnoses were a review of clinical records and a semi-structured developmental history interview that included screening questions for psychiatric disorders using the Schedule for Affective Disorders and Schizophrenia for School-Age Children, administered by an experienced master's-level clinician as an interview with each child and parent. After a review of all available information, two senior child psychiatrists independently assigned DSM-IV diagnoses using a best-estimate consensus procedure(5). Kappa statistics for the ADHD group were 0.66(6). Exclusion criteria for patients with ADHD included a history of obsessive-compulsive, bipolar, psychotic, anxiety, tic, conduct, or pervasive developmental disorders.

A parent of each participant also completed an 18-item DuPaul Barkley ADHD rating scale(7).This rating scale includes items directly adapted from the DSM-IV criteria for combined-type ADHD.

Image Acquisition and Preprocessing

High-resolution magnetic resonance images were obtained using a single 1.5-T scanner (GE Signa, Milwaukee, Wisconsin). Head position was standardized using canthomeatal landmarks. T-1 weighted brain images were obtained for morphometric analyses using a sagittal 3-dimensional spoiled-gradient echo sequence (repetition time: 24 milliseconds; echo time: 5 milliseconds; 45° flip angle; frequency encoding: superior to inferior; no wrap; matrix: 256 X 192; field of view: 30 cm; excitations: 2; section thickness: 1.2mm; contiguous section reconstruction: 124; and voxel dimensions: 1.17x1.17x2mm).

Trained operators processed the T-1 weighted images on computer workstations (Sun Ultra 10; Sun Microsystems Inc, Santa Clara, California) using standardized software (ANALYZE 7.5; Biomedical Imaging Resource, Mayo Foundation, Rochester, Minnesota). All operators performed image processing while blind to subject characteristics and hemisphere (images were randomly flipped in the transverse plan). Large-scale variations in image intensity were removed (8), and images were reformatted to a standard orientation before region definition. Whole-brain volume (WBV) was calculated on brains isolated from extracerebral tissues using an isointensity contour function with manual editing.

Definition of Basal Ganglia Nuclei

Manual techniques for defining subcortical structures provide enhanced accuracy compared to automated techniques (9, 10). Our procedure for manually defining the basal ganglia nuclei is described in detail elsewhere (11, 12); here we provide a brief summary. Images were cropped down to the cortices surrounding the basal ganglia and then enlarged 8-fold in each image dimension to minimize mechanical tracing error. The caudate, putamen, and globus pallidus were traced in the transaxial, coronal, and sagittal planes (**Supplemental Fig.1**). The caudate, putamen, and globus pallidus were traced initially in the transaxial plane; accuracy of the initial tracing was confirmed in the coronal and sagittal planes. If corrections are made in any of these two latter planes, their accuracy was corroborated in the orthogonal views. All tracings were reviewed for accuracy by a senior investigator (BSP). Interrater intraclass reliability coefficients were greater than 0.95 for the caudate and putamen, and greater than 0.90 for the globus pallidus.

Basal Ganglia Regions of Interest

The surface of each basal ganglia nucleus is defined as the set of all voxels along the boundary of that nucleus that was delineated by an expert in basal ganglia morphology. We then applied a marching cubes method (13) to fit a triangulated mesh through these voxels, and that mesh was used for surface morphometry."

Correction for Multiple Comparisons in Surface Analysis

For a priori hypothesis testing (diagnosis effects, stimulant effects) as well as post-hoc (symptom score correlation) analyses, we computed corrected p-values using the theory of Gaussian Random Fields (GRFs). We tested the null hypothesis at each point on the surface of each nucleus, thereby performing hundreds of statistical

comparisons for each basal ganglia region. To minimize the number of false positives that may be generated with multiple statistical comparisons, we applied the theory of GRFs to correct for multiple comparisons. Because the surface of a brain region deforms smoothly, the signed-Euclidean distances on the neighboring voxels on the surface of each nucleus are spatially intercorrelated. To account for these spatial intercorrelations across voxels on the surface of each structure, we modeled the distribution of signed-Euclidean distances as a GRF *f*. We then applied the theory of GRFs to compute the expected value of the Euler characteristic, which approximates the p-value for the GRF being greater than a specified value. Therefore, the hypothesis testing generated a t-statistic at every voxel, which we first converted into a value from a Gaussian random variable, and then computed the expected Euler characteristic to approximate the p-value for that value. The p-values smaller than the specified significance level are color encoded and displayed across the entire surface of the BG regions.

The symptom severity scale entailed an assessment of combined-type symptoms related to inattention and hyperactivity, and therefore, only one correlation analysis was conducted to determine the correlation between total symptom severity and surface features.

Supplemental Figure Legends

Supplemental Fig.1: Definition of the Basal Ganglia A. Regional definitions of basal ganglia subregions are shown in the axial, coronal, and sagittal views. C indicates caudate; P, putamen; and GP, globus pallidus. B. Three-dimensional basal ganglia illustrations are shown initially in the anterior-inferior view at the far left, with the structures moving through a 180° rotation around the anterior-posterior axis from left to right, ending in an anterior-dorsal view on the far right.

Supplemental Fig.2: Main Effects of Diagnosis on Surface Morphologic Features (ADHD Subgroup without Comorbid Depression; n=35) The main effects of diagnosis on surface features of the BG nuclei (**Figure 1**) are not appreciably influenced by excluding patients in the ADHD group with a comorbid diagnosis of depression. The right and left caudate, putamen, and globus pallidus are displayed in rotational views and in their dorsal and ventral perspectives. Anterior (A), posterior (P), lateral (L) and medial (M) views of each nucleus are shown. The curved arrow at the top of each column indicates the direction of rotation. The color bar at the bottom indicates the significance value for group comparisons at each point on the surface. Yellow and red values ($P<0.0001$) represent outward deformations of the surfaces, or local volume increases, whereas blue and purple represent inward deformations of the surfaces, or local volume reductions ($P<0.0001$). Gaussian Random Field (GRF)-corrected maps are shown for each nucleus.

Supplemental Fig.3: Main Effects of Diagnosis on Surface Morphologic Features (ADHD Subgroup without Comorbid Oppositional-Defiant Disorder; n=35) The main effects of diagnosis on surface features of the BG nuclei (**Figure 1**) are not appreciably influenced by excluding patients in the ADHD group with a comorbid diagnosis of oppositional-defiant disorder. The right and left caudate, putamen, and globus pallidus are displayed in rotational views and in their dorsal and ventral perspectives. Anterior (A), posterior (P), lateral (L) and medial (M) views of each nucleus are shown. The curved arrow at the top of each column indicates the direction of rotation. The color bar at the bottom indicates the significance value for group comparisons at each point on the surface. Yellow and red values ($P<0.0001$) represent outward deformations of the surfaces, or local volume increases, whereas blue and purple represent inward deformations of the surfaces, or local volume reductions ($P<0.0001$). Gaussian Random Field (GRF)-corrected maps are shown for each nucleus.
Abbreviations: ODD, Oppositional Defiant Disorder.

Supplemental Fig.4: Main Effects of Diagnosis on Surface Morphologic Features (ADHD Subgroup without Comorbid Specific-Developmental Disorder; n = 40) The main effects of diagnosis on surface features of the BG nuclei (**Figure 1**) are not appreciably influenced by excluding patients in the ADHD group with a comorbid diagnosis of specific developmental disorder. The right and left caudate, putamen, and globus pallidus are displayed in rotational views and in their dorsal and ventral perspectives. Anterior (A), posterior (P), lateral (L) and medial (M) views of each nucleus are shown. The curved arrow at the top of each column indicates the direction of

rotation. The color bar at the bottom indicates the significance value for group comparisons at each point on the surface. Yellow and red values ($P<0.0001$) represent outward deformations of the surfaces, or local volume increases, whereas blue and purple represent inward deformations of the surfaces, or local volume reductions ($P<0.0001$). Gaussian Random Field (GRF)-corrected maps are shown for each nucleus.

Abbreviations: SDD, Specific Developmental Disorder (e.g., reading, mathematics, written expression, or motor coordination problems).

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