Original Investigation

Developmentally Stable Whole-Brain Volume Reductions and Developmentally Sensitive Caudate and Putamen Volume Alterations in Those With Attention-Deficit/Hyperactivity Disorder and Their Unaffected Siblings

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IMPORTANCE Attention-deficit/hyperactivity disorder (ADHD) is a heritable neurodevelopmental disorder. It has been linked to reductions in total brain volume and subcortical abnormalities. However, owing to heterogeneity within and between studies and limited sample sizes, findings on the neuroanatomical substrates of ADHD have shown considerable variability. Moreover, it remains unclear whether neuroanatomical alterations linked to ADHD are also present in the unaffected siblings of those with ADHD.

OBJECTIVE To examine whether ADHD is linked to alterations in whole-brain and subcortical volumes and to study familial underpinnings of brain volumetric alterations in ADHD.

DESIGN, SETTING, AND PARTICIPANTS In this cross-sectional study, we included participants from the large and carefully phenotyped Dutch NeuroIMAGE sample (collected from September 2009-December 2012) consisting of 307 participants with ADHD, 169 of their unaffected siblings, and 196 typically developing control individuals (mean age, 17.21 years; age range, 8-30 years).

MAIN OUTCOMES AND MEASURES Whole-brain volumes (total brain and gray and white matter volumes) and volumes of subcortical regions (nucleus accumbens, amygdala, caudate nucleus, globus pallidus, hippocampus, putamen, thalamus, and brainstem) were derived from structural magnetic resonance imaging scans using automated tissue segmentation.

RESULTS Regression analyses revealed that relative to control individuals, participants with ADHD had a 2.5% smaller total brain (β = −31.92; 95% CI, −52.69 to −11.16; P = .0027) and a 3% smaller total gray matter volume (β = −22.51; 95% CI, −35.07 to −9.96; P = .0005), while total white matter volume was unaltered (β = −10.10; 95% CI, −20.73 to 0.53; P = .06). Unaffected siblings had total brain and total gray matter volumes intermediate to participants with ADHD and control individuals. Significant age-by-diagnosis interactions showed that older age was linked to smaller caudate (P < .001) and putamen (P = .01) volumes (both corrected for total brain volume) in control individuals, whereas age was unrelated to these volumes in participants with ADHD and their unaffected siblings. Attention-deficit/hyperactivity disorder was not significantly related to the other subcortical volumes.

CONCLUSIONS AND RELEVANCE Global differences in gray matter volume may be due to alterations in the general mechanisms underlying normal brain development in ADHD. The age-by-diagnosis interaction in the caudate and putamen supports the relevance of different brain developmental trajectories in participants with ADHD vs control individuals and supports the role of subcortical basal ganglia alterations in the pathophysiology of ADHD. Alterations in total gray matter and caudate and putamen volumes in unaffected siblings suggest that these volumes are linked to familial risk for ADHD.

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Attention-deficit/hyperactivity disorder (ADHD) is a common neurodevelopmental disorder characterized by symptoms of inattention and hyperactivity/impulsivity.[1] Anatomical magnetic resonance imaging (MRI) studies have associated ADHD with a 3% to 5% smaller total brain size compared with control individuals.[2-4] Meta-analyses have further documented smaller volumes in ADHD across several specific brain regions, most consistently in basal ganglia volumes: right globus pallidus and right putamen and caudate.[5-8] These abnormalities are in accordance with a neurodevelopmental theory that hypothesizes ADHD to be caused by early-emerging persistent subcortical abnormalities.[9]

Existing brain volumetric studies in ADHD face some limitations. First, the child and adult literature have largely been kept separate, ignoring the transition from adolescence into early adulthood in studying age effects. Hyperactive/impulsive more than inattentive symptoms of ADHD tend to decrease with age.[10-12] Moreover, cross-sectional evidence suggests that some brain volumetric alterations observed in childhood may normalize with age.[7,8] Second, findings on brain volumetric alterations in ADHD have been variable (eg, one meta-analysis reported that only 25% to 50% of included studies revealed similar results).[8] Heterogeneity in sample composition within and between studies and small samples sizes may explain inconsistencies; individual studies included in meta-analyses ranged from 17 to 291 participants with ADHD and control individuals, with only 4 studies exceeding a sample size of 100.[5-8] The use of a large well-defined sample has added value over and extends existing meta-analyses, as meta-analyses are limited by shortcomings of the individual studies. Third, ADHD is more common in boys than girls,[1,13] and brain volumetric alterations in ADHD may be hemisphere specific.[5-8] However, most studies used small samples to study sex and lateralization effects or revealed inconsistent findings.[5,7,8,14] Finally, ADHD runs in families[15-17] and is heritable (76%[18]), and brain volumes are also heritable (total brain volume, 66%-97%[19]; subcortical volumes, 44%-88%[20]). Two studies reported alterations in prefrontal gray matter and occipital gray and white matter,[4] as well as inferior frontal gyrus gray matter and inferior fronto-occipital fasciculus white matter[21] not only in participants with ADHD, but also in their unaffected siblings relative to control individuals. Because first-degree relatives on average share 50% of their genetic information, as well as all familywide environmental influences, these findings suggest familial (ie, shared genetic and/or shared environmental) underpinnings to associations between ADHD and brain volumes. However, whether ADHD-brain associations are influenced by familial factors remains widely unexplored.

The present cross-sectional study addresses these shortcomings through studying the brain volumetric correlates of ADHD in a large well-characterized sample of adolescents and young adults with ADHD, their unaffected siblings, and typically developing control individuals. First, we investigated whether ADHD was linked to whole-brain and subcortical volumes and whether results were influenced by age, sex, or lateralization. Second, familial underpinnings of brain volumetric alterations in ADHD were examined.

Methods

Sample

Participants came from the NeuroIMAGE project,[22] a follow-up of the Dutch part of the International Multicenter ADHD Genetics (IMAGE) Study performed between 2003 and 2006.[23-26] The IMAGE Study recruited ADHD families with at least 1 child with combined subtype ADHD and at least 1 biological sibling (regardless of ADHD diagnosis) and control families with at least 1 child and 1 biological sibling with no formal or suspected ADHD diagnosis in first-degree family members. Inclusion criteria were age between 8 and 30 years; European white descent; intelligence quotient (IQ) greater than or equal to 70; and no diagnosis of autism, epilepsy, general learning difficulties, brain disorders, and known genetic disorders. Dutch participants of the IMAGE Study were invited for follow-up measurement and (re) assessed in the NeuroIMAGE Study (follow-up rate: ADHD families, 75.6%; control families, 75.1%; mean [SD] time between measurements, 5.9 [0.74] years). Inclusion criteria were largely consistent with the IMAGE Study, except that inclusion of any ADHD subtype was allowed. Following exclusion for contraindications to MRI scanning and quality control of MRI scans (described further on), the final sample consisted of 307 participants with ADHD, 169 unaffected siblings, and 196 control participants (siblings from 389 families) (**Table 1**). The group with ADHD (n = 307) included 128 siblings (only siblings from ADHD families where each sibling had an ADHD diagnosis), the unaffected siblings group (n = 169) included 53 siblings (only siblings from ADHD families without an ADHD diagnosis), and the control group (n = 196) included 142 siblings (only siblings from control families). Ethical approval for the current study was obtained from CMO Regio Arnhem-Nijmegen, and all participants provided written informed consent. For details on diagnostic assessment, see eAppendix 1 in the Supplement.

Image Acquisition and Segmentation

Imaging was conducted at 2 locations (VU University Amsterdam, Amsterdam, and Radboud University Medical Center, Nijmegen) using 2 comparable 1.5-T scanners and scan protocols (Sonata and Avanto; Siemens) with the same product 8-channel head-coil and closely matched scan protocols.[22] The protocol included 2 high-resolution T1-weighted magnetization-prepared rapid acquisition gradient echo anatomical scans (176 sagittal slices; repetition time = 2730 milliseconds; echo time = 2.95 milliseconds; inversion time = 1000 milliseconds; flip angle = 7°; GRAPPA (generalized autocalibrating partial parallel acquisition) 2; voxel size = 1.0 × 1.0 × 1.0 mm; field of view = 256 mm). Magnetic resonance imaging scans that yielded relevant incidental findings or in which manual ratings revealed poor quality or motion artifacts were excluded.[28] In participants with 2 good-quality scans, volume estimates were averaged across scans (eTable 1 in the Supplement).

Whole-Brain Volumes

Normalization, bias correction, and segmentation into gray matter, white matter, and cerebrospinal fluid volumes were

Table 1. Participant Characteristics

Characteristic	ADHD (n = 307)	Siblings[a] (n = 169)	Controls (n = 196)
Male, %	68	43	49
Age, mean (SD), y	17.06 (3.42)	17.52 (4.11)	16.66 (3.07)
Total ADHD, mean (SD)[b]	69.99 (12.88)	47.60 (6.58)	45.74 (5.24)
Median	70.00	46.00	45.00
Inattentive Behavior Scale, mean (SD)[b]	66.10 (11.16)	47.72 (6.56)	46.27 (5.61)
Median	66.00	45.00	45.00
Hyperactive-Impulsive Behavior Scale, mean (SD)[b]	69.85 (14.48)	48.29 (7.11)	46.27 (4.93)
Median	68.00	46.00	44.00
IQ, mean (SD)	97.08 (15.18)	102.19 (14.54)	106.61 (13.70)

Abbreviations: ADHD, attention-deficit/hyperactivity disorder; IQ, intelligence quotient.

[a] Unaffected siblings of participants with ADHD.

[b] Refers to *t* scores on the *DSM* Total, Inattentive Behavior, and Hyperactive-Impulsive Behavior scales of the Conners' Parent Rating Scale–Revised[27] (scales N, L, and M). *T* scores ≥63 are considered clinically elevated.

performed using the unified procedure of the VBM 8.1 toolbox (http://dbm.neuro.uni-jena.de/vbm/) in SPM (default settings). Total gray and white matter volumes were calculated by summation of their tissue probability maps. Total brain volume was the sum of total gray and white matter volumes.

Subcortical Volumes

Automated FIRST (FMRIB's Integrated Registration and Segmentation Tool) subcortical segmentation was applied to estimate total, left, and right volumes of the amygdala, caudate nucleus, hippocampus, nucleus accumbens, globus pallidus, putamen, thalamus, and brainstem. Previous research has shown these volumes to be heritable.[20] FIRST is part of FMRIB's Software Library and performs registration and shape modeling of the just-mentioned regions in Montreal Neurological Institute 152 standard space.[29] FIRST-based segmentation includes the hippocampus as a subcortical region, although it is not usually considered subcortical.[29]

Assessment of IQ and Medication Use

Participants' full-scale IQ was estimated using the Vocabulary and Block Design subtests of the Wechsler Intelligence Scale for Children III or the Wechsler Adult Intelligence Scale III (for participants aged ≥17 years).[22] Cumulative medication intake, calculated as treatment duration corrected for age multiplied by the mean daily dose in milligrams, was gathered from pharmacy transcripts and questionnaire reports (eAppendix 1 in the Supplement).

Analyses

Comparisons Between Participants With ADHD and Control Individuals

Brain volumetric measures were normally distributed and outliers more than 3 SDs greater than or less than the mean were removed. Overall, there were few outliers (1-5 individuals per volume). Associations between ADHD and brain volumes were examined using regression analyses that included brain volumes 1 by 1 as outcome measures, with scanner location (Amsterdam or Nijmegen), age, age squared, and sex as covariates.[20,30,31] Total brain volume was included as an additional covariate for regressions of subcortical volumes to enable inferences about subcortical alterations unconfounded by total brain volume.[32] The regression model included binary ADHD diagnosis (ADHD and control) as a main effect, as well as the 2-way interaction effects between binary ADHD diagnosis and age, age squared, and sex (ADHD by age; ADHD by age squared; and ADHD by sex). Interaction effects not reaching nominal significance (.05) were dropped from the final model. Centering of variables was used[33] before creating interaction terms, and multicollinearity statistics were examined. To correct for the nonindependence of the data of siblings in the ADHD and control groups (see Sample description), the correlation structure of the data was accounted for by calculating robust standard errors using the cluster command in Stata (StataCorp).[34,35] This was merely a correction to account for the underlying assumption in regression that observations are independent and does not preclude examination of familiality effects underlying brain-ADHD associations.

Correction for Multiple Testing

A multiple-testing correction was applied, which adjusts correlated tests based on an effective number of independent comparisons[36] derived from the eigenvalues of a correlation matrix between the included outcome measures adjusted for covariates. The multiple-testing adjusted *P* value was determined to be .003 (eTable 2 in the Supplement) and applied to analyses comparing participants with ADHD and control individuals. Any follow-up analyses of volumes surviving multiple-testing correction used the nominal significance level (.05) and should be seen as exploratory.

Comparisons of Unaffected Siblings With Participants With ADHD and Control Individuals

For volumes surviving multiple-testing correction, the previously mentioned regression models were repeated, replacing binary ADHD diagnosis with a 3-level group membership variable (ADHD, unaffected sibling, and control individual). All other model parameters were kept the same as in the analyses comparing participants with ADHD and control individuals and the cluster command, and the same covariates were used. Familiality was considered present if the unaffected siblings differed in brain volumes from control individuals but not from participants with ADHD or differed from both groups showing intermediate brain volumes.

Table 2. Participants With ADHD, Unaffected Siblings, and Control Individuals

Region	Brain Volume, Mean (SE), mL[a]		
	ADHD (n = 307)	Siblings (n = 169)[b]	Controls (n = 196)
Total brain[c]	1230.59 (6.08)	1250.72 (8.27)	1262.31 (8.15)
Gray matter	724.49 (3.49)	737.32 (4.97)	746.82 (5.07)
White matter	505.59 (3.21)	513.11 (4.17)	515.52 (4.15)
Accumbens			
Total volume of left and right hemispheres summed	1.15 (0.01)	1.11 (0.01)	1.11 (0.01)
Volume of left hemisphere	0.61 (0.01)	0.60 (0.01)	0.59 (0.01)
Volume of right hemisphere	0.54 (0.01)	0.51 (0.01)	0.52 (0.01)
Amygdala			
Total volume of left and right hemispheres summed	2.67 (0.02)	2.67 (0.03)	2.63 (0.03)
Volume of left hemisphere	1.30 (0.01)	1.28 (0.02)	1.25 (0.02)
Volume of right hemisphere	1.36 (0.02)	1.38 (0.02)	1.37 (0.02)
Caudate			
Total volume of left and right hemispheres summed	8.11 (0.05)	7.99 (0.06)	8.09 (0.06)
Volume of left hemisphere	3.98 (0.02)	3.92 (0.03)	3.97 (0.03)
Volume of right hemisphere	4.13 (0.02)	4.07 (0.03)	4.12 (0.03)
Globus pallidus			
Total volume of left and right hemispheres summed	3.76 (0.02)	3.74 (0.02)	3.71 (0.02)
Volume of left hemisphere	1.87 (0.01)	1.85 (0.01)	1.83 (0.01)
Volume of right hemisphere	1.90 (0.01)	1.89 (0.01)	1.88 (0.01)
Hippocampus			
Total volume of left and right hemispheres summed	7.81 (0.04)	7.82 (0.05)	7.80 (0.06)
Volume of left hemisphere	3.84 (0.02)	3.83 (0.03)	3.81 (0.03)
Volume of right hemisphere	3.97 (0.02)	3.99 (0.03)	4.00 (0.03)
Putamen			
Total volume of left and right hemispheres summed	10.87 (0.06)	10.85 (0.07)	10.73 (0.07)
Volume of left hemisphere	5.45 (0.03)	5.44 (0.04)	5.38 (0.03)
Volume of right hemisphere	5.43 (0.03)	5.41 (0.03)	5.35 (0.04)
Thalamus			
Total volume of left and right hemispheres summed	16.88 (0.06)	16.79 (0.07)	16.80 (0.08)
Volume of left hemisphere	8.53 (0.03)	8.48 (0.04)	8.49 (0.05)
Volume of right hemisphere	8.34 (0.03)	8.31 (0.04)	8.30 (0.04)
Brainstem	22.10 (0.11)	22.18 (0.14)	22.03 (0.12)

Abbreviation: ADHD, attention-deficit/hyperactivity disorder.

[a] Means are based on estimated marginal means corrected for age, age squared, sex, and scanner location; for subcortical volumes, correction for total brain volume is also included.

[b] Unaffected siblings of participants with ADHD.

[c] Sum of total gray and white matter volumes.

Sensitivity Analyses

For volumes surviving multiple-testing correction, sensitivity analyses were conducted to examine potential effects of total brain volume, IQ, medication, scanner location, and sex distribution (eAppendix 2 in the Supplement).

Results

Descriptives

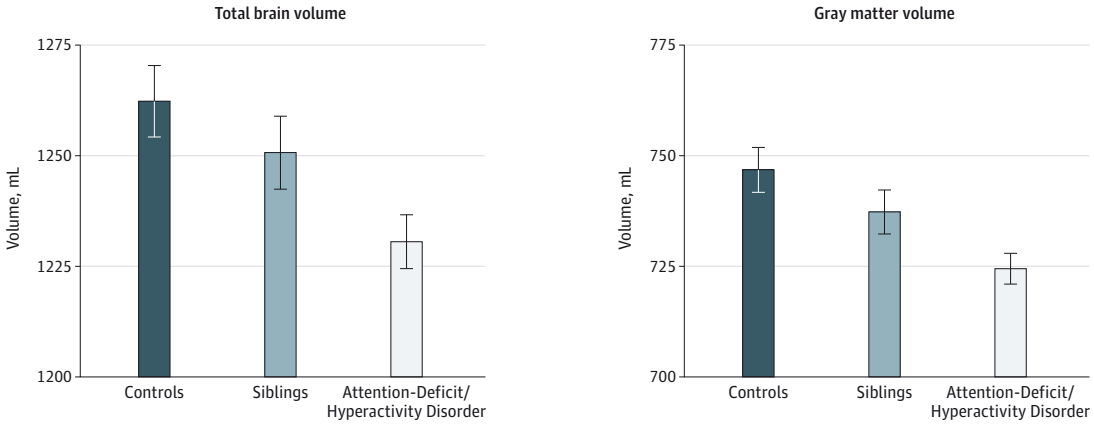
Mean brain volumes corrected for covariates and for raw data are shown in **Table 2** and eTable 3 in the Supplement, respectively. For mean volumes relating to the sensitivity analyses, see eTables 4 through 7 in the Supplement.

Comparisons Between Participants With ADHD and Control Individuals

Whole-Brain Volumes

Compared with control individuals, participants with ADHD had smaller total brain (β = −31.92; 95% CI, −52.69 to −11.16; P = .0027) and total gray matter (β = −22.51; 95% CI, −35.07 to −9.96; P = .0005) volumes. Total brain volume was 2.5% (32 mL) smaller and total gray matter volume was 3% (22 mL) smaller (**Figure 1**; **Table 3**). No significant group differences were found for total white matter volume (β = −10.10; 95% CI, −20.73 to 0.53; P = .06). None of the interactions between ADHD diagnosis and sex, age, and age squared on whole-brain volumes were significant (Table 3). Hence, differences between participants with ADHD and control individuals in total brain and gray matter volumes were stable across age and sex.

Figure 1. Mean Total Brain and Total Gray Matter Volumes in Participants With Attention-Deficit/Hyperactivity Disorder, Unaffected Siblings, and Control Individuals



Siblings indicate the unaffected siblings of participants with attention-deficit/hyperactivity disorder. The means are based on estimated marginal means corrected for age, age squared, sex, and scanner location. The error bars represent standard errors.

Subcortical Volumes

Main effects of binary ADHD diagnosis on subcortical volumes were nonsignificant (Table 3). However, the interaction between binary ADHD diagnosis and age on total, left, and right caudate and putamen volumes was significant (total: $P = .0004$; left: $P = .0003$; and right: $P = .0035$ for caudate) (total: $P = .0011$; left: $P < .0004$; and right: $P = .0018$ for putamen) (Table 3). Because results were similar for left, right, and total volumes, subsequent results are described only for total caudate and putamen volumes. Post hoc analyses revealed that older age was related to smaller total caudate ($P < .001$) and putamen ($P = .01$) volumes in control individuals but not in participants with ADHD (caudate: $P = .82$; putamen: $P = .16$). Dividing the sample into 3 roughly equal age bands (younger: ≤15 years; middle: >15-≤22 years, and older: >22 years) revealed that relative to control individuals, participants with ADHD had significantly smaller total caudate (0.33 mL; 3.9%; $P = .04$) and total putamen (0.36 mL; 3.3%; $P = .0061$) volumes in the younger group, had nonsignificantly larger total caudate volume (0.04 mL; 0.5%; $P = .67$) and significantly larger putamen volumes in the middle group (0.26 mL; 2.4%; $P = .02$), and had significantly larger total caudate (0.87 mL; 12.0%; $P = .0088$) and total putamen (0.89 mL; 8.6%; $P = .0038$) volumes in the older group (eTable 8 and the eFigure in the Supplement). No significant interaction effects were present for the other subcortical volumes.

Comparisons of Unaffected Siblings With Participants With ADHD and Control Individuals

Whole-Brain Volumes

Compared with participants with ADHD, unaffected siblings had a 1.6% (20 mL; $P = .04$) larger total brain volume and a 1.8% (13 mL; $P = .03$) larger total gray matter volume (Tables 2 and 3). Compared with control individuals, unaffected siblings had nonsignificantly smaller total brain (0.9%; 12 mL; $P = .32$) and total gray matter (1.3%; 10 mL; $P = .18$) volumes. Nonetheless, a linear trend was present in these volumes across the 3 groups (total brain: $P = .0018$; total gray matter: $P < .0003$; eAppendix 3 in the Supplement), indicating that unaffected siblings had total brain and gray matter volumes intermediate to participants with ADHD and control individuals.

Subcortical Volumes

The interaction between group membership unaffected siblings vs control individuals and age was a significant predictor of caudate and putamen volumes (total caudate: $P = .05$; total putamen: $P = .0086$); however, the interaction between group membership unaffected sibling vs ADHD and age was not significant (total caudate: $P = .15$; total putamen: $P = .48$) (**Figure 2**). This suggests that the unaffected siblings differed from control individuals but not from participants with ADHD. As was the case for participants with ADHD, age was not significantly related to caudate and putamen volumes in unaffected siblings (total caudate: $P = .09$; total putamen: $P = .47$).

Sensitivity Analyses

Findings were robust across sensitivity analyses (eAppendix 2 in the Supplement).

Discussion

We found that ADHD was linked to a 2.5% smaller total brain volume relative to control individuals, driven by a 3% smaller total gray matter volume. Moreover, ADHD was linked to alterations in caudate and putamen volumes, which were developmentally sensitive. Unaffected siblings showed a pattern of results intermediate to participants with ADHD and control individuals. In this large sample, neurobiological alterations associated with ADHD were neither sex nor hemisphere specific.

Globalized differences between participants with ADHD and control individuals in gray matter volume across the brain could indicate alterations to general mechanisms underlying

Table 3. Regression of Binary ADHD Diagnosis on Brain Volumes[a]

Region	ADHD		ADHD by Age		ADHD by Age Squared		ADHD by Sex	
	β (95% CI)[b]	*P* Value	β (95% CI)[b]	*P* Value	β (95% CI)[b]	*P* Value	β (95% CI)[b]	*P* Value
Total brain[c]	**−31.92 (−52.69 to −11.16)**	**.0027**[d]	NA	NA	NA	NA	NA	NA
Gray matter	**−22.51 (−35.07 to −9.96)**	**.0005**[d]	NA	NA	NA	NA	NA	NA
White matter	−10.10 (−20.73 to 0.53)	.06	NA	NA	NA	NA	NA	NA
Accumbens								
Total volume of left and right hemispheres summed	0.04 (0.10 to 0.07)	.0082	NA	NA	NA	NA	NA	NA
Volume of left hemisphere	0.01 (−0.01 to 0.03)	.45	0.01 (0.00 to 0.01)	.02	0.00 (0.00 to 0.00)	.03	NA	NA
Volume of right hemisphere	0.02 (0.01 to 0.04)	.0079	NA	NA	NA	NA	NA	NA
Amygdala								
Total volume of left and right hemispheres summed	−0.05 (−0.15 to 0.05)	.33	NA	NA	NA	NA	0.18 (0.04 to 0.32)	.01
Volume of left hemisphere	0.00 (−0.05 to 0.06)	.87	NA	NA	NA	NA	0.09 (0.01 to 0.17)	.04
Volume of right hemisphere	−0.06 (−0.12 to 0.01)	.08	NA	NA	NA	NA	0.03 (0.01 to 0.18)	.03
Caudate								
Total volume of left and right hemispheres summed	−0.10 (−0.29 to 0.09)	.31	**0.08 (0.03 to 0.12)**	**.0004**[d]	0.01 (0.00 to 0.02)	.03	NA	NA
Volume of left hemisphere	−0.05 (−0.14 to 0.05)	.33	**0.04 (0.02 to 0.06)**	**.0003**[d]	0.01 (0.00 to 0.01)	.04	NA	NA
Volume of right hemisphere	−0.04 (−0.14 to 0.06)	.45	**0.03 (0.01 to 0.06)**	**.0035**[e]	0.00 (0.00 to 0.01)	.05	NA	NA
Globus pallidus								
Total volume of left and right hemispheres summed	0.06 (0.00 to 0.12)	.05	0.02 (0.01 to 0.04)	.0073	NA	NA	NA	NA
Volume of left hemisphere	0.04 (0.01 to 0.07)	.01	0.01 (0.00 to 0.02)	.02	NA	NA	NA	NA
Volume of right hemisphere	0.02 (−0.01 to 0.05)	.17	0.01 (0.00 to 0.02)	.0081	NA	NA	NA	NA
Hippocampus								
Total volume of left and right hemispheres summed	0.00 (−0.15 to 0.14)	.96	NA	NA	NA	NA	NA	NA
Volume of left hemisphere	0.02 (−0.06 to 0.10)	.67	NA	NA	NA	NA	NA	NA
Volume of right hemisphere	−0.03 (−0.11 to 0.05)	.48	NA	NA	NA	NA	NA	NA
Putamen								
Total volume of left and right hemispheres summed	0.18 (0.00 to 0.36)	.04	**0.09 (0.04 to 0.15)**	**.0011**[d]	NA	NA	NA	NA
Volume of left hemisphere	0.09 (0.00 to 0.17)	.05	**0.05 (0.02 to 0.07)**	**.0004**[d]	NA	NA	NA	NA
Volume of right hemisphere	0.10 (0.00 to 0.20)	.06	**0.04 (0.02 to 0.07)**	**.0018**[d]	NA	NA	NA	NA
Thalamus								
Total volume of left and right hemispheres summed	0.08 (−0.13 to 0.29)	.44	NA	NA	NA	NA	NA	NA
Volume of left hemisphere	0.04 (−0.08 to 0.15)	.51	NA	NA	NA	NA	NA	NA
Volume of right hemisphere	0.04 (−0.06 to 0.14)	.45	NA	NA	NA	NA	NA	NA
Brainstem	0.11 (−0.23 to 0.44)	.54	NA	NA	NA	NA	NA	NA

Abbreviations: ADHD, attention-deficit/hyperactivity disorder; NA, not applicable (interaction was dropped from the final model because it did not reach nominal significance [$P < .05$]).

[a] Results from the final regression model examining associations between binary ADHD diagnosis (ADHD vs control) and brain volumes. Boldface indicates results surviving multiple-testing correction.

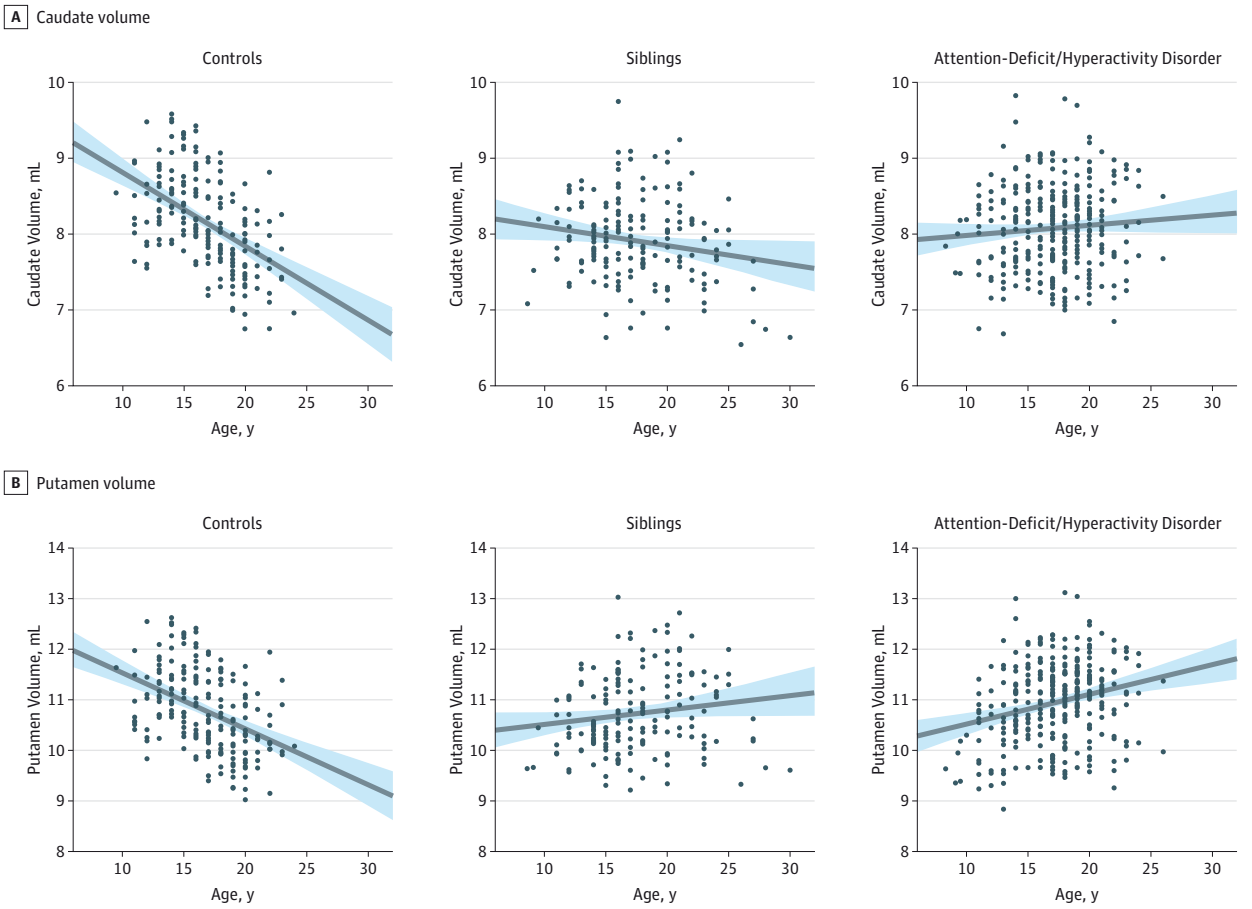
[b] For main effects, β (unstandardized regression coefficient) is equal to the difference in mean brain volumes (in milliliters) between the diagnostic groups adjusted for covariates in the model (eg, β = −31.92 denotes that participants with ADHD had a 31.9-mL-smaller total brain volume than control individuals). The main effect of ADHD was never dropped from the model. Included covariates were age, age squared, sex, and scanner location; for subcortical volumes, covariates also included total brain volume.

[c] Sum of total gray and white matter volumes.

[d] Indicates *P* value remains significant following multiple testing (effective number–adjusted *P* value threshold of .003).

[e] Although the ADHD-by-age interaction on right caudate volume just failed to meet the multiple-testing–corrected threshold, plotting the data revealed that the pattern of results was highly similar for left, right, and total caudate volumes.

Figure 2. Group-by-Age Interaction on Caudate Nucleus Volume (A) and Putamen Volume (B)



Siblings indicate the unaffected siblings of participants with attention-deficit/hyperactivity disorder. The same pattern of results was found for total, left, and right volumes. The lines represent the regression lines, with the shading representing the 95% CIs.

normal brain development such as those concerning neuron number (eg, neurogenesis and naturally occurring neuron death) and neuronal migration.[37,38] This is in line with results from genome-wide association and bioinformatics analyses that implicated abnormal neuronal migration and directed neurite outgrowth in ADHD.[39,40] Such mechanisms could be probed further through studying post-mortem brain tissue or animal models. Smaller total brain and gray matter volumes in participants with ADHD, relative to control individuals, were found at different ages, consistent with previous research that related smaller total brain size to ADHD in children and adolescents,[2,4] as well as in adults.[41]

The caudate and putamen play important roles in several basal ganglia-thalamocortical circuits[42] involved in motor control and learning, as well as selecting and enabling cognitive, executive, and emotional programs.[43] Several of these processes (eg, motor functions, reward processing, and cognitive and attentional control) are impaired in ADHD.[9,26] We found that older age was significantly related to smaller caudate and putamen volumes in control individuals, in line with previous studies in typically developing individuals reporting a decline in basal ganglia volumes across childhood development.[30,44] In contrast, in participants with ADHD, age was not significantly related to caudate and putamen volumes. As a result, participants with ADHD had smaller caudate and putamen volumes than control individuals in childhood and early adolescence (aged 8-15 years); these differences diminished in midadolescence to late adolescence. Previous studies also found smaller, or different-shaped, basal ganglia volumes in ADHD[5-8,45,46]; further, the different developmental trajectories in participants with ADHD and control individuals may provide a potential explanation for previous studies suggesting that alterations in basal ganglia volumes in ADHD normalize with age.[2,7,8] By early adulthood (aged 22-30 years), ADHD was related to larger caudate and putamen volumes relative to control individuals, inconsistent with previous studies in adults with ADHD showing smaller basal ganglia volumes[14,47,48] or no differences.[49-51] Most adult studies included older participants than the current study, potentially explaining this inconsistency. Delays in developmental trajectories of the caudate and putamen[30,44] in ADHD may potentially explain why larger volumes observed in the current study are no longer observed in studies on older samples. Alternatively, the larger volumes in early adulthood may repre-

sent overcompensatory mechanisms or could be related to reduced neuronal pruning. In a longitudinal study of children and adolescents (aged 4-19 years), participants with ADHD had smaller basal ganglia volumes and total surface areas compared with control participants; however, inconsistent with our results, these differences were fixed over time.[52] Only in a small region involved in reward processing, the ventral striatal surface area, did developmental trajectories differ between participants with ADHD and control participants.[52] Hence, a next step to extend the present findings would be to study the mechanisms underlying the age-by-diagnosis interaction effects in caudate and putamen volumes in a longitudinal design and to apply complementary methods in the same participants (eg, surface area and voxel-based morphometry) to reveal findings that may be undetectable by the volumetric technique used here. Overall, our results were consistent with the hypothesis that subcortical alterations are key in the pathophysiology of ADHD.[9]

Findings in the unaffected siblings provided evidence that total brain, gray matter, caudate, and putamen volumes are linked to familial risk for ADHD. As familial underpinnings of ADHD are thought to be largely genetic,[17,53] it is plausible that genetic mechanisms may underlie the reported ADHD-brain associations, creating possible new targets for molecular genetic research. Given the small percentage of volume difference and additional challenges added by age-dependent effects in the caudate and putamen, multisite international consortia comprising large data sets from different age groups are necessary in such gene-identification efforts.

Although effect sizes were small, effects were robust across sensitivity analyses. The only exception was that the intermediate position of unaffected siblings for total brain and gray matter volumes was carried by only 1 of our scanner locations (Nijmegen). Hence, familiality with regard to total brain and gray matter volumes should be interpreted with some caution. When IQ was included as a covariate, alterations in total brain and gray matter volumes were attenuated but remained. There is an active debate whether studies on ADHD should adjust for IQ group differences[54] because IQ is likely to share meaningful variance with ADHD.[55] Therefore, including IQ as a covariate may lead to overcorrection. Hence, we report findings with and without adjustment for IQ. Two cross-sectional meta-analyses and a review, based on binary medication use or percentage treated, concluded that ADHD medication may decrease structural brain alterations in participants with ADHD.[7,8,56] In contrast, a longitudinal study found no significant association between using/not using medication or the proportion of time taking medication and developmental trajectories of basal ganglia.[52] The present study is in line with the latter results, as we found no association between cumulative medication intake and brain volumes in participants with ADHD. Hence, our findings do not support a normalizing effect of stimulant medication on structural brain alterations. Nonetheless, medication effects need to be explored more fully longitudinally before drawing firm conclusions (eg, through studying age at medication initiation, long- vs short-acting stimulants, and stimulants vs nonstimulants).

A major innovation of this study was the inclusion of unaffected siblings, allowing the study of familial effects, the use of a large sample, and the use of a more precise measure of medication (cumulative medication intake) for which we had complete data. The present sample followed a naturalistic design, allowing greater generalization to families with ADHD as a whole, in contrast to the common approach to use a matched-sample design. Nonetheless, our findings were also robust when groups were matched for sex. Further, our sample included adolescents and young adults, which are an underrepresented age group because most studies have focused either on child or adult samples. Therefore, the current study contributes to fill several gaps in the literature and helps to investigate the influence of age on brain volumetric alterations in ADHD.

Naturally, this study also comes with limitations. First, the current study was cross sectional. Longitudinal follow-up is underway. Second, because most of this sample was adolescent, age-dependent results in early adulthood should be interpreted with some caution. Third, although we had clear reasons to focus on total and subcortical volumes, there are other relevant brain regions such as the cerebellum and frontal areas.[2,4,9] Finally, the FIRST algorithm used to segment the subcortical volumes comes with limitations[29]; nonetheless, it is more objective than manual segmentation methods.

Conclusions

Our cross-sectional findings point to the relevance of different trajectories of brain development in ADHD vs control participants that are influenced by familial factors. Our results also support the role of subcortical basal ganglia alterations as key to understanding the pathophysiology of ADHD.

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