

Quantitative Brain Magnetic Resonance Imaging in Attention-Deficit Hyperactivity Disorder

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Background: Anatomic magnetic resonance imaging (MRI) studies of attention-deficit hyperactivity disorder (ADHD) have been limited by small samples or measurement of single brain regions. Since the neuropsychological deficits in ADHD implicate a network linking basal ganglia and frontal regions, 12 subcortical and cortical regions and their symmetries were measured to determine if these structures best distinguished ADHD.

Method: Anatomic brain MRIs for 57 boys with ADHD and 55 healthy matched controls, aged 5 to 18 years, were obtained using a 1.5-T scanner with contiguous 2-mm sections. Volumetric measures of the cerebrum, caudate nucleus, putamen, globus pallidus, amygdala, hippocampus, temporal lobe, cerebellum; a measure of prefrontal cortex; and related right-left asymmetries were examined along with midsagittal area measures of the cerebellum and corpus callosum. Interrater reliabilities were .82 or greater for all MRI measures.

Results: Subjects with ADHD had a 4.7% smaller total cerebral volume ($P=.02$). Analysis of covariance for total cerebral volume demonstrated a significant loss of normal right>left asymmetry in the caudate ($P=.006$), smaller right globus pallidus ($P=.005$), smaller right anterior frontal region ($P=.02$), smaller cerebellum ($P=.05$), and reversal of normal lateral ventricular asymmetry ($P=.03$) in the ADHD group. The normal age-related decrease in caudate volume was not seen, and increases in lateral ventricular volumes were significantly diminished in ADHD.

Conclusion: This first comprehensive morphometric analysis is consistent with hypothesized dysfunction of right-sided prefrontal-striatal systems in ADHD.

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ATENTION-DEFICIT hyperactivity disorder (ADHD) is the most common psychiatric disorder of children, affecting approximately 5% of the school-age population¹ and accounting for over 40% of clinic referrals.²⁻⁴ Family, twin, and adoption studies implicate genetic factors as etiologic, but evidence for environmentally mediated fetal brain insult has also been reported.⁵⁻⁷ Prospective longitudinal studies⁸⁻¹⁰ indicate that up to 50% of subjects with ADHD continue to experience impairment from some symptoms of the disorder, if not the full syndrome, in adolescence and early adulthood and that ADHD is a risk factor for conduct disorder, antisocial personality disorder, and substance abuse.

Neuropsychological studies suggest that the core deficit in ADHD is a failure to inhibit or delay motor responses,¹¹ while sensory detection or early information processing is intact.^{12,13} Phenomenological and neuropsychological studies¹⁴⁻¹⁸ have implicated prefrontal dysfunction in ADHD. In light of findings of partial left visual field "ne-

glect," deficits on delayed response tasks, and poor gating of irrelevant stimuli, Heilman and colleagues¹⁹ proposed a right-sided dysfunction of frontal-striatal circuitry for ADHD. This relatively specific anatomic hypothesis received support from early imaging studies. Lou and colleagues,²⁰ using xenon blood flow in a heterogeneous group of patients with ADHD, found striatal hypoperfusion particularly on the right side, which was reversed by methylphenidate. Subsequent functional imaging studies have been less clear. Using positron emission tomography, Zametkin and colleagues reported decreased 2-deoxy-2-[¹⁸F]-glucose uptake in adults with ADHD,²¹ particularly in frontal regions, but this was not replicated for adolescent subjects with ADHD.^{22,23} Further, positron emission tomographic studies of short- and long-term stimulant drug

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SUBJECTS AND METHODS

SUBJECTS

Normal Controls

Fifty-five healthy male subjects (mean age, 12.0 years; range, 5.5 to 17.8 years) were recruited from the community. Screening included telephone interview; parent and teacher rating scales; and in-person assessment, which included physical and neurological examinations, the 12 handedness items from the Revised Physical and Neurological Examination for Subtle Signs,³⁵ structured psychiatric interview using the Child and Parent Diagnostic Interview for Children and Adolescents,³⁶ Child Behavior Checklist,³⁷ Conners Parent and Teacher Rating Scales,³⁸ the Vocabulary and Block Design subtests of the Wechsler Intelligence Scale for Children-Revised (WISC-R),³⁹ and Wide Range Achievement Test-Revised.⁴⁰ Group means were substituted for two subjects from each diagnostic group who did not undergo psychological assessment. Family psychiatric history for first- and second-degree relatives was ascertained from one or both parents. Individuals with physical, neurological, or lifetime history of psychiatric abnormalities, or who had any first-degree relatives or greater than 20% of second-degree relatives with major psychiatric disorders, were excluded. Approximately five candidates were screened for each one enrolled, with the most common exclusions being family psychiatric history, Conners Teacher Hyperactivity ratings greater than 1 SD above published age norms,³⁸ and probable psychiatric diagnosis based on structured interviews.³⁶

Subjects With ADHD

Fifty-seven male subjects with ADHD (mean age, 11.7 years; range, 5.8 to 17.8 years) were recruited for a National Institute of Mental Health ADHD pharmacotherapy study within a specialized day treatment program. Fifty-three of them had been previously treated with psychostimulants, and 56 participated in a 12-week double-blind trial of methylphenidate, dextroamphetamine, and placebo, as described elsewhere.⁴¹ A previous study³⁴ used 50 of these patients and 48 of the control subjects. Inclusion criteria were a history of hyperactive, inattentive, and impulsive behaviors that were impairing in at least two settings (home, school, or day program) and a Conners Teacher Hyperactivity rating greater than 2 SDs above age mean.³⁸ The DSM-III-R⁴² diagnosis of ADHD was based on the Diagnostic Interview for Children and Adolescents with a parent and the patient, and Conners Parent and Teacher Rating Scales.³⁸ Exclusion criteria were a full-scale WISC-R IQ of less than 80, evidence of medical or neurological disorders on examination or by history, Tourette's disorder, or any other Axis I psychiatric disorder, with the exception of mild-moderate conduct disorder ($n=9$) or oppositional defiant disorder ($n=20$). Two subjects met criteria for mild anxiety disorders, and nine subjects had specific learning disorders meeting Axis II diagnostic criteria, confirmed for reading disorder by discrepancy ($z > 1.65$) between Woodcock-Johnson Psychoeducational Battery and WISC-R standard scores.^{43,44}

Assent from the child and written consent from the parents were obtained. The National Institute of Mental Health Institutional Review Board approved the protocol.

METHODS

Behavioral Measures

Behavioral measures for patients were obtained after at least 4 weeks off psychoactive medications. Conduct and hyperactivity factors were extracted from the Conners Parent and Teacher Rating Scales.^{38,45} The Continuous Performance Test (CPT)⁴⁶ yielded omission (CPT-O) and commission (CPT-C) errors.

MRI Image Acquisition

All subjects were scanned on the same scanner (1.5-T GE Signa, Oxford Instruments Inc, Oxford, England). T₁-weighted images with contiguous 1.5-mm sections in the axial and sagittal planes and 2.0-mm sections in the coronal plane were obtained using three-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. Vitamin E capsules, wrapped in gauze and placed in each auditory meatus, were used to help standardize head placement. A third capsule was taped to the lateral aspect of the left inferior orbital ridge. The capsules are readily identifiable on MRI and were used to define a reference plane and to verify laterality. The patient's head was aligned in a padded head holder, so that a narrow guide light passed through each capsule. A sagittal-localizing plane was acquired and from this a multiecho axial series. If all three capsules were not contained within a single axial section, the patient was realigned until this criterion was met. Subjects were scanned in the evening to facilitate sleep. Younger children brought blankets and stuffed animals and were read to by their parents. Three normal children (ages, 5, 7, and 11 years) and two boys with ADHD (ages, 6 and 10 years) were included to complete the scan because of claustrophobia or excessive anxiety. Scans for two normal boys had excessive motion artifact and were omitted. No sedation was used for normal subjects. Approximately 15 of the subjects with ADHD were sedated with oral lorazepam (2 mg) or chloral hydrate (2 g). Further details are provided elsewhere.⁴⁷

Image Analysis

Clinical Interpretation. T₂-weighted images were also obtained for evaluation by a clinical neuroradiologist. Two control subjects had an increased T₂ signal in the left semi-ovale and right parietal lobe, respectively. One subject with ADHD who had a subarachnoid cyst in the right temporal fossa with decrease in volume of the right temporal cortex was excluded. No other gross abnormalities were reported. All raters were blind to subjects' characteristics.

Cerebrum and Cerebellar Quantification. After standardizing spatial orientation using midline anterior and posterior commissures (AC-PC line) and the interhemispheric fissure, a novel image analysis technique was used to remove the brain from the intracranial cavity and quantify the cerebral and cerebellar hemispheres.⁴⁸ This method models the brain surface as an elastically deformable structure and uses an energy minimization function to bring template surfaces into close correspondence with those of the

individual brain. The resulting image was then edited section by section to remove artifacts (dura or eyeballs). This technique has been validated by comparison with postmortem specimens and with volumes obtained from conventional section-by-section hand-tracing through all axial sections on which brain matter is visible (intraclass correlation [ICC] = .95). Further details are provided elsewhere.^{47,48}

Due to variability in gyral and sulcal patterns, prefrontal brain volume was estimated.⁴⁹ A coronal plane perpendicular to the AC-PC line was used to determine the volume of brain in front of the most anterior point of corpus callosum for both left and right hemispheres, excluding temporal lobe. This anterior frontal region overlaps primarily with prefrontal cortex, but it also includes subcortical white matter. Intrarater ICC for this semiautomated measure was .98.

Subcortical Gray Matter. The caudate (head and body) and putamen were manually outlined from coronal sections on a Macintosh II FX workstation using NIH Image (version 1.55).⁵⁰ Since the sum of areas from the odd- and even-numbered sections correlated highly for the first 20 subjects (ICC = .98), subsequent outlining was done on every other section. Intrarater reliability (ICC = .89 and .85 for caudate and putamen, respectively) was assessed initially and periodically during analyses to monitor potential operator drift. Interrater ICCs were .88 and .84 for caudate and putamen, respectively.

Globus pallidus, bounded medially by internal capsule and laterally by putamen, was also measured on coronal sections, but included every section, beginning 2 mm anterior to anterior commissure and proceeding posteriorly for a total of 14 mm. Limiting sampling to this domain, which encompassed almost the entire globus pallidus in the majority of subjects, was necessary to achieve adequate intrarater (ICC = .85) and interrater (ICC = .82) reliabilities. This measure does not distinguish internal and external segments.

Temporal Lobe Structures. Measures of temporal lobe, amygdala, and hippocampus were manually traced in the coronal plane. The temporal lobe is readily separated from frontal and parietal lobes by the sylvian fissure. The temporal stem was divided by a line connecting the most inferior point of the insular cisterns to the most lateral point of the hippocampal fissure. The coronal section including the posteriormost aspect of the corpus callosum was arbitrarily designated the temporal lobe posterior boundary (inclusive).⁴⁹ The section containing the most anterior portions of the mammillary bodies was used as the amygdala-hippocampus boundary.⁵¹ Intrarater and interrater ICCs for amygdala were .89 and .86; for hippocampus, .89 and .87; and for temporal lobe, .99 and .98, respectively.

Lateral Ventricles. Lateral ventricular volumes were measured in the coronal plane using an operator-supervised thresholding technique that required little subjectivity, yielding high intrarater and interrater reliabilities (ICC = .99).

Midsagittal Area Measures. Corpus callosum area was obtained from a single midsagittal section reconstructed from the axial series. Resectioning allows more precise

designation of the midsagittal plane than choosing a "best" midsagittal section.⁴⁷ Using the three-dimensional data set, a line was drawn to bisect the cerebral hemispheres in the axial plane. From this line, a midsagittal image was reconstructed in the same plane as the AC-PC line. Criteria to confirm a midsagittal orientation were patency of the cerebral aqueduct and presence of the septum pellucidum. An elliptical region of interest was drawn, and, within this region, a supervised thresholding technique was used to determine the corpus callosum perimeter x-y coordinates. These coordinates were saved and analyzed along radial lines to compute areas of seven subregions: rostrum, genu, rostral body, anterior midbody, posterior midbody, isthmus, and splenium, as defined by Witelson.⁵² Intrarater ICC averaged .92 for the corpus callosum subdivisions.

For quantification of the cerebellar vermicular lobules, we resectioned the axial series to determine the midsagittal plane with reference to vermicular structures.⁵³ *Total midsagittal area* was defined as the sum of vermicular lobules I-V, VI-VII, and VIII-X.⁵⁴ Intrarater ICC for midsagittal cerebellar area was .86.

Statistical Analysis

Volumetric measurements of the right and left brain regions (anterior frontal region, caudate, putamen, globus pallidus, lateral ventricles, amygdala, hippocampus, temporal lobe, and cerebellum) were analyzed by two-way repeated-measures analyses of covariance (ANCOVA) (BMDP P2V software program⁵⁵) with diagnosis as the between-subjects factor, side (right and left) as the repeated factor, and total cerebral volume (TCV) as the covariate. *Percent asymmetry* was defined as $\{(R-L)/[(R+L)/2]\} \times 100$. Midsagittal cerebellar and corpus callosal areas and symmetries for bilateral structures were analyzed by one-way ANCOVA with TCV as the covariate. Since the diagnostic groups also differed significantly in IQ subscores, all analyses were retested by ANCOVA with both WISC-R Vocabulary score and TCV as covariates. Vocabulary subscore was chosen because it has the highest correlation to full-scale IQ³⁹ and because we measured it directly, although results were unchanged when short-form full-scale IQ (combining Vocabulary and Block Design)⁵⁶ was used. Bonferroni tests were used to determine post hoc significance of least-square adjusted means.⁵⁷

The relations between volumetric and asymmetry measures and behavioral and demographic variables were examined with Pearson's correlations except for CPT errors (CPT-O and CPT-C), which were nonparametric and for which we used Spearman's correlations (SAS Version 6.07, SAS Institute Inc, Cary, NC). Partial correlations controlled for potentially confounding variables such as age or IQ. Because of the large number of comparisons, we set $\alpha = .01$ for correlations. Age-related changes in regions that differed significantly between groups were examined with linear regression. After significance testing with linear regression, linearity and constant variance assumptions were relaxed by use of a "local regression" procedure that retained subtle nonlinearities in the data (a "super-smoother")⁵⁸ to yield curvilinear fits to the scatter plots of structure volumes by age, diagnosis, and side, as shown in **Figure 1** and **Figure 2**.

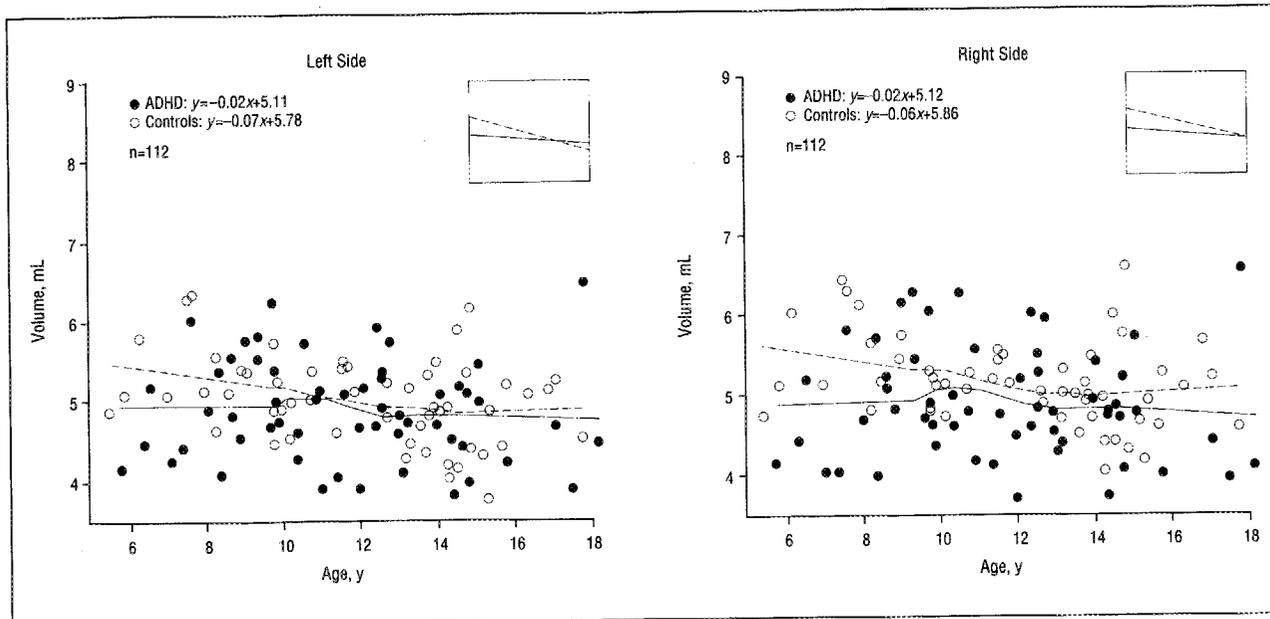


Figure 1. Volumes of caudate nuclei in relation to age for 57 boys with attention-deficit hyperactivity disorder (ADHD) and 55 healthy control subjects. Local regression lines for each group are indicated in the main plot; linear regression coefficients and lines appear in the upper portion of the graph.

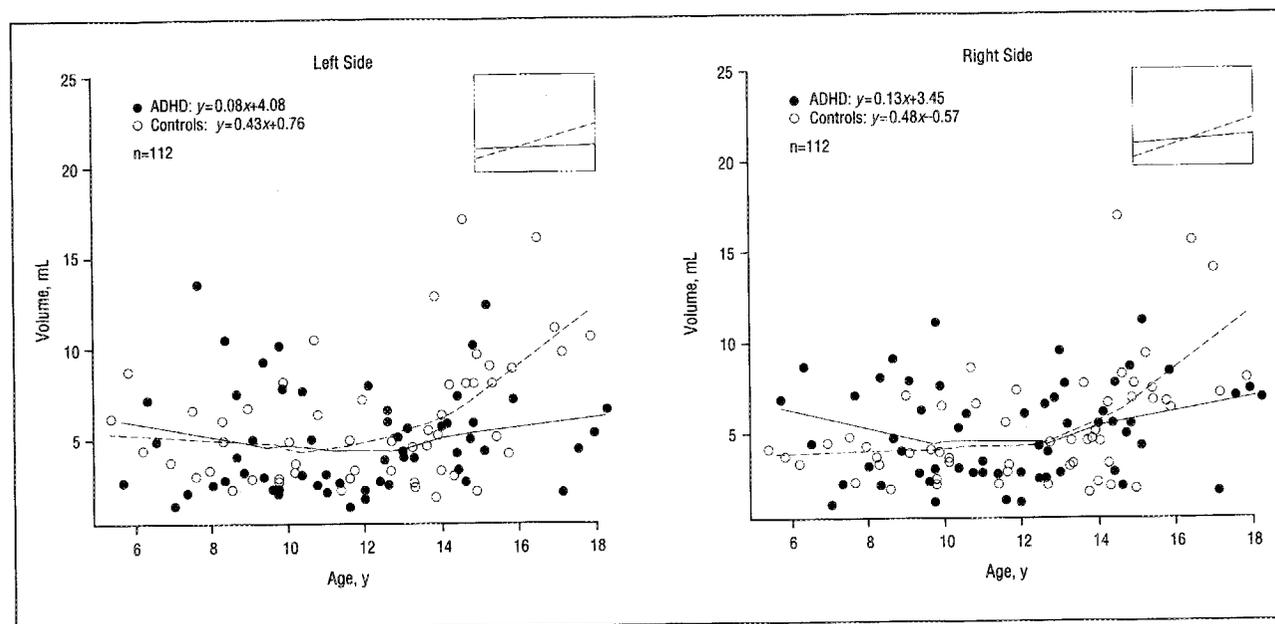


Figure 2. Volumes of lateral ventricles in relation to age for 57 boys with attention-deficit hyperactivity disorder (ADHD) and 55 healthy control subjects. Local regression lines for each group are indicated in the main plot; linear regression coefficients and lines appear in the upper portion of the graph.

treatment in adults with ADHD did not produce consistent changes.^{24,25}

Early computed tomographic studies of children with ADHD reported nonspecific abnormalities^{26,27} that were not confirmed when quantitative techniques and an ap-

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617, and 625**

propriate contrast group were employed.²⁸ In a series of magnetic resonance imaging (MRI) studies with seven to 11 children with ADHD compared with control subjects, Hynd and colleagues reported a narrower right fron-

tal cortex,²⁹ smaller total midsagittal corpus callosum area,³⁰ and a reversal of "normal" (reported to be left > right) caudate asymmetry based on a single 5-mm axial section.³¹ Two other groups^{32,33} also reported significantly smaller callosal areas in patients with ADHD. However, neither group found differences in total corpus callosum midsagittal area: one found differences in the rostrum and rostral body³²; the other, only in the splenium.³³ Both studies used small samples (18 and 15 subjects per diagnostic group, respectively), and the latter found a significant difference only in the splenium when five stimulant nonresponders were combined with 10 stimulant responders.

In a subsequent report,³⁴ the present authors com-

Table 1. Demographic Characteristics of Boys With ADHD and Controls*

Characteristics	ADHD (n=57)	Controls (n=65)
Age, y	11.65±2.97	12.03±3.06
Height, cm	147.62±17.45	153.75±19.33
Weight, kg	41.72±16.80	46.21±16.54
Tanner stage	2.19±1.65	2.38±1.63
Handedness, % right-handed	81	87
WISC-R subscales scores		
Vocabulary	11.89±3.22	13.84±2.87†
Block Design	11.86±3.48	13.44±2.69†
WISC-R Full-Scale IQ	109.21±17.47	
Estimated Full-Scale IQ§	110.84±17.19	121.09±13.34†
Conners Teacher Rating Scale hyperactivity ratings (0-3)		
Teacher	1.65±0.72	0.31±0.47†
Parent	2.03±0.75	0.33±0.34†
DSM-III-R diagnoses, No.		
ADHD	57	
Conduct disorder	9	
Oppositional defiant disorder	20	
Learning disorders	9	
Anxiety disorders	2	
Enuresis	11	

*ADHD indicates attention-deficit hyperactivity disorder; WISC-R, Wechsler Intelligence Scale for Children-Revised.

† $P < .001$.

‡ $P < .01$.

§Short Form Full-Scale IQ using WISC-R Vocabulary and Block Design subscales.⁵⁶

pared MRI caudate volumes in 50 boys with ADHD and 48 normal boys. In contrast to findings by Hynd et al,³¹ a normal right>left caudate asymmetry was found for controls, which was absent in subjects with ADHD ($P = .001$). The strengths of this study included a large sample size, well-characterized patients who were sufficiently impaired to participate in controlled stimulant trials, 2-mm coronal sections to minimize partial voluming effects, and a wide age range (6 to 18 years) that provided a developmental perspective.

Herein, we present a comprehensive morphometric MRI study for an expanded sample. We hypothesized right-sided frontal-striatal abnormalities, and we included contrast regions for which no abnormalities were hypothesized. Thus, the present study compared cerebral, prefrontal, and basal ganglia (caudate, putamen, and globus pallidus) volumes and corpus callosum area for which abnormalities were predicted, as well as exploratory analyses of cerebellar, temporal lobe, amygdala, and hippocampal volumes and midsagittal cerebellar areas.

RESULTS

SUBJECTS

Table 1 presents patient and control characteristics. There were no significant group differences in age, height, weight, Tanner pubertal stage, or handedness. Scores of WISC-R Vocabulary and Block Design subscale and full-scale scores were higher for control subjects ($P < .01$), although for both groups, subtests and estimated full-scale scores were above average (subscore population mean, 10 ± 3).

Total cerebral volume was significantly smaller for ADHD on analysis of variance ($F[1,110]=5.69, P=.02$; not shown). Right hemispheric volume was larger than left for both groups ($F[1,110]=24.33, P=.001$), but the between-group disparity was larger for the right (5.2%) than for the left hemisphere (4.2%) ($F[1,110]=4.62, P=.03$). Total cerebral volume was used as a covariate for all subsequent analyses.

As shown in **Table 2**, there was a significant ($P=.02$) diagnosis-by-side interaction for the anterior frontal region. Post hoc testing revealed that the groups differed significantly in right anterior frontal volume ($P < .05$).

Total caudate volume also did not differ between groups. The loss of normal right>left caudate asymmetry in ADHD (reflected in the significant side-by-diagnosis interaction, $P=.006$) was due to reduced right caudate volume for the subjects with ADHD ($P < .05$, by Bonferroni test). This loss of asymmetry was seen across our entire age range (data not shown).

The left putamen was larger than the right for both groups, and there were no diagnostic differences with respect to volume or symmetry.

Although both the main effect of diagnosis and the interaction of diagnosis by side are significant for the globus pallidus, differences between groups were, again, most prominent for the right-sided structure (adjusted between-group difference of 10.3% on the right vs 4.3% on the left side). There were no age-related changes for globus pallidus volumes or symmetry. As **Table 3** shows, the absolute magnitude of the right globus pallidus between-group difference, while highly significant (interaction $P=.005$), is only 0.12 mL.

Since some prior studies⁵⁹⁻⁶¹ discuss the lenticular nucleus as a unit (globus pallidus plus putamen), our data include statistics for this measure (Tables 2 and 3 and **Table 4**). The lenticular nucleus retains the left>right asymmetry of the putamen; no diagnostically relevant differences were seen.

Midsagittal area was calculated for total corpus callosum and seven subregions.^{32,52} Only total measurements appear in Table 4, but no significant group differences were found for total region or any subregion.

Cerebellar volume was significantly smaller in ADHD, although the groups did not differ in midsagittal cross-sectional area.⁵³

Temporal lobe measures revealed a robust right>left asymmetry for both groups but no group effects. While ANCOVA suggested smaller amygdala volume for ADHD ($P=.07$), unlike our other findings, this was not significant when Vocabulary IQ subscale score and TCV were covaried ($P=.19$). Overall lateral ventricular volume did not differ between groups, but the left lateral ventricle was significantly smaller for ADHD than for control subjects.

SYMMETRY

Analysis of symmetry indexes is a common way of comparing bilateral structures, although it is comparable to a side-by-diagnosis interaction. Symmetry indexes and ANCOVA statistics are presented in Table 4 primarily for comparison to other data sets. A positive symmetry index in-

Table 2. Repeated Measures ANCOVA for Diagnosis, Side, and Diagnosis by Side Interactions for Brain Volumes of 57 Boys With ADHD and 55 Controls*

	Diagnosis		Side		Diagnosis×Side		Comment
	F	P	F	P	F	P	
Anterior frontal region	0.95	.33	3.42	.07	5.64	.02	Control>ADHD only on right
Caudate	0.32	.58	11.56	.001	7.94	.006	Control>ADHD only on right
Putamen	0.25	.62	119.91	.0001	0.27	.6	...
Globus pallidus	6.79	.01	0.17	.68	8.04	.005	Control>ADHD right and left; effect larger on right
Lenticular nucleus	1.80	.18	78.86	.0001	3.13	.08	...
Cerebellum	3.97	.05	3.60	.06	1.81	.18	Control>ADHD
Temporal lobe	2.57	.11	25.54	.0001	0.43	.51	...
Amygdala	3.43	.07	8.60	.004	3.01	.09	...
Hippocampus	2.10	.15	10.1	.002	1.11	.30	...
Lateral ventricles	1.09	.30	3.69	.06	4.61	.03	Control>ADHD only on left; control left>control right

* ANCOVA indicates analysis of covariance (covarying for total cerebral volume; df=1,104-110, due to missing data); ADHD, attention-deficit hyperactivity disorder. Statistically significant values are boldfaced.

Table 3. Unadjusted and Adjusted Mean Volumes for 57 Boys With ADHD and 55 Controls*

	Volume, mL							
	Unadjusted Means±SDs				Adjusted Least Square Means†			
	Left		Right		Left		Right	
	ADHD	Controls	ADHD	Controls	ADHD	Controls	ADHD	Controls
Cerebral volume	557.38±58.2	581.64±65.3	561.52±58.8	592.19±63.2
Anterior frontal region	80.03±15.6	82.83±15.2	79.41±14.7	87.84±13.2	81.82	80.93	81.20	85.94
Caudate	4.87±0.6	4.99±0.6	4.88±0.7	5.14±0.5	4.93	4.92	4.95	5.07
Putamen	5.50±0.6	5.60±0.5	5.26±0.5	5.39±0.4	5.53	5.57	5.29	5.35
Globus pallidus	1.13±0.2	1.18±0.2	1.10±0.1	1.22±0.2	1.13	1.18	1.10	1.22
Lenticular nucleus	6.63±0.6	6.79±0.6	6.36±0.6	6.61±0.5	6.66	6.76	6.40	6.58
Cerebellum	77.28±11.4	86.31±16.6	80.30±11.9	86.83±17.3	78.65	84.86	81.67	85.38
Temporal lobe	84.13±9.3	88.68±11.9	87.46±9.5	93.01±10.3	85.32	87.46	88.66	91.79
Amygdala	2.23±0.5	2.34±0.5	2.29±0.5	2.56±0.5	2.25	2.33	2.30	2.55
Hippocampus	4.57±0.7	4.55±0.4	4.75±0.7	4.65±0.5	4.61	4.51	4.79	4.60
Lateral ventricles	4.96±2.8	5.90±3.5	5.00±2.6	5.22±3.2	4.96	5.90	5.00	5.22

* ADHD indicates attention-deficit hyperactivity disorder.
† Adjusted for total cerebral volume.

icates right>left and is seen for control subjects for all structures except for putamen, lenticular nuclei, and ventricles. Significant decreases in asymmetry are noted for the boys with ADHD in the cerebral hemispheres, anterior frontal region, caudate, and globus pallidus.

AGE-RELATED CHANGES

Caudate volume decreases with age for control subjects between 6 and 12 years old in this cross-sectional analysis. This is reflected in a significant negative slope (for right plus left caudate, $\beta = -0.12$ mL/y, $P = .01$), which is greater in magnitude than in subjects with ADHD ($\beta = -0.03$ mL/y, $P = .60$), although between-group differences were not significant ($z = 1.16$, $P > .20$). Figure 1 presents these data along with local regression curves, with linear regressions shown in inset boxes.

Since ventricular volumes change significantly with age in normal male subjects in this age group,^{47,59} age-related effects were examined. Ventricular volume in-

creased significantly with age for normal male subjects ($\beta = 0.48$ and 0.43 mL/y for right and left ventricles, $P < .001$ and $P = .002$, respectively), while for subjects with ADHD, there were no significant age-related changes (right $\beta = .13$ mL/y, $P = .21$; left $\beta = .08$ mL/y, $P = .51$). Slopes for right, left, and total ventricular volumes differed significantly between diagnostic groups ($z = 1.96, 2.07$, and 2.12 , respectively; $P < .05$).

A "super-smoother" analysis of lateral ventricular volume detected a significant slope change point at age 11 years for the normal boys. Prior to that age, the non-significant age slope was 0.08 mL/y, increasing to 2.19 mL/y after age 11 years ($P = .03$).⁵⁸ No significant age changes in slope were seen for the ADHD group (see Figure 2).

ABILITY TO DISTINGUISH BETWEEN GROUPS

A stepwise discriminant function using jackknife validation was performed, which included all measures (in-

Table 4. Unadjusted and Adjusted Means and ANCOVA for Subjects With ADHD and Controls*

Measures	Unadjusted Means±SDs		Adjusted Least Square Means†		ANCOVA	
	ADHD (n=57)	Controls (n=55)	ADHD (n=57)	Controls (n=55)	F	P
Total cerebral volume, mL	1118.90±116.3	1173.83±127.2
Area measures, mm ²						
Cerebellum	1135.31±154.0	1171.18±116.0	1142.00	1164.12	0.72	.40
Corpus callosum	625.54±83.2	630.69±79.9	630.93	624.89	0.16	.69
Symmetry measures, %‡						
Cerebrum	0.7±2.4	1.9±3.3
Anterior frontal region	-0.6±16.0	6.3±14.3	-0.79	6.46	5.81	.02
Caudate	0.09±5.4	2.9±4.5	0.26	2.77	6.89	.01
Putamen	-4.4±4.3	-3.9±4.0	-4.41	-3.57	9.01	.08
Globus pallidus	-2.4±11.3	3.4±9.5	-2.55	3.96	9.06	.003
Lenticular nucleus	-4.1±4.4	-2.6±3.8	-4.13	-2.61	3.57	.06
Cerebellum	3.8±13.3	0.4±11.7	3.81	0.47	1.81	.18
Temporal lobe	3.9±8.3	5.3±9.5	3.76	5.19	0.63	.43
Amygdala	2.3±22.4	9.3±23.6	2.10	9.53	2.66	.11
Hippocampus	4.0±9.4	1.8±10.0	4.10	1.70	1.56	.21
Lateral ventricles	0.5±29.9	-11.5±30.2	-0.39	-10.51	3.05	.08

*ANCOVA indicates analysis of covariance; ADHD, attention-deficit hyperactivity disorder.

†Adjusted for total cerebral volume; df=1,104-110 due to missing data.

‡Percentage of asymmetry defined as $[(R-L)/((R+L)/2)] \times 100$. Statistically significant values are boldfaced.

cluding asymmetry scores). Right globus pallidus volume, caudate symmetry, and left cerebellum volume emerged, in that order, as significant, independent predictors of group membership. These three measures correctly classified 72% of 106 subjects (the number of subjects was smaller owing to missing data; 78% of the subjects with ADHD, and 65% of the control subjects) and together accounted for 27% of total variance. When TCV was forced in as the first variable, the classification remained virtually unchanged, with 72% of subjects (75% of subjects with ADHD, 69% of control subjects) correctly classified and 29% of total variance accounted for.

ANATOMIC-BEHAVIOR CORRELATIONS

Within the ADHD group, Full-Scale WISC-R IQ score correlated with total cerebral volume ($n=57, r=.32, P=.01$) and with right and left prefrontal regions ($n=55, r=.43$, and $r=.40$, respectively, $P<.003$). Within the relatively restricted range of the healthy control subjects, similar, but attenuated, correlations were also found (right prefrontal regions correlated significantly with Vocabulary ($n=52, r=.33, P=.016$), while left prefrontal correlations were not significant ($r=.20$).

Correlations within the ADHD group between regions differing across groups and ratings of ADHD severity, demographics (Hollingshead socioeconomic status), perinatal risk taken from the Diagnostic Interview for Children and Adolescents,⁶² as well as a measure of learning disability (reading discrepancy score)⁴³ showed a significant association (at $\alpha<.01$) between caudate asymmetry index and prenatal, perinatal, and infancy complications ($n=47, r=-.42, P=.003$). Decreased (normal) caudate asymmetry was associated with increasing perinatal risk in the ADHD group and not in the healthy boys.

IQ-MATCHED ANALYSIS

Analysis of variance was also performed for a subgroup of ADHD and control subjects matched by WISC-R Vocabulary score. The groups thus defined, composed of 44 subjects with ADHD and 55 normal control boys, did not differ significantly on age, height, weight, Tanner pubertal stage, block Design score, or full-scale IQ (short-form for control subjects).⁵⁶ The results were virtually identical to those shown in Tables 2 through 4 except that the group difference in total cerebral volume (diagnosis analysis of variance $F[1,97]=1.87, P=.17$) was no longer significant.

COMMENT

This is the first comprehensive regional morphometric analysis of ADHD and age-matched healthy boys. Using large samples, thin MRI sections, and highly reliable measurement algorithms, we found subtle yet statistically robust hypothesized between-group differences in the right anterior frontal region^{14-16,18} (approximating prefrontal gray and white matter volumes), right caudate,^{17,19,31,34} and globus pallidus,⁶³ most prominently on the right side. Unexpectedly, we did not replicate prior reports of differences in corpus callosum,^{30,32,33} nor did we find expected differences in putaminal volume or symmetry. Exploratory analyses were generally negative except in lateral ventricles, where age-related changes appear to diverge, and in cerebellar volume.

Our groups differed significantly in IQ scores. Since IQ differences may be intrinsic to ADHD,⁶⁴ we did not covary IQ (or its surrogate, Vocabulary) in primary analyses.⁶⁵ However, results were essentially unchanged after covarying IQ alone, when combined with TCV (data not presented), or when IQ-matched subgroups were compared. It is also worth noting that while socioeconomic sta-

tus correlated significantly with full-scale IQ in ADHD subjects ($n=52$, $r=-.43$, $P=.001$), it did not correlate significantly with any brain regions, including total cerebral volume.

In normal adults, three independent groups have now reported right > left caudate asymmetry.⁶⁶⁻⁶⁸ In the largest of these studies, as with our pediatric normative study,⁴⁷ the magnitude of the asymmetry is also quite modest (3.9% in normal male subjects), but the level of statistical significance is very high ($F[1,179]=84$, $P<.001$).⁶⁸ Lateral ventricles were significantly larger on the left side for our normal subjects, as was also noted in adult samples.^{68,69} Lack of normal asymmetry has been reported in neuropsychiatric disorders linked to early neurodevelopmental deviations,⁷⁰⁻⁷² including dyslexia,^{73,74} Tourette's disorder,^{60,61} and schizophrenia.^{49,66,75} We found diagnostic differences in asymmetry in our measures of prefrontal cortex, caudate, globus pallidus, and lateral ventricles as well as in the cerebral hemispheres. We speculate that an early, presumably fetal, event affecting normal development of asymmetry is etiologically related to ADHD. In this respect, the significant correlation between decreased normal caudate asymmetry and a measure of pregnancy, delivery, or infancy complications is of great interest. If replicated, the "markers" for ADHD reported here may be useful for future high-risk, genetic, and treatment studies.

There are several limitations of this study. The absence of true boundaries for most brain regions necessitates manual tracing of individual sections. When clear boundaries are adopted, highly reliable morphometry is possible. However, arbitrary boundaries inherently limit validity. For example, some groups only quantify the head of the caudate,⁷⁶ whereas we included both head and body, but not the tail. Likewise, in globus pallidus, we limited our mensuration to a seven-slice "frame," which did not always include the entire structure. Thus, in spite of blind and reliable ratings, diagnostic differences may not be strictly comparable across studies.

Given the variability of sulcal and gyral patterns between even genetically identical individuals^{77,78} and current methodological limits, valid subdivision of cortical regions was not feasible. Our estimate of anterior frontal region is susceptible to between-group shape differences in corpus callosum and includes both gray and white matter, which diverge with increasing age.^{79,79} The findings of age-related changes in lateral ventricular and caudate volumes suggest that, in ADHD, a more general process possibly linked to synaptic pruning⁸⁰ may continue into adolescence. A prospective longitudinal study of patients and control subjects is under way to validate these maturational differences. Technical advances are needed for gray-white segmentation and quantification of other relevant regions, such as nucleus accumbens, anterior cingulate gyrus, and thalamus.

Because almost all (93%) subjects with ADHD had been exposed to stimulants, we cannot be certain that our results are not drug related. A replication study with stimulant-naïve boys with ADHD is under way. Our findings for male individuals, if replicated, need to be extended to female individuals with ADHD.

The differences that we found in the caudate and not in the putamen are consistent with preclinical studies implicating caudate lesions in hyperactivity.^{81,82} The

lack of differences in putaminal volumes between subjects with ADHD and control subjects is consistent with the hypothesis that the ADHD-relevant corticostriatal-thalamocortical circuits are those that link the caudate and prefrontal regions such as orbital-frontal cortex,¹¹ rather than the parallel circuits linking the putamen and motor or supplementary motor cortex,⁸³ which have been linked to Tourette's disorder.^{60,61}

Comorbidity between ADHD and oppositional defiant disorder, conduct disorder, and with specific learning disorders is well established.^{1,2,84,85} It has been argued that most of the impairment associated with ADHD is actually owing to comorbid conditions and that ADHD is merely a variant of normal exuberant behavior.⁸⁶ We examined this question by comparing all measures in our 55 control subjects with those in the 48 subjects with ADHD without a specific learning disability and in the 28 boys with ADHD who did not have either oppositional defiant disorder or conduct disorder. In both cases, all of our hypothesized findings remained statistically significant. In fact, despite decreasing our ADHD sample by half, this subanalysis was even more robust for the 28 subjects with ADHD and without comorbid disruptive behavior disorders. Finally, although our groups did not differ in handedness, we reanalyzed our results for only strongly right-handed subjects and found no differences from our primary analyses for this subset of 46 boys with ADHD and 48 control subjects.

Reports on morphologic characteristics of the corpus callosum morphometry in ADHD have been inconsistent. Three independent groups, using small samples, found diagnostic differences in three different regions. In the present large sample, we fail to replicate our own³² and our colleagues'^{30,33} work. Our sample was relatively "clean," with only nine subjects (16%) having had specific learning disorders. The possibility that corpus callosal differences may be more pertinent to comorbidity with developmental disorders should be explored.^{87,88}

There were no diagnostically relevant differences in the total temporal lobe, amygdala, or hippocampus. Since the amygdala and hippocampus partially overlap when measured in the coronal plane, the volumes that we obtained are not independent, and our negative findings should not be taken as definitive. However, we hypothesized that temporal lobe structures would not differentiate the groups based on reports of intact posterior parietal⁸⁹ and temporal lobe performance⁹⁰ in ADHD in the face of subtle deficits in tasks that require prefrontal involvement.⁹⁰⁻⁹³

Decreased cerebellar volume, if replicated, is intriguing in light of recent anatomic,⁹⁴ clinical,⁹⁵⁻⁹⁷ and functional⁹⁸ results, suggesting that the cerebellum may have a prominent role in cognitive processes and executive functioning.^{99,100}

In summary, we have found decreased volume of several candidate brain regions previously hypothesized to be involved in the pathophysiology of ADHD, ie, prefrontal cortex,^{14-16,18} caudate nucleus,^{17,19,31,34} and globus pallidus,⁶³ predominantly on the right side. These support other converging evidence that a lack of normal asymmetry mediates the expression of ADHD.^{19,88,101-103} In humans, the functional significance of basal ganglia asymmetry is un-

known. Interestingly, a study of rats not demonstrating the usual behavioral side preference reported them to be "the most active and the poorest overall learners on all tasks studied."¹⁰⁴ Lateralized rodent behavior has been associated with asymmetric basal ganglia neurochemistry.¹⁰⁴⁻¹⁰⁸ These observations led to the suggestion that rats that exhibit low behavioral asymmetry may serve as an animal model of ADHD.¹⁰⁹ Other indirect evidence for the right-hemisphere abnormality in ADHD comes from positron emission tomographic studies in normal adults, in which the right hemisphere was preferentially activated in vigilance tasks.^{110,111} In ADHD, subtle left-hemisphere "neglect" is normalized by administration of methylphenidate.^{102,103,112,113} The significance of basal ganglia asymmetry is being examined in functional imaging studies.

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