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 and of the cerebellar vermis. Although there has been substantial convergence of results, some inconsistencies remain. For example, most studies have reported decreased caudate volume in ADHD, but laterality has varied, and one study found larger caudate area in adolescents with ADHD.

Of the patients described in the anatomic studies cited above, 92% were male, reflecting in part the male preponderance in the disorder. Combining males and females (as has sometimes been done), making this sexual dimorphism particularly interesting in a study of girls with ADHD.

Studying girls with ADHD raises questions regarding severity and diagnostic validity, 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. 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 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.
vocabulary subscale score. Girls with ADHD had significantly lower block design subscale and estimated full-scale \(^2\) 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
guide light passed through each capsule. A sagittal local-
izing 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 sen-
sitivity 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 re-
feral for eventual excision. No other gross abnormalities
were reported. All raters were blind to subject character-
istics.

**Cerebrum and Cerebellar Quantification**

An automated technique was used to quantify white and
gray matter in the cerebrum and to quantify the cerebel-
um by combining an artificial neural network to classify
tissues based on voxel intensity with nonlinear registra-
tion to a template brain for which tissue regions had been
manually defined.26,35 Total cerebral volume was defined
as the algebraic sum of all gray-matter pixels and white-
matter pixels, excluding the cerebellum and brainstem. In-
track 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).36 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. Intrarater and interrater intra-
class correlation coefficients were 0.87 and 0.88, respec-
tively. Globus pallidus, bounded medially by internal
capsule and laterally by putamen, was also measured on
coronal sections but included every slice on which the struc-
ture was found. This measure does not distinguish intern-
al and external segments. Intrarater (intraclass correla-
tion coefficient, 0.85) and interrater (0.82) reliabilities were
acceptable.

**Cerebellar Vermis**

Volumetric measures of the posterior-inferior vermal lob-
ules (VIII-X) and of the entire vermis were hand traced in
all 3 image planes by means of morphometric software (Dis-
play; McConnell Brain Imaging Centre, McGill Univer-
sity, Montreal, Quebec)39 as described previously.7,40 In-
trarater and interrater intraclass correlation coefficients were
0.95 and 0.97, respectively.

**STATISTICAL ANALYSIS**

Although values of bilateral structures are reported for com-
pleteness, the structures of interest in this replication study
were limited to regions that differed significantly in our stud-
ies of boys with ADHD.2,7 While the same methods and rat-
ers were used for subcortical and vermal measures, the au-
tomated algorithms we used previously to quantify TCV
and cerebellum41 are no longer in use and do not function
on current computer hardware.

We report unadjusted analyses of variance with diag-
osis 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 analy-
ses of covariance because it is the single best predictor of
full-scale IQ.21 We chose to control for group differences
in intelligence, since there are moderate intercorrelations
among caseness, TCV, and vocabulary score. Meehl42 chal-
 lenged 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 in-
trinsic to ADHD,43 but the relationship between IQ and re-
geonal 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 dif-
fered significantly between groups and continuous behav-
ioral measures were examined with Pearson correlations. Pos-
sible 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≤.05.

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

**ANATOMIC-BEHAVIOR CORRELATIONS**

Within the ADHD group, TCV correlated with esti-
mated 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 cor-
related significantly with Global Assessment Scale score
(n=49; \( r = 0.35, P = .01 \)) and with Child Behavior Check-
list anxiety-depression score (n=48; \( r = -0.35, P = .01 \)).
All significant correlations were in the predicted direc-
tion, 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 vocabu-
lar subscale score (n=41; \( r = 0.46, P = .002 \)).
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 ($P > .20$).

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.

Our finding in the posterior-inferior cerebellar vermis (lobules VIII-X in the newly standardized cerebellar nomenclature) of girls with ADHD replicates our previous report in boys with ADHD. 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.

Little is known about the nonvestibular functions of the posterior-inferior vermis. Forming part of the phylogenetically ancient paleocerebellum, the vermis...
has come to mean “midline cerebellum,” although, as Schmahmann and colleagues 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. In contrast, the posterior vermis is almost entirely isolated from the adjacent cerebellar hemispheres.

The output nuclei for medial cerebellum, including the vermis, are the paired fastigial nuclei. Vermal stimulation evokes short-latency responses in limbic structures, which can modulate seizure activity in the medial temporal lobe. Vermal lesions profoundly ameliorate intense affective states such as rage or fear in animals, 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.

The posterior vermis includes the central lobules (VI-VII), which are involved in oculomotor control. 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. Impairments in executive function, difficulties with visuospatial cognition, and memory or language deficits characterize the syndrome. 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, 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 partialled) 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. 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.

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, including oculomotor executive function tasks. 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 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. 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, rather than in the right. In boys with ADHD we found a difference in right-left caudate asymmetry. 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 (F1,94 = 6.49; P = .01), consistent with several adult normative samples showing less lateralization for women. The caudate was also proportionately larger in our present sample of control girls than in our previously studied control boys (t96 = 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.

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-naïve 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
range of quantitative approaches. 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. 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. 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. Human functional brain imaging studies have documented the sensitivity of the cerebellum, and particularly the vermis, to the effects of psychostimulants.

Schmahmann proposed that cerebellar dysfunction produces not only motor dysmetria but also “dysmetric 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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