ORIGINAL ARTICLE

Quantitative Brain Magnetic Resonance Imaging in Girls With Attention-Deficit/Hyperactivity Disorder

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Background: Anatomic studies of boys with attention-deficit/hyperactivity disorder (ADHD) have detected decreased volumes in total and frontal brain, basal ganglia, and cerebellar vermis. We tested these findings in a sample of girls with ADHD.

Methods: Anatomic brain magnetic resonance images from 50 girls with ADHD, of severity comparable with that in previously studied boys, and 50 healthy female control subjects, aged 5 to 15 years, were obtained with a 1.5-T scanner with contiguous 2-mm coronal slices and 1.5-mm axial slices. We measured volumes of total cerebrum, frontal lobes, caudate nucleus, globus pallidus, cerebellum, and cerebellar vermis. Behavioral measures included structured psychiatric interviews, parent and teacher ratings, and the Wechsler vocabulary and block design subtests.

Results: Total brain volume was smaller in girls with ADHD than in control subjects (effect size, 0.40; $P = .05$). As in our previous study in boys with ADHD, girls with ADHD had significantly smaller volumes in the posterior-inferior cerebellar vermis (lobules VIII-X; effect size, 0.54; $P = .04$), even when adjusted for total cerebral volume and vocabulary score. Patients and controls did not differ in asymmetry in any region. Morphometric differences correlated significantly with several ratings of ADHD severity and were not predicted by past or present stimulant drug exposure.

Conclusions: These results confirm previous findings for boys in the posterior-inferior lobules of the cerebellar vermis. The influence of the cerebellar vermis on prefrontal and striatal circuitry should be explored.

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INVESTIGATIONS of attention-deficit/hyperactivity disorder (ADHD) with the use of magnetic resonance (MR) imaging implicate dysfunction of prefrontal cortical-striatal-pallidal circuitry[1-6] and of the cerebellar vermis.[7,8] Although there has been substantial convergence of results,[9] some inconsistencies remain. For example, most studies have reported decreased caudate volume in ADHD, but laterality has varied,[2,3,10,11] and one study found larger caudate area in adolescents with ADHD.[11]

Of the patients described in the anatomic studies cited above, 92% were male, reflecting in part the male preponderance in the disorder.[12] Combining males and females (as has sometimes been done[10,11]) is problematic because there are robust (approximately 10%) male-female differences in overall brain volume. Most regional brain volumes are also approximately 10% smaller in females, but there are important exceptions, such as the caudate nucleus, which is proportionately larger in females.[13,14] Differences in caudate nucleus volume or asymmetry have been found by every group that has examined ADHD samples,[2,3,10,11] making this sexual dimorphism particularly interesting in a study of girls with ADHD.

Studying girls with ADHD raises questions regarding severity and diagnostic validity,[15,16] which we addressed by recruiting girls with ADHD in whom severity and phenomenologic characteristics were comparable with those of our previously studied boys with ADHD.[17] We now report, to our knowledge, the first anatomic brain MR imaging study of female patients with ADHD. Our hypothesis was that prefrontal-striatal-pallidal and cerebellar abnormalities similar to those noted in boys with ADHD[2,7] would be observed in girls.

RESULTS

SUBJECTS

Table 1 presents patient and control characteristics. There were no significant group differences in age, height, weight, Tanner pubertal stage, handedness, or WISC-R

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SUBJECTS AND METHODS

Subjects With ADHD

Girls with combined-type ADHD (meeting both hyperactivity-impulsivity and inattention criteria) (n=50; mean age, 9.7 years; range, 5.3-16.0 years) were recruited for National Institute of Mental Health ADHD drug treatment studies[17] within a specialized day program (n=36) or specifically for this imaging study (n=14). Inclusion criteria were hyperactive, inattentive, and impulsive behaviors that were impairing in at least 2 settings (home, school, or day program), and a Conners' Teacher Hyperactivity rating greater than 2 SDs above age mean.[18] The *DSM-IV*[19] diagnosis of ADHD was based on the Diagnostic Interview for Children and Adolescents,[20] with a parent and separately with the patient if she was older than 9 years; Conners Teacher Rating Scale[18]; and the Teacher Report Form.[21] The Wechsler Intelligence Scale for Children–Revised (WISC-R)[22] was used for 32 patients and the Wechsler Intelligence Scale for Children–Third Edition (WISC-III)[23] for 17 (1 missing). To allow comparison with our previous studies of boys, WISC-III full-scale, vocabulary, and block design subscale scores were converted to WISC-R equivalents on the basis of published data.[24-27]

Thirty-five patients (70%) had been previously treated with stimulants, as determined from parental reports. Measures of stimulant drug exposure were lifetime exposure (yes or no), current daily dose in methylphenidate hydrochloride equivalents at the time of scanning (1 mg of amphetamine sulfate=2 mg of methylphenidate hydrochloride), and estimated cumulative lifetime methylphenidate equivalent dose calculated from parental reports.

Exclusion criteria were a full-scale WISC-R IQ less than 80, evidence of medical or neurologic disorders on examination or by history, Tourette disorder, or any other Axis I psychiatric disorder requiring treatment with medication. Thirteen subjects met lifetime criteria for mild anxiety or mood disorders, and 5 had reading disorder confirmed by discrepancy ($z>1.65$) between Woodcock-Johnson Psychoeducational Test Battery and WISC-R standard scores.[28,29] Other demographic and diagnostic characteristics are included in **Table 1**.

Normal Control Subjects

Unrelated healthy girls (n=50; mean age, 10.0 years; range, 4.7-15.9 years) were recruited from the community. Screening included telephone interview, parent and teacher rating scales, and in-person assessment, which included physical and neurologic examinations, the 12 handedness items from the Revised Physical and Neurological Examination for Subtle Signs,[31] structured psychiatric interview using the Diagnostic Interview for Children and Adolescents,[20] Child Behavior Checklist,[21] the WISC-R (n=24) or WISC-III (n=16) vocabulary and block design tests, and Wide Range Achievement Test, Revised Edition.[32] Family psychiatric history for first- and second-degree relatives was ascertained from 1 or both parents. Individuals with physical, neurologic, 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 4 candidates were screened for every 1 accepted, with the most common exclusions being family psychiatric history and possible psychiatric diagnosis based on structured interview or teacher report.

Assent from the child and written consent from the parents were obtained. The National Institute of Mental Health institutional review board approved the protocol.

BEHAVIORAL MEASURES

Patients underwent a psychoeducational evaluation (full WISC-R and Woodcock-Johnson Psychoeducational Test Battery–Revised) by a clinical psychologist (Barbara Keller, PhD) during medication-free baseline. The hyperactivity factor, extracted from the Conners' Parent and Teacher Rating Scales,[18,33] was averaged from the 3 weekly placebo ratings, as were physician ratings on the Children's Global Assessment Scale[34] and Clinical Global Impressions scale for severity of illness.[35] Baseline ratings were substituted for patients who did not participate in medication trials (n=14). Parents also provided ratings on the Child Behavior Checklist.[21]

MR IMAGE ACQUISITION

All subjects were studied on the same 1.5-T scanner (Signa; General Electric Co, Milwaukee, Wis). T1-weighted images with contiguous 1.5-mm slices in the axial plane and 2.0-mm slices in the coronal plane were obtained by means of 3-dimensional spoiled gradient recalled echo in the steady state. Imaging variables 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 standardize head placement. A third capsule was taped to the lateral aspect of the left inferior orbital ridge. The capsules are readily identifiable on MR images 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

vocabulary subscale score. Girls with ADHD had significantly lower block design subscale and estimated full-scale[30] scores than control subjects.

Roughly one third of the sample (n=15) had never been exposed to psychotropic medications, including stimulants, before MR imaging. At the time of imaging, the remaining subjects were taking an average of 17.4±16.7 mg of methylphenidate equivalents (range, 10-60 mg/d). We estimated that their average cumulative lifetime exposure was 9.9±11.0 g of methylphenidate equivalents (range, 0.05-37.0 g). The medications previously used were methylphenidate hydrochloride (n=33) and dextroamphetamine sulfate (n=2).

MORPHOMETRY

As shown in **Table 2**, TCV was smaller in girls with ADHD (effect size, d=0.40, analysis of variance $P=.047$), although this difference was not significant after analysis of covariance adjusting for vocabulary subscale score (adjusted d=0.32, $P=.12$). After adjustment for TCV and vocabulary score, girls with ADHD had significantly smaller

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guide light passed through each capsule. A sagittal localizing plane was acquired, and from this a multiecho axial series was obtained. If all 3 capsules were not contained within a single axial slice, 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. Four healthy control subjects (aged 5, 7, 8, and 11 years) and 3 subjects with ADHD (aged 5, 6, and 10 years) were unable to complete the scan because of excessive anxiety or sensitivity to noise. No sedation was used for either group.

IMAGE ANALYSIS

Clinical Interpretation

T2-weighted images were also obtained for evaluation by a clinical neuroradiologist. A 1.7-cm cystic mass was found in the left cerebellar peduncle–pons of a 9-year-old girl with ADHD. A presumptive diagnosis of pilocytic astrocytoma led to her exclusion from this study and neurosurgical referral for eventual excision. No other gross abnormalities were reported. All raters were blind to subject characteristics.

Cerebrum and Cerebellar Quantification

An automated technique was used to quantify white and gray matter in the cerebrum and to quantify the cerebellum by combining an artificial neural network to classify tissues based on voxel intensity with nonlinear registration to a template brain for which tissue regions had been manually defined.[36,37] Total cerebral volume was defined as the algebraic sum of all gray-matter pixels and white-matter pixels, excluding the cerebellum and brainstem. Intraclass correlation coefficients for subjects rescanned within several hours were 0.98 for total cerebral volume (TCV) and 0.99 for cerebellum.

Subcortical Gray Matter

The caudate (head and body) was manually outlined from coronal slices on a computer workstation (Macintosh II FX; Apple Computers Inc, Cupertino, Calif) with the use of NIH Image (version 1.55).[38] Since the sums of areas from the odd- and even-numbered slices correlated highly with the sum obtained by adding all slices for 118 scans ($r>0.97$, $P<.001$; unpublished data), the same method of outlining every other slice was used.[2] Intrarater and interrater intraclass correlation coefficients were 0.87 and 0.88, respectively. Globus pallidus, bounded medially by internal capsule and laterally by putamen, was also measured on coronal sections but included every slice on which the structure was found. This measure does not distinguish internal and external segments. Intrarater (intraclass correlation coefficient, 0.85) and interrater (0.82) reliabilities were acceptable.

Cerebellar Vermis

Volumetric measures of the posterior-inferior vermal lobules (VIII-X) and of the entire vermis were hand traced in all 3 image planes by means of morphometric software (Display; McConnell Brain Imaging Centre, McGill University, Montreal, Quebec)[39] as described previously.[7,40] Interrater and intrarater intraclass correlation coefficients were 0.95 and 0.97, respectively.

STATISTICAL ANALYSIS

Although values of bilateral structures are reported for completeness, the structures of interest in this replication study were limited to regions that differed significantly in our studies of boys with ADHD.[2,7] While the same methods and raters were used for subcortical and vermal measures, the automated algorithms we used previously to quantify TCV and cerebellum[41] are no longer in use and do not function on current computer hardware.

We report unadjusted analyses of variance with diagnosis as the between-group factor, as well as analyses of covariance adjusted for TCV and Wechsler vocabulary score and corresponding adjusted effect sizes. As in our study of boys, the vocabulary subscale score was selected for analyses of covariance because it is the single best predictor of full-scale IQ.[23] We chose to control for group differences in intelligence, since there are moderate intercorrelations among caseness, TCV, and vocabulary score. Meehl[42] challenged the practice of controlling "nuisance variables" such as social class or IQ that may be inexorably linked to the phenomenon under study. Differences in IQ may be intrinsic to ADHD,[43] but the relationship between IQ and regional brain volume is statistically equivalent in all brain regions we have examined to date (unpublished data), and we believe a conservative approach is warranted to focus on the most specific anatomic correlates of ADHD.

The relations between morphometric measures that differed significantly between groups and continuous behavioral measures were examined with Pearson correlations. Possible effects of medication history were assessed by stepwise multiple regression. All statistical analyses were performed with SAS for Windows software (SAS Institute Inc, Cary, NC).[44] Two-tailed significance levels were used at $P\leq.05$.

volumes in the posterior-inferior lobules (lobules VIII-X) of the cerebellar vermis (d=0.54). None of the 5 other regions previously reported in boys with ADHD (right frontal, right caudate, right globus pallidus, left cerebellum, or total vermis) remained significant after covariance.

ANATOMIC-BEHAVIOR CORRELATIONS

Within the ADHD group, TCV correlated with estimated full-scale IQ score (n=40; $r=0.36$, $P=.01$) and with Child Behavior Checklist attention problems score (n=49; $r=-0.29$, $P=.04$). Posterior-inferior vermal volume correlated significantly with Global Assessment Scale score (n=49; $r=0.35$, $P=.01$) and with Child Behavior Checklist anxiety-depression score (n=48; $r=-0.35$, $P=.01$). All significant correlations were in the predicted direction, ie, smaller volumes were associated with greater severity.

Within the normal control group, posterior-inferior vermal volume correlated significantly with estimated full-scale IQ score (n=41; $r=0.41$, $P=.008$) and with vocabulary subscale score (n=41; $r=0.46$, $P=.002$).

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One third of the sample of patients had never been exposed to psychiatric medications before MR imaging. When TCV and severity of ADHD symptoms were controlled for, none of the measures of stimulant drug exposure (lifetime exposure, approximate lifetime cumulative dose, or current dose) were significantly related to regional brain volumes ($P>.20$).

Table 1. Characteristics of Girls With ADHD and Control Subjects*

Characteristics	ADHD (n = 50)	Controls (n = 50)	*P*
Age, y	9.7 (2.6)	10.0 (2.5)	.62
Height, cm	136.2 (14.6)	140.4 (15.9)	.18
Weight, kg	33.2 (11.4)	35.2 (11.6)	.41
Tanner stage	1.9 (1.3)	2.0 (1.1)	.85
Handedness, % right-handed†	92	92	>.99
WISC-R subscale scores			
Vocabulary	11.3 (2.9)	12.4 (2.8)	.08
Block design	10.6 (3.0)	12.2 (4.0)	.03
Estimated full-scale IQ‡	105.5 (15.1)	113.3 (16.8)	.02
DSM-IV diagnoses			
ADHD, combined type	50	. . .	. . .
Conduct disorder	1	. . .	. . .
Oppositional defiant disorder	23	. . .	. . .
Learning disorders	5	. . .	. . .
Anxiety/mood disorders	13	. . .	. . .
Enuresis	8	. . .	. . .

*ADHD indicates attention-deficit/hyperactivity disorder; WISC-R, Wechsler Intelligence Scale for Children, Revised; and ellipses, not applicable. P values are for 2-tailed t tests except handedness. Values are mean (SD) unless otherwise stated.

†P value for χ^2_1.

‡Short-form full-scale IQ using WISC-R vocabulary and block design subscales.[30]

COMMENT

In this comprehensive brain morphometric analysis of girls with ADHD, we found a between-group difference in TCV that did not remain significant when Wechsler vocabulary score was covaried. For all other analyses, we used analysis of covariance adjusting for TCV and vocabulary score to focus on regions that are most selectively affected in girls with ADHD. Analysis of covariance demonstrated selectively smaller posterior-inferior lobules of the cerebellar vermis. We did not confirm previously reported smaller volumes in right frontal lobe, right caudate, right globus pallidus, left cerebellum, or cerebellar vermis in toto.[2,7]

Our finding in the posterior-inferior cerebellar vermis (lobules VIII-X in the newly standardized cerebellar nomenclature)[45] of girls with ADHD replicates our previous report in boys with ADHD.[7] In that study, we found that the entire vermis was also smaller, but this was primarily accounted for by a smaller posterior-inferior vermis. The finding of a smaller midsagittal area in the posterior-inferior vermis was replicated in an independent sample of boys with ADHD, which also confirmed that the posterior-superior lobules (VI-VII) did not differ from those of control subjects.[8]

Little is known about the nonvestibular functions of the posterior-inferior vermis. Forming part of the phylogenetically ancient paleocerebellum, the vermis

Table 2. Cerebral Volumes, With Adjustment for Total Cerebral Volume and Vocabulary, for Girls With ADHD (Present Study) and Summary Unadjusted and Adjusted Statistics for Previously Studied Boys With ADHD*

	Girls With ADHD vs Normal Control Subjects									Comparison Boys With ADHD vs Normal Control Subjects†					
	Normal Control Girls		Girls w/ ADHD		ANOVA		ANCOVA,			ANOVA		ANCOVA,			
	Mean (SD)	No.	Mean (SD)	No.	F	*P*	*P*	d	95% CI	F	*P*	*P*	*df*	d	95% CI
Total cerebral volume‡	1033.3 (102.7)	50	992.6 (99.9)	50	4.03	**.05**	.12	0.32	(–0.11-0.75)	5.69	**.02**	.13	1,109	0.29	(–0.10-0.67)
Frontal right§	171.3 (17.8)	50	164.5 (18.7)	50	3.44	.07	.72	–0.08	(–0.51-0.34)	9.74	**.002**	.15	1,105	0.27	(–0.12-0.67)
Frontal left§	173.6 (17.0)	50	165.3 (18.8)	50	5.49	**.02**	.09	0.37	(–0.06-0.80)	0.89	.35	.32	1,105	–0.24	(–0.63-0.16)
Caudate right	4.82 (0.62)	50	4.56 (0.59)	50	4.71	**.03**	.07	0.41	(–0.02-0.84)	4.73	**.03**	.48	1,109	0.19	(–0.26-0.51)
Caudate left	4.88 (0.55)	50	4.59 (0.55)	50	7.09	**.009**	**.03**	**0.50**	(0.06-0.93)	1.30	.26	.66	1,109	–0.06	(–0.44-0.33)
Globus pallidus right	1.19 (0.15)	49	1.16 (0.14)	50	0.89	.34	.66	0.07	(–0.35-0.50)	13.91	**<.001**	**<.001**	1,109	**0.75**	(0.34-1.16)
Globus pallidus left	1.21 (0.18)	49	1.14 (0.16)	50	4.45	**.04**	.35	0.18	(–0.24-0.61)	2.48	.12	.17	1,109	0.27	(–0.12-0.65)
Cerebellum right‡	62.0 (6.1)	50	59.4 (5.9)	50	4.99	**.03**	.69	–0.06	(–0.48-0.36)	2.76	.10	.40	1,109	0.17	(–0.22-0.55)
Cerebellum left‡	58.9 (5.7)	50	57.0 (5.5)	50	3.10	.08	.87	0.07	(–0.35-0.49)	10.62	**.001**	**.03**	1,109	**0.42**	(0.03-0.81)
Vermis	5.89 (1.1)	49	5.52 (1.2)	49	2.59	.11	.81	–0.05	(–0.48-0.38)	4.34	**<.001**	**.03**	1,90	**0.54**	(0.10-0.97)
Posterior-inferior vermis	2.01 (0.44)	50	1.74 (0.44)	49	6.98	**<.001**	**.04**	**0.54**	(0.10-0.98)	4.25	**<.001**	**.001**	1,90	**0.66**	(0.22-1.11)

*ADHD indicates attention-deficit/hyperactivity disorder; ANOVA, analysis of variance; ANCOVA, analysis of covariance adjusting for total cerebral volume and Wechsler vocabulary score, except total cerebral volume is adjusted only for vocabulary score; d, effect size adjusted for total cerebral volume and vocabulary score; and CI, confidence interval. All P values are 2-tailed. Significant values are in boldface. Regions in italics were significant in previous studies in boys. Other regions are included for completeness.

†Previously studied boys (n = 57 with ADHD, n = 55 normal controls) from Castellanos et al,[2] except vermis and posterior-inferior vermis (n = 46/group)(from Berquin et al[7]).

‡Total cerebral, cerebellar, and frontal volumes obtained by means of a semiautomated method for boys and a fully automated method for girls. See "Subjects and Methods" section.

§Frontal volumes include gray and white pixels; boundaries defined arbitrarily for boys at genu of corpus callosum and anatomically for girls.

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has come to mean "midline cerebellum," although, as Schmahmann and colleagues[45] have pointed out, there is no true vermis in the anterior lobe. The anterior midline cerebellum (lobes I-V) is often indistinct from overlying hemispheric cortex, and its lateral boundaries vary depending on the section and definition of lateral boundaries.[45] In contrast, the posterior vermis is almost entirely isolated from the adjacent cerebellar hemispheres.[45]

The output nuclei for medial cerebellum, including the vermis, are the paired fastigial nuclei. Vermal or fastigial stimulation evokes short-latency responses in limbic structures,[46] which can modulate seizure activity in the medial temporal lobe.[47] Vermal lesions profoundly ameliorate intense affective states such as rage or fear in animals,[48-50] and similar robust effects were reported in early studies using long-term implanted electrodes in vermis in humans with a range of severe behavioral or psychiatric disorders.[51,52]

The posterior vermis includes the central lobules (VI-VII), which are involved in oculomotor control.[53] Lobules I, IX, and X form the vestibulocerebellum, because of their massive direct and indirect connections to the vestibular system. Patients with lesions in the nearby posterior vermal lobe (lobules VI, crus I, crus II, and VIIB) can present with what has been termed *cerebellar cognitive affective syndrome*.[54] Impairments in executive function, difficulties with visuospatial cognition, and memory or language deficits characterize the syndrome.[55] Affective changes, which can include flattening of affect or disinhibited, impulsive, immature, or inappropriate behavior, are most common when lesions involve the vermis. None of our subjects had brain lesions, except for one who had a cerebellar tumor and was not included in further analyses. However, as previously found in adults with mood disorders,[56] the subgroup of our patients who had a lifetime history of comorbid unipolar mood and/or anxiety disorders (n=13) had the smallest posterior-inferior vermis volumes (1.93±0.45 mL). This relationship was exemplified by the significant partial correlation (that remained significant with TCV and vocabulary score partialed) between posterior-inferior vermal volume and Child Behavior Checklist anxiety-depression score (n=48; $r=-0.45$, $P=.002$). However, the between-group difference in posterior-inferior vermis remained significant even when the patients with comorbid mood or anxiety disorders were removed or when we controlled statistically for lifetime history of mood and/or anxiety disorders, demonstrating that our finding was not merely driven by the affectively comorbid group.

Before these results are considered further, the limitations of this study should be noted. Our subjects were highly screened to match previously studied boys with combined-type ADHD in impairment and symptomatic severity.[17] Accordingly, our results may not be generalizable to community-based samples of girls with ADHD, who may differ from affected boys in symptomatic severity and in ADHD typology.[16]

As is typical in studies of ADHD, our patient group had extensive comorbidity, particularly for oppositional defiant disorder. However, supplementary analyses limited to the 26 girls with ADHD who did not have other disruptive behavior disorders confirmed our findings despite the smaller sample (data not shown).

Before proceeding with this study, we confirmed that our sample of girls with ADHD was comparable to our previously studied boys on a range of categorical and dimensional measures,[17] including oculomotor executive function tasks.[57] However, we did not study girls and boys contemporaneously, and the use of historical controls is potentially problematic. Besides possible subject-based cohort effects, we encountered a technological cohort effect. The semiautomated quantification techniques we used in our previous studies[2,41] are now obsolete. Comparisons between our previous study in boys with ADHD and the current study are least tenable for the frontal lobe measure. Previously, we quantified the anterior pole by setting the posterior boundary at the anterior-most point of the corpus callosum.[2] Our current measure is more than twice as large and comprises the entire frontal lobe. Thus, the question of whether prefrontal brain volumes are decreased in girls with ADHD remains unresolved until improved quantification algorithms are available that can then be applied to both sexes.

We continued to use the same manual techniques for subcortical and subcerebellar structures, but "rater drift" poses a potential problem here as well. Accordingly, summary data for boys with ADHD are provided for comparison, but conclusions about sex differences in ADHD, particularly with respect to asymmetry indexes, must remain tentative until verified in contemporaneously collected and analyzed longitudinal scans, which are in progress.

In the meantime, we believe that, although we did not replicate the specific finding of a smaller right caudate in ADHD, our data still support the hypothesis that the caudate is etiologically implicated in ADHD. Most anatomic studies have detected volume differences in the left caudate,[1,3,10] rather than in the right.[2,11] In boys with ADHD we found a difference in right-left caudate asymmetry.[2] By contrast, girls with ADHD did not differ in asymmetry, but differed significantly in left caudate volume considered alone or in total caudate volume. Our current control girls were significantly less lateralized in caudate than our control boys[2] ($F_{1,94}=6.49$; $P=.01$), consistent with several adult normative samples showing less lateralization for women.[58-60] The caudate was also proportionately larger in our present sample of control girls than in our previously studied control boys ($t_{96}=2.96$; $P=.004$). These normative sex differences suggest that the caudate nucleus as a whole, rather than just the left caudate, is preferentially smaller in girls with ADHD. Other data supporting a role for the caudate nucleus in ADHD have been discussed extensively elsewhere.[2,5,61-67]

Longitudinal studies are also needed to definitively examine the potentially confounding role of previous medication exposure. Nevertheless, this is the first anatomic neuroimaging study in ADHD to include a sizable subgroup of medication-naive patients (n=15). Though causality cannot be addressed in a naturalistic cross-sectional study of referred patients, we did not detect any evidence that our findings are related to medication history or current stimulant treatment.

Our finding of 4% decreased TCV in girls with ADHD is consistent with previous studies, which have used a

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range of quantitative approaches.[1-3,68] Using an automated segmentation algorithm, we found similar volumetric decreases in both white matter (d=0.40) and gray matter (d=0.35) compartments. The volumes for all 4 major lobes were proportionately decreased in girls with ADHD (data not presented).

Significant decrease in posterior-inferior vermal volume was also detected in pediatric subjects with childhood-onset schizophrenia.[40] The potential relevance of the posterior-inferior vermis for dopaminergically related psychiatric disorders such as ADHD and schizophrenia has been highlighted by the selective finding of dopamine transporter immunoreactivity in ventral cerebellar vermis, particularly in lobules VIII to X, and to a lesser extent in lobules I to II, in nonhuman primates.[69] Dopamine transporter immunoreactivity was not present in cerebellar hemispheres. The function and origin of these presumably dopaminergic fibers are not known, but they may form the afferent portion of a cerebellar circuit that is known to influence midbrain monoaminergic systems.[70,71] Human functional brain imaging studies have documented the sensitivity of the cerebellum, and particularly the vermis, to the effects of psychostimulants.[72-75]

Schmahmann[76] proposed that cerebellar dysfunction produces not only motor dysmetria but also "dysmetria of thought" in a range of neuropsychiatric disorders. Our cerebellar finding suggests that dysmetria of thought should be further explored in ADHD. The selective and significant decreased volume in girls of one of the candidate brain regions previously hypothesized to be involved in the pathophysiology of ADHD, ie, the posterior-inferior lobules of the vermis, extends studies in boys with ADHD and focuses our attention on this long-neglected region. The cerebellar abnormality does not appear to reflect stimulant drug exposure or comorbid conditions. Ongoing studies are extending measurements to other cerebellar regions and to further explore abnormalities of cerebellar connectivity in ADHD.

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