Developmental Trajectories of Brain Volume Abnormalities in Children and Adolescents With Attention-Deficit/Hyperactivity Disorder

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ATTENTION-DEFICIT/HYPERACTIVITY DISORDER (ADHD), the most common childhood psychiatric disorder, is thought to reflect subtle abnormalities in central nervous system functioning. For this reason, ADHD is being studied increasingly with a variety of brain imaging techniques throughout the life span. Magnetic resonance imaging (MRI) is particularly suitable for the study of pediatric patients, providing high-resolution images without ionizing radiation. Previous MRI neuroimaging studies, most with small samples, have reported smaller anatomic areas and/or volumes in patients with ADHD in regions of the cerebral cortex and cerebellum. However, there has been no systematic study comparing regional brain volumes at initial scan and their change over time in medicated and previously unmedicated male and female patients with ADHD and healthy controls.

Various anatomic brain abnormalities have been reported for attention-deficit/hyperactivity disorder (ADHD), with varying methods, small samples, cross-sectional designs, and without accounting for stimulant drug exposure.

To compare regional brain volumes at initial scan and their change over time in medicated and previously unmedicated male and female patients with ADHD and healthy controls.

Case-control study conducted from 1991-2001 at the National Institute of Mental Health, Bethesda, Md, of 152 children and adolescents with ADHD (age range, 5-18 years) and 139 age- and sex-matched controls (age range, 4.5-19 years) recruited from the local community, who contributed 544 anatomic magnetic resonance images.

Using completely automated methods, initial volumes and prospective age-related changes of total cerebrum, cerebellum, gray and white matter for the 4 major lobes, and caudate nucleus of the brain were compared in patients and controls.

On initial scan, patients with ADHD had significantly smaller brain volumes in all regions, even after adjustment for significant covariates. This global difference was reflected in smaller total cerebral volumes (−3.2%, adjusted F1,280=8.30, P=.004) and in significantly smaller cerebellar volumes (−3.5%, adjusted F1,280=12.29, P=.001).

Compared with controls, previously unmedicated children with ADHD demonstrated significantly smaller total cerebral volumes (overall F2,288=6.65; all pairwise comparisons Bonferroni corrected, −5.8%; P=.002) and cerebellar volumes (−6.2%, F2,288=8.97, P<.001). Unmedicated children with ADHD also exhibited strikingly smaller total white matter volumes (F2,288=11.65) compared with controls (−10.7%, P<.001) and with medicated children with ADHD (−8.9%, P<.001). Volumetric abnormalities persisted with age in total and regional cerebral measures (P=.002) and in the cerebellum (P=.003). Caudate nucleus volumes were initially abnormal for patients with ADHD (P=.05), but diagnostic differences disappeared as caudate volumes decreased for patients and controls during adolescence. Results were comparable for male and female patients on all measures. Frontal and temporal gray matter, caudate, and cerebellar volumes correlated significantly with parent- and clinician-rated severity measures within the ADHD sample (Pearson coefficients between −0.16 and −0.26; all P values were <.05).

Developmental trajectories for all structures, except caudate, remain roughly parallel for patients and controls during childhood and adolescence, suggesting that genetic and/or early environmental influences on brain development in ADHD are fixed, nonprogressive, and unrelated to stimulant treatment.
were impairing in at least 2 settings and a Conners’ Teacher Hyperactivity rating greater than 2 SD above age- and sex-specific means.22,23 The DSM-IV diagnosis of ADHD was based on the Parent Diagnostic Interview for Children and Adolescents,24 Conners’ Teacher Rating Scales,22,23 and the Teacher Report Form.25 A clinical psychologist administered the Wechsler Intelligence Scale for Children–Revised26 to 110 patients with ADHD and the Wechsler Intelligence Scale for Children–III27 to 41 patients (I was too young to be tested). 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.

A total of 56 unrelated healthy female (mean initial age, 10.0 years; range, 5.2-16.1) and 83 male (mean initial age, 10.9; range, 4.5-19.0) controls were recruited from the community via the National Institutes of Health Normal Volunteer Office and outreach to local schools. Screening included an initial telephone interview, parent and teacher rating scales,25 in-person assessment including physical and neurological examinations including handedness,28 and clinical history obtained by a child and adolescent psychiatrist (J.N.G.). Vocabulary and block design subtests from the Wechsler Intelligence Scale for Children–Revised30 (n=10), Wechsler Intelligence Scale for Children–III27 (n=23), Wechsler Abbreviated Scale of Intelligence29 (n=20), Wechsler Preschool and Primary Scale of Intelligence30 (n=10), and Wechsler Adult Intelligence Scale–Revised31 (n=1) were obtained. Five controls were not tested but were within the healthy range by reported academic history. Approximately 4 candidates were screened for every 1 accepted,32 with the most common exclusions being positive family psychiatric history and possible psychiatric diagnosis based on teacher report.

This study was conducted at the Child Psychiatry Branch of the National Institute of Mental Health in Bethesda, Md, between 1991 and 2001. The institutional review board approved the research protocol, and written informed consent and assent to participate in a study of brain development were obtained from parents and children, respectively, at study entry and at each subsequent MRI examination. Healthy volunteers and patients not currently participating in treatment studies were paid to participate.

**Behavioral Measures**

Primary symptom severity measures were those that remained constant across the study decade using the Attention Problems Factors from the Child Behavior Checklist and Teacher Report Form23 and the Clinical Global Impressions scale for Severity of Illness.33 Medication status was obtained from parental history.

**MRI Acquisition**

All patients and controls were studied on the same 1.5-T General Electric Signa scanner (Milwaukee, Wis). T2-weighted images with contiguous 1.5-mm slices in the axial plane and 2.0-mm slices in the coronal plane were obtained using 3-dimensional spoiled gradient recalled echo in the steady state. Imaging parameters were echo time of 5 ms, repetition time of 24 ms, flip angle of 45°, acquisition matrix of 256 × 192, number of excitations equals 1, and 24 cm field of view. Head placement was standardized as previously described.16

**Image Analysis**

T2-weighted images were obtained for evaluation by a clinical neuroradiologist. All raters were blind to demographic characteristics. Quantification of MRI images was performed via a 3-part fully automated image analysis process that determines the volumes of gray and white matter compartments in frontal, temporal, parietal, and occipital lobes as well as basal ganglia and cerebellum with excellent test-retest reliability as described elsewhere in detail.34-36
were processed successfully; 50 were excluded because of classification and segmentation errors due to motion. Failure rate was significantly higher (χ² with Yates correction = 4.08, P = .04) in 34 of 317 patients (11%) than in 16 of 277 controls (6%). All remaining scans from patients with ADHD (283 scans) were used. The comparison group was selected from a pool of healthy controls after excluding siblings in order not to violate the statistical assumption of independence. The remaining 139 potential controls (ie, no more than 1 per family within the age range of our patients) were selected by the data manager (L.S.C.) to best match each target patient for sex, age, and longitudinal intervals, prior to morphometric analyses. Whenever precise matching on all parameters was not possible, patients and controls were matched on average age across their own scans. Because we were unable to match all patients and controls 1-to-1, we made every effort to maintain proportional scan-densities across the entire age-range of the 152 patients.

Statistical Analyses
Demographic and clinical measures were compared by 2-way analyses of variance (testing main effects of diagnoses and sex and their interaction) or 2-sample t tests for continuous measures, and with χ² or Fisher exact test for nominal measures. Analyses of variance of the 10 regional brain measures and 3 summary measures obtained at initial scan (n = 291 independent participants) were initially performed with diagnoses and sex as between-participant factors. Because we did not obtain full-scale IQ scores from controls, Wechsler vocabulary standard score was used, as it is the single best predictor of full-scale IQ. 37

To account for between-group differences in vocabulary, height, weight, handedness, and medication status, analyses of covariance were performed with these potential covariates. Nonsignificant covariates were deleted from the final models. Pearson correlations were computed for symptom severity measures and brain volumes in the patient sample.

To examine the influence of medications more closely we compared patients with ADHD who were never previously treated with psychotropic medications (unmedicated ADHD), medicated patients (medicated ADHD), and controls. The unmedicated ADHD patients were significantly younger than the medicated ADHD and controls; thus, we confirmed findings in age-matched subgroups (n = 128). All pairwise comparisons were conducted with Bonferroni corrections.

Finally, longitudinal analytic methods 37, 38 were used to examine growth patterns of caudate, cerebellum, total cerebrum, and the white and gray components of the 4 major lobes. The initial full longitudinal growth model was expressed as a cubic:

\[
\text{Size} = \text{Intercept} + \beta_1 \times (\text{Age} - \text{Mean Age}) + \beta_2 \times (\text{Age} - \text{Mean Age})^2 + \beta_3 \times (\text{Age} - \text{Mean Age})^3 + \epsilon
\]

The model parameters (intercept and β coefficients) were initially allowed to reflect interactions between sex and diagnostic group. To account for within-person correlations, intercepts were treated as normally distributed random effects that varied by individual, while β coefficients for age, age-squared, and age-cubed terms were modeled as fixed effects. The full cubic model was compared with simpler quadratic, linear, and constant models with interactions. Once the order of the model was established, testing was performed to determine whether an additive model could replace the interactions between sex and diagnostic group for the height and shape parameters of the curves. With respect to shape of the curves, there were neither significant sex differences nor sex by diagnosis interactions for any structure. Consequently, final models allowed for sex and diagnosis effects in the height parameters (intercept) of the curves and included only diagnostic differences in shape parameters.

Hypothesis tests and model selection were based on F statistics. We included data from individuals who had only a single scan (about 40% of both groups), because single scans provide additional information about between-participant variation and overall curve shape. These methods have been useful for combining cross-sectional and longitudinal anatomic MRI data. 39-41 Statistical power exceeded 80% at P = .05 for all brain measures. Minimally detectable adjusted differences ranged from 2.7% (caudate and cerebellum) to 5% for occipital gray matter, and averaged 3% for cortical volumes. Statistical analyses were performed using SPSS version 10.0 (SPSS Inc, Chicago, Ill), except for the mixed-model random regression analyses, which were performed with SAS version 8.02 (SAS Institute Inc, Cary, NC), and the power analyses, which were conducted with PASS 2000 (NCSS Statistical Software, Kaysville, Utah). Two-tailed significance levels were defined as P ≤ .05.

RESULTS
Participants
Final study participants consisting of 152 children and adolescents with ADHD and 139 controls were each successfully scanned up to 4 times over a decade. As Table 1 shows, there were several group differences between male and female patients (females were younger, shorter, and weighed less), and between patients and controls. Patients were shorter and weighed less, had lower vocabulary standard scores, and a lower percentage of individuals were strongly right-handed (scoring 10 or more of 12 items). Sex and diagnosis did not interact significantly for any demographic measure. Female and male patients with ADHD were comparable on vocabulary, handedness, parent and teacher attention problem scores, and prevalence of learning disorders. 42 Physicin’s Clinical Global Impressions ratings reflected significantly greater severity in females, who also had a higher percentage of combined-type ADHD, mood disorder (history of major depression and/or dysthymia) and lower prevalence of conduct disorder and tic disorder not otherwise specified. At the time of the first scan, 103 patients (68%)
were being treated with psychostimul-

The 49 patients with ADHD (22 fe-
male) who were successfully scanned
before ever being treated with psycho-
tropic medications (unmedicated
ADHD) were significantly younger than
the medicated patients (medicated
ADHD) and controls (TABLE 2). Un-
medicated patients with ADHD were
rated as comparable in severity by par-
ents, but as significantly less severely
affected by physicians and teachers.
They also tended to score higher on the
vocabulary IQ subtest, but not signifi-
cantly (P = .06).

Sixty-one patients (40%) were scanned
once, 61 (40%) twice, 20 (13%) 3 times,
and 10 (7%) 4 times. Fifty-two controls
(37%) were scanned once, 55 (40%)
twice, 29 (21%) 3 times, and 3 (2%) 4
times. Mean ages at each scan did not dif-
fer significantly between diagnostic
groups (at first scan, F = 22.8, P = .13;
at second scan, F = 0.88, P = .78; at
third scan, F = 0.02, P = .89; at fourth
scan, F = 1.06, P = .32). Female partici-
pants (mean, 9.7 years [SD, 2.6]) were
significantly younger than male partici-
pants (mean, 10.7 years [SD, 3.3];
P = .006), regardless of diagnosis. Mean
intervals between scans did not differ sig-
ificantly between diagnostic groups
(mean for patients with ADHD, 2.6 years
[1.1]; mean for controls, 2.4 years [1.0];
F = 1.60, P = .11).

Analyses of Initial Scans
TABLE 3 contains the unadjusted means
(SDs) of the 291 initial cross-sectional
scans by diagnosis as well as the means
(SES) adjusted for all significant covar-
iates. Three summary measures were
obtained for the cerebrum, defined by
excluding cerebellum, brainstem, and
cerebrospinal fluid.

As expected, all measures were
significantly smaller in female partici-

Table 1. Demographic and Diagnostic Characteristics of 152 Patients With ADHD and 139 Control Patients*

<table>
<thead>
<tr>
<th>Characteristic</th>
<th>Patients With ADHD</th>
<th>Controls</th>
<th>P Value for Female vs Male†</th>
<th>P Value for Patients With ADHD vs Controls</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Female (n = 63)</td>
<td>Male (n = 89)</td>
<td>Male (n = 56)</td>
<td>Male (n = 83)</td>
</tr>
<tr>
<td>Age at initial scan, mean (SD), y</td>
<td>9.4 (2.6)</td>
<td>10.5 (3.1)</td>
<td>10.0 (2.6)</td>
<td>10.9 (3.5)</td>
</tr>
<tr>
<td>Height, mean (SD), cm</td>
<td>134.9 (15.0)</td>
<td>141.7 (18.0)</td>
<td>140.2 (16.0)</td>
<td>147.3 (20.3)</td>
</tr>
<tr>
<td>Weight, mean (SD), kg</td>
<td>33.0 (12.2)</td>
<td>36.9 (14.4)</td>
<td>35.8 (12.5)</td>
<td>42.0 (16.5)</td>
</tr>
<tr>
<td>Birth weight, mean (SD), g</td>
<td>3264 (573) [n = 54]</td>
<td>3449 (606) [n = 66]</td>
<td>3396 (414) [n = 33]</td>
<td>3584 (544) [n = 48]</td>
</tr>
<tr>
<td>Scores, mean (SD)</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Vocabulary standard score</td>
<td>11.6 (3.1)</td>
<td>11.9 (3.0)</td>
<td>12.5 (3.1)</td>
<td>12.6 (3.0)</td>
</tr>
<tr>
<td>Clinical Global Impression</td>
<td>4.6 (1.0)</td>
<td>4.3 (0.9)</td>
<td>NA</td>
<td>NA</td>
</tr>
<tr>
<td>CBCL attention problems T-score</td>
<td>74.6 (7.7)</td>
<td>70.8 (9.6)</td>
<td>NA</td>
<td>NA</td>
</tr>
<tr>
<td>TRF attention problems T-score</td>
<td>68.2 (8.7)</td>
<td>68.9 (9.3)</td>
<td>NA</td>
<td>NA</td>
</tr>
<tr>
<td>Strongly right-handed, No. (%)</td>
<td>52 (82)</td>
<td>73 (82)</td>
<td>52 (83)</td>
<td>76 (93)</td>
</tr>
<tr>
<td>Prior stimulant treatment, No. (%)</td>
<td>41 (65)</td>
<td>62 (70)</td>
<td>NA</td>
<td>NA</td>
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<tr>
<td>DSM-IV diagnosed disorders, No. (%)</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>ADHD, combined type</td>
<td>63 (100)</td>
<td>83 (93)</td>
<td>.04</td>
<td></td>
</tr>
<tr>
<td>Oppositional defiant</td>
<td>26 (41)</td>
<td>30 (34)</td>
<td>.34</td>
<td></td>
</tr>
<tr>
<td>Conduct</td>
<td>1 (2)</td>
<td>10 (11)</td>
<td>.02</td>
<td></td>
</tr>
<tr>
<td>Learning</td>
<td>7 (11)</td>
<td>9 (10)</td>
<td>.84</td>
<td></td>
</tr>
<tr>
<td>Mood</td>
<td>6 (9)</td>
<td>1 (1)</td>
<td>.01</td>
<td></td>
</tr>
<tr>
<td>Anxiety</td>
<td>7 (11)</td>
<td>6 (7)</td>
<td>.34</td>
<td></td>
</tr>
<tr>
<td>Tic, not otherwise specified</td>
<td>1 (2)</td>
<td>10 (11)</td>
<td>.02</td>
<td></td>
</tr>
</tbody>
</table>

*ADHD indicates attention-deficit/hyperactivity disorder; CBCL, Child Behavior Checklist (rated by parents); TRF, Teacher Report Form; DSM-IV, Diagnostic and Statistical Manual of Mental Disorders, Fourth Edition; and NA, not applicable.
†None of the sex by diagnosis interactions on 2-way analysis of variance approached statistical significance. Frequencies compared with χ² or Fisher exact tests.
‡Frequency compared with χ² test.

Table 2. Comparison Between Previously Unmedicated and Medicated Patients With ADHD*

<table>
<thead>
<tr>
<th></th>
<th>Unmedicated Patients With ADHD (n = 49)</th>
<th>Medicated Patients With ADHD (n = 103)</th>
<th>P Value‡</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age at initial scan, y</td>
<td>8.3 (2.6)</td>
<td>10.9 (2.7)</td>
<td>.001</td>
</tr>
<tr>
<td>Vocabulary standard score</td>
<td>12.5 (3.3)</td>
<td>11.5 (2.9)</td>
<td>.06</td>
</tr>
<tr>
<td>Clinical Global Impression</td>
<td>4.2 (1.0)</td>
<td>4.6 (0.9)</td>
<td>.02</td>
</tr>
<tr>
<td>CBCL attention problems T-score</td>
<td>71.7 (9.7)</td>
<td>72.9 (8.6)</td>
<td>.47</td>
</tr>
<tr>
<td>TRF attention problems T-score</td>
<td>66.2 (9.1)</td>
<td>69.9 (8.7)</td>
<td>.02</td>
</tr>
</tbody>
</table>

*ADHD indicates attention-deficit/hyperactivity disorder; CBCL, Child Behavior Checklist; and TRF, Teacher Report Form.
†All previously and/or currently treated with stimulant medications.
‡Using 2-sample t test.
patients (F1,287 ranged from 10.65 for parietal gray matter to 98.61 for cerebellum; P < .001), but sex did not interact significantly with diagnosis for any brain anatomy measure. Accordingly, mean values for sex and corresponding statistics are not presented here (they can be found at http://intramural.nimh.nih.gov/research/chp/index2.html). A significant main effect of diagnosis was found between patients with ADHD and controls for all measures with small-to-medium effect sizes ranging from 0.30 to 0.46, which remained significant or were somewhat enhanced (eg, adjusted effect size for temporal white matter = 0.64) when adjusted for the significant covariates of vocabulary, height, or medication status. When we adjusted for the significant group differences in total cerebral volume, the only brain region that remained significantly smaller in ADHD was the cerebellum (d = 0.27; 95% confidence interval [CI], 0.03-0.50; F1,287 = 4.97; P = .03).

Effects of Prior Drug Treatment

Table 3 displays the contrasts between 3 nonoverlapping groups consisting of 49 unmedicated patients with ADHD, 103 medicated patients with ADHD, and 139 healthy controls. Unmedicated patients with ADHD did not differ significantly from medicated patients with ADHD on any gray matter measures, or in caudate or cerebellum. By contrast, unmedicated patients with ADHD had strikingly smaller white matter volumes (F2,288 = 11.65) compared with controls (−10.7%, P < .001) and with medicated children with ADHD (−8.9%; P < .001; all pairwise comparisons Bonferroni corrected). Unmedicated patients with ADHD had smaller cerebral volumes (−6.2%, P < .001), smaller temporal gray (−4.6%, P = .02), and smaller

| Table 3. Initial Regional Brain Volumes, Unadjusted, and Adjusted Analyses for Patients With ADHD and Controls* |
|-----------------------------------------|-----------------|----------|-----------------|-----------------|
| **Patients With ADHD** (n = 152) | Controls (n = 139) | **F** Statistic | **P** Value | **Difference Between the Means,** % | **Effect Size (95% Confidence Interval)** |
| **Unadjusted Analysis§** | | | | | |
| Total cerebral volume | 1059.4 (117.5) | 1104.5 (111.3) | 12.55 | < .001 | −4.1 | 0.39 (0.16-0.63) |
| Total gray matter | 700.9 (77.3) | 727.9 (74.3) | 9.27 | .003 | −3.7 | 0.36 (0.12-0.59) |
| Total white matter | 358.5 (53.5) | 376.6 (49.8) | 10.42 | .001 | −4.8 | 0.35 (0.11-0.59) |
| Frontal gray matter | 217.3 (24.9) | 225.2 (22.5) | 8.06 | .005 | −3.5 | 0.33 (0.10-0.57) |
| Parietal gray matter | 116.6 (13.0) | 122.0 (12.9) | 11.42 | .001 | −4.4 | 0.41 (0.17-0.65) |
| Temporal gray matter | 174.0 (18.5) | 181.6 (18.2) | 13.02 | .001 | −4.2 | 0.42 (0.18-0.66) |
| Occipital gray matter | 62.5 (9.6) | 66.5 (10.5) | 11.54 | .001 | −6.1 | 0.40 (0.16-0.64) |
| Frontal white matter | 135.8 (21.4) | 141.9 (18.5) | 8.31 | .004 | −4.3 | 0.30 (0.07-0.54) |
| Parietal white matter | 70.6 (10.4) | 74.9 (9.8) | 13.94 | .001 | −5.7 | 0.42 (0.18-0.66) |
| Temporal white matter | 74.4 (11.0) | 77.6 (10.6) | 11.42 | .001 | −4.4 | 0.42 (0.18-0.66) |
| Occipital white matter | 30.3 (5.5) | 32.2 (5.9) | 8.68 | .003 | −6.0 | 0.34 (0.10-0.57) |
| Caudate | 10.4 (1.1) | 10.8 (1.0) | 10.59 | .001 | −3.7 | 0.37 (0.13-0.61) |
| Cerebellum | 124.1 (12.3) | 129.8 (12.7) | 17.44 | .001 | −4.4 | 0.46 (0.22-0.70) |

| **Adjusted Analysis†** | | | | | |
| **Mean (SE)** | | | | | |
| Total cerebral volume | 1055.54 (8.17) | 1090.06 (8.69) | 8.30 | .004 | −3.2 | 0.34 (0.10-0.58) |
| Total gray matter | 699.81 (5.70) | 719.72 (6.07) | 5.67 | .02 | −2.8 | 0.28 (0.04-0.52) |
| Total white matter | 351.92 (4.31) | 375.50 (4.64) | 10.04 | .002 | −6.3 | 0.45 (0.20-0.69) |
| Frontal gray matter | 216.87 (1.83) | 222.94 (1.94) | 5.13 | .02 | −2.7 | 0.27 (0.03-0.51) |
| Parietal gray matter | 116.75 (1.03) | 120.81 (1.10) | 7.18 | .008 | −3.4 | 0.32 (0.08-0.56) |
| Temporal gray matter | 173.56 (1.37) | 179.51 (1.46) | 8.75 | .003 | −3.3 | 0.35 (0.11-0.59) |
| Occipital gray matter | 62.49 (0.80) | 65.72 (0.85) | 7.67 | .006 | −4.9 | 0.33 (0.09-0.57) |
| Frontal white matter | 132.97 (1.68) | 141.89 (1.80) | 9.52 | .002 | −6.3 | 0.44 (0.19-0.68) |
| Parietal white matter | 69.51 (0.90) | 74.77 (0.97) | 11.37 | .001 | −7.0 | 0.48 (0.23-0.72) |
| Temporal white matter | 71.65 (0.92) | 78.89 (1.00) | 21.59 | < .001 | −9.2 | 0.64 (0.39-0.88) |
| Occipital white matter | 30.03 (0.42) | 31.57 (0.45) | 6.13 | .01 | −4.9 | 0.30 (0.06-0.53) |
| Caudate | 10.32 (0.08) | 10.63 (0.09) | 6.99 | .009 | −2.9 | 0.32 (0.08-0.56) |
| Cerebellum | 123.58 (0.87) | 128.07 (0.93) | 12.29 | .001 | −3.5 | 0.42 (0.18-0.66) |

*ADHD indicates attention-deficit/hyperactivity disorder.
†Potential covariates tested were vocabulary (V), medication status (M), height (H), weight, and handedness. Only significant covariates were included in final models, as indicated.
‡Two-way analysis of variance (diagnoses, sex); main effect of sex, F1,287 > 10 for all measures; no sex by diagnosis interactions approached significance.
§Two-way analysis of covariance; main effect of sex, F1,287 > 9 for all measures; no sex by diagnosis interactions approached significance.
Brain Volume Abnormalities in ADHD

Total cerebral volumes (−5.8%, P = .002) compared with controls. Differences between unmedicated patients with ADHD and controls in frontal (−3.8%) and parietal gray matter (−4.1%) would also have been significant if not corrected for multiple comparisons. Medicated patients with ADHD did not differ significantly from controls in any white matter measure. Robust differences from controls remained for all gray matter measures (ranging from −3.4% to −6.6%), caudate (−4.3%), cerebellum (−3.6%), and the summary measures of total cerebral volume (−3.3%) and total gray volume (−3.9%).

Because the unmedicated patients with ADHD were significantly younger than the other 2 subgroups, and white matter increases with increasing age throughout the age range,43 we performed secondary analyses restricted to an age-matched subset of 128 participants (consisting of 24 unmedicated patients with ADHD, 50 medicated patients with ADHD, and 54 controls [61 females]). All measures remained essentially unchanged.

Relationship to Clinical Measures

We examined correlations between the 10 regional measures and behavioral ratings. Within the patient group, smaller volumes were significantly correlated in the expected direction with greater symptom severity. Frontal and temporal gray matter, caudate, and cerebellar volumes were significantly and negatively correlated with physician’s Clinical Global Impressions rating (r = 0.139, Pearson coefficients ranged between −0.16 for frontal gray and −0.26 for cerebellum, all P < .05). The same 4 regions were also significantly and negatively correlated with parent-rated child behavior checklist attention problems with Pearson coefficients between −0.16 and −0.22 (all P < .05). Correlations were largely unaffected when adjusted for age.

Wechsler vocabulary standard score was significantly and positively correlated with all anatomic volumes in patients with ADHD (n = 151; r ranged from 0.19–0.35; all P < .02) and in frontal and occipital gray and white matter and cerebellar volumes in controls (n = 134; r ranged from 0.18–0.24; all P < .02). Although the magnitude of the correlations was greater in patients than in controls, none of the coefficients differed significantly from each other, and all regional volumes correlated significantly with the vocabulary score when the 2 groups were combined (n = 285; eg, for total cerebral volume, r = 0.31; P < .001).

Analyses of Initial and Follow-up Scans

Sixty percent of all participants had at least 2 scans (n = 178), including 62 (21%), who had at least 3 scans and 13 (4%), who had 4 scans obtained at 2- to 3-year intervals. Data from all 544 resulting scans were used to derive longitudinal growth curves for patients and controls of both sexes. The age range for male participants extended between 4.6 and 19.0 years, while female participants ranged between 5.2 and 16.3 years, reflecting our initial focus on males with ADHD.

Predicted longitudinal growth curve parameters did not differ significantly between male and female participants except for the height of each curve (intercept) at the corresponding age midpoint, which were significantly higher for males for all measures, regardless of diagnosis (empirical P < .001, derived from F statistics confirmed with permutation tests with 1000 iterations). There were no significant interactions between sex and diagnosis for any developmental growth patterns (intercepts or curve parameters B1, B2).

Figure 1 shows the predicted developmental growth curves along with 95% CIs for each group’s average total cerebral volume. Developmental curves

Table 4. Unadjusted Brain Volumes for Unmedicated and Medicated Patients With ADHD and Controls

<table>
<thead>
<tr>
<th></th>
<th>Unmedicated (n = 49)</th>
<th>Medicated (n = 103)</th>
<th>Controls (n = 139)</th>
<th>F Statistic†</th>
<th>P Values‡</th>
</tr>
</thead>
<tbody>
<tr>
<td>Total cerebral volume</td>
<td>1040.4 (98.9)</td>
<td>1068.4 (124.9)</td>
<td>1104.5 (111.3)</td>
<td>6.65</td>
<td>.001</td>
</tr>
<tr>
<td>Total gray matter</td>
<td>704.2 (70.0)</td>
<td>699.3 (80.8)</td>
<td>727.9 (74.3)</td>
<td>4.67</td>
<td>.01</td>
</tr>
<tr>
<td>Total white matter</td>
<td>336.2 (41.9)</td>
<td>369.1 (55.3)</td>
<td>376.6 (49.8)</td>
<td>11.65</td>
<td>&lt;.001</td>
</tr>
<tr>
<td>Frontal gray matter</td>
<td>216.6 (20.7)</td>
<td>217.6 (26.8)</td>
<td>225.2 (22.5)</td>
<td>4.06</td>
<td>.02</td>
</tr>
<tr>
<td>Parietal gray matter</td>
<td>117.0 (11.4)</td>
<td>116.4 (13.7)</td>
<td>122.0 (12.9)</td>
<td>6.22</td>
<td>.002</td>
</tr>
<tr>
<td>Temporal gray matter</td>
<td>173.2 (15.6)</td>
<td>174.4 (19.7)</td>
<td>181.6 (18.2)</td>
<td>6.32</td>
<td>.002</td>
</tr>
<tr>
<td>Occipital gray matter</td>
<td>63.2 (9.5)</td>
<td>62.1 (9.7)</td>
<td>66.5 (10.5)</td>
<td>6.05</td>
<td>&lt;.001</td>
</tr>
<tr>
<td>Frontal white matter</td>
<td>127.1 (16.6)</td>
<td>140.0 (22.2)</td>
<td>141.9 (18.5)</td>
<td>10.59</td>
<td>&lt;.001</td>
</tr>
<tr>
<td>Parietal white matter</td>
<td>66.5 (7.8)</td>
<td>72.6 (10.8)</td>
<td>74.9 (9.8)</td>
<td>12.86</td>
<td>&lt;.001</td>
</tr>
<tr>
<td>Temporal white matter</td>
<td>69.7 (8.5)</td>
<td>76.6 (11.3)</td>
<td>77.6 (10.6)</td>
<td>10.54</td>
<td>&lt;.001</td>
</tr>
<tr>
<td>Occipital white matter</td>
<td>28.6 (4.6)</td>
<td>31.1 (5.8)</td>
<td>32.2 (5.9)</td>
<td>7.39</td>
<td>&lt;.001</td>
</tr>
<tr>
<td>Caudate</td>
<td>10.50 (1.07)</td>
<td>10.29 (1.16)</td>
<td>10.75 (0.98)</td>
<td>5.69</td>
<td>&lt;.001</td>
</tr>
<tr>
<td>Cerebellum</td>
<td>121.8 (11.7)</td>
<td>125.1 (12.4)</td>
<td>129.8 (12.7)</td>
<td>8.97</td>
<td>&lt;.001</td>
</tr>
</tbody>
</table>

*ADHD indicates attention-deficit/hyperactivity disorder.
†Two-way analysis of variance (group [medicated vs unmedicated vs control] by sex); df (2, 288) for all regions. No sex by diagnoses interactions approached significance.
were significantly higher in controls than in patients with ADHD for total cerebral volume and for all other brain measures. Diagnostic differences in curve height remained significant after adjusting for vocabulary standard score (total cerebral volume, \(P = .002\)). There were no significant differences in curve shape between patients and controls, except for caudate. After adjustment for diagnostic differences in total cerebral volume, only caudate (\(P = .02\)) and cerebellum (\(P = .003\)) remained significantly smaller in patients with ADHD.

Figure 2 depicts unadjusted predicted growth curves for caudate nucleus and cerebellum. Caudate was the only region in which the developmental trajectories did not remain statistically parallel for patients and controls (adjusted, \(P = .05\)). These differences in shape represent a normalization of caudate volume for patients by midadolescence. By contrast, diagnostic differences in cerebellar curves continue throughout our age range (unadjusted, \(P < .001\); adjusted, \(P = .003\), with a nonsignificant tendency toward a greater difference in late adolescence (unadjusted, \(P = .10\)). The general absence of diagnostic differences in curve shapes indicates that developmental curves for patients with ADHD, although significantly lower, were essentially parallel to curves for healthy controls, with the exception of the caudate nucleus.

### COMMENT

Fully automated measures of brain cortical and subcortical volumes from the initial scans of 291 male and female patients show that the cerebrum as a whole and the cerebellum are smaller in children and adolescents with predominantly combined-type ADHD. Rather than reflecting a selective frontostriatal effect, volumes were decreased to a comparable extent in all 4 lobes and were statistically more prominent only in the cerebellum. Our findings were not ascribable to differences in cognitive level, height, age, weight, or handedness and were not related to comorbid diagnoses (data not shown).

This is the first neuroimaging study to our knowledge to include a substantial number (\(n = 49\)) of previously unmedicated children and adolescents with ADHD. We attempted to recruit children with equivalent severity of ADHD symptoms by using identical diagnostic and symptom severity criteria. Unmedicated patients with ADHD did not differ from medicated children with ADHD on parent-rated attention problems, but they had significantly lower teacher and physician ratings, and higher vocabulary standard scores. These differences should have minimized anatomic brain differences between unmedicated patients with ADHD and controls. In fact, findings were generally as striking for the unmedicated patients with ADHD as for those who were being treated with medications, and were more pronounced for white matter volumes. Thus, our analyses show that decreased brain volumes in ADHD in both white and gray matter compartments

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**Figure 1.** Predicted Unadjusted Longitudinal Growth Curves for Total Cerebral Volumes for Patients With ADHD and Controls

**Figure 2.** Predicted Unadjusted Longitudinal Growth Curves for Total Caudate and Cerebellar Volume for Patients With ADHD vs Controls

ADHD indicates attention-deficit/hyperactivity disorder. Curvature cubic, quadratic, and linear coefficients did not differ significantly between male and female patients, and sex did not interact significantly with diagnosis. Although all data were used in analyses, graphs of developmental curves are restricted to the central 90% of each sample’s age distribution because fitted polynomial curves may be heavily influenced by outliers at the age range extremes.
are not due to drug treatment. Conversely, we have no evidence that stimulant drugs cause abnormal brain development. 

Patients with ADHD had developmental trajectories for nearly all brain regions that paralleled growth curves for controls but on a lower track. The one exception, foreshadowed by an earlier cross-sectional study, was the caudate nucleus, for which differences between patients and controls became negligible by midadolescence. As the caudate nucleus reaches its maximum volume around 10 years, the potential relationship between normalization of caudate volume in ADHD and decreased ratings of hyperactivity/impulsivity in children with ADHD, as well as in quantitative measures of movement in normative samples, should be addressed in future studies.

Longitudinal follow-up of functional outcome is continuing; hence, we cannot report definitively on the relationship between continuing anatomic deviance or normalization vs outcome. Preliminarily, global functional outcome in 64 patients with ADHD (20 females) evaluated 4 years after initial scan does not suggest any significant relationships between continuing anatomic deviance and clinical follow-up status. We did not find evidence of a primarily frontal abnormality in ADHD. Instead, we found the smallest diagnostic effect sizes in frontal lobes. However, these results cannot be interpreted as definitive evidence against the frontal-striatal hypothesis of ADHD pathogenesis, because our units of analysis, while highly reliable, were too large. These methods have been useful in detecting age-, sex-, and diagnosis-specific differences in growth curves, and their application to ADHD was warranted. Alternate approaches, such as unbiased pixel-based analyses, may be needed to detect more localized anatomic abnormalities in regions such as cingulate, orbitofrontal, or dorsolateral prefrontal cortex in patients with ADHD. However, these methods may also require even larger or more closely matched contrast groups (eg, twin or sibling controls) given the mostly modest effect sizes and substantial between-subject variations in brain anatomy.

Limitations of this study include the use of referred samples for patients and highly screened controls that may not be optimally representative. We recruited female patients with ADHD who were comparable in severity with our previous samples of males, but in so doing may have selected females who are atypical of most community and clinical samples. We lost significantly more scans from children with ADHD because of excessive motion, but again, this bias should have removed the most symptomatic patients.

In conclusion, ADHD is associated with about a 3% (adjusted; 4% unadjusted) decrease in volume throughout the brain. Intriguingly, this decrease is most marked in white matter of unmedicated patients. Furthermore, with the exception of caudate nucleus, longitudinal growth curves are roughly parallel, suggesting that the fundamental developmental processes active during late childhood and adolescence are essentially healthy in ADHD, and that neuropsychiatric symptoms appear to reflect fixed earlier neurobiological insults or abnormalities. Future studies should focus on younger patients being enrolled into controlled treatment studies while in preschool and on the development of improved quantitative measures of brain anatomy and of the component endophenotypes of ADHD. Finally, despite the importance of these findings, anatomic MRI studies remain appropriate only for research, as they cannot yet contribute to the diagnostic assessment of ADHD.

**REFERENCES**

12. Hynd GW, Henm KL, Novey ES, et al. Attention...
deficit hyperactivity disorder and asymmetry of the caudate nucleus. J Child Neurol. 1993;8:339-347.