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Original Article

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ABSTRACT

Evidence from animal and human research suggests that the cerebellum may play a role in cognition. This includes domains of executive function that are normally attributed to the prefrontal cortex and are typically deficient in individuals with attention-deficit hyperactivity disorder (ADHD). To investigate cerebellar structure in ADHD, magnetic resonance imaging morphometry was used to measure the area of the cerebellar vermis in 12 males with ADHD and 23 male controls matched for age and Wechsler Full-Scale IQ. Analyses were conducted to evaluate group differences, as well as differences between matched pairs of subjects with ADHD and those without ADHD. All measurements were corrected for overall brain size. Both analyses revealed that the size of the posterior vermis was significantly decreased in males with ADHD ($P < .05$ in both analyses), and that within the posterior vermis, the inferior posterior lobe (lobules VIII–X) was involved in this reduction ($P < .05$ for group analysis, $P < .005$ for matched pair analysis), while the superior posterior lobe (lobules VI/VII) was not involved in the reduction. The finding of abnormal inferior posterior vermal size suggests that dysfunction within this region of the cerebellum may underlie clinical deficits seen in individuals with ADHD. (*J Child Neurol* 1998; 13:434–439).

Attention-deficit hyperactivity disorder (ADHD) is characterized by symptoms of hyperactivity, impulsivity, and a decreased ability to maintain attention, particularly during nonpreferred tasks. Currently, the *DSM-IV* uses the term attention deficit/hyperactivity disorder, and includes three subtypes: "predominantly inattentive," "predominantly hyperactive/impulsive," and a combined type.[1] The disorder is thought to be fairly common, with a prevalence estimated to be between 3% and 5% among elementary school children.[2,3] Despite this and the fact that the diagnostic classification for attention-deficit disorder (ADD) /attention-deficit hyperactivity disorder (ADHD) has existed under a variety of names for more than 20 years, the precise neurobiologic basis of the disorder remains unclear.

Leading hypotheses suggest that ADHD is the result of dysfunction in frontal-striatal circuits, which are critical for an organism's "preparedness to act."[4–6] In this model, the core symptoms of the disorder are thought to be secondary to abnormal selection of motor response to stimuli.[4,5] The result is inattention to stimuli that should lead to action and defective response inhibition to those that should not, with the latter resulting in impulsive and hyperactive behavior.[4]

Investigations using imaging techniques have provided evidence to support a frontal-striatal model of ADHD. A single-photon emission computed tomography (SPECT) study revealed decreased cerebral blood flow in the striatum bilaterally, more so on the right than the left.[7] Imaging studies using positron emission tomography (PET) revealed reduced overall cerebral glucose metabolism with right frontal accentuation in adults with residual ADHD who were parents of children with ADHD, and in adolescent girls with ADHD.[8,9]

Frontal-striatal abnormalities have also been reported in studies using magnetic resonance imaging (MRI)-based morphometric techniques. Two studies reported smaller left caudate size in individuals with ADHD,[10,11] while another reported smaller right caudate volume in males with the disorder.[12] A study focused on children with Tourette syndrome found that those with Tourette syndrome and ADHD had decreased volume of the left globus pallidus compared

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to a group of patients with Tourette syndrome only.[13] A follow-up study found decreased volume of the left basal ganglia in a group of ADHD subjects compared with controls.[14]

Hynd et al reported that children with ADHD have frontal symmetry (rather than a more normal right-larger-than-left asymmetry).[15] More recently, Filipek et al found smaller volume of the right anterior-superior (frontal) region of the cerebrum in males with ADHD.[11] The anterior rostrum and rostral body of the corpus callosum, which serve prefrontal regions, have also been shown to be decreased in size in males with ADHD.[16,17]

Findings on neuroanatomic studies in ADHD, however, have not been restricted to frontal-striatal regions of the brain.[11] Interestingly, children with other volumetric abnormalities (specifically, decreased volume of parietal-occipital white matter and small splenium of the corpus callosum) have been characterized as stimulant non-responders.[11,18]

A recent study found abnormalities of the cerebellar vermis in patients with ADHD.[19] Compared to controls, decreased size of the inferior portion of the posterior vermis (lobules VIII–X) in a group of males with ADHD was reported. The vermis of the cerebellum has a history of being studied in detail in other developmental disorders. A decrease in size of the superior posterior vermis (lobules VI/VII) was found in a group of individuals with autism,[20] and small posterior vermis size is a reported feature of males and females with fragile-X syndrome, including those without autistic features.[21–23]

Traditionally, the cerebellum has been viewed as a motor coordination center; however, over the past decade, this notion has been expanded. Approximately one third of the efferent connections from the cerebellum are non-motor, and recent studies have revealed direct projections from the dentate nucleus to higher-order association areas of the cerebral cortex.[24,25] In addition, evidence from animal and human research suggests that the cerebellum may play a role in cognitive function. This includes components of executive function, such as cognitive planning and error detection, which are normally attributed to the prefrontal cortex and are typically deficient in individuals with ADHD.[26–31] We therefore evaluated the size of the vermis in 12 males with ADHD and 23 male controls to determine whether portions of the cerebellar vermis are decreased in size in individuals with ADHD.

METHODS

Subjects

Subjects with ADHD consisted of 12 males with a mean age of 11.3 years (range 8.2–14.6 years), and a mean Wechsler Full-Scale IQ of 107 (range 87–131). Individuals with ADHD were recruited as outpatients, and diagnoses were made by a team of experienced clinicians. For 10 of the subjects, the diagnosis was based on *DSM-III-R* criteria for ADHD; the other two subjects met *DSM-IV* criteria for ADHD (predominantly inattentive type). None of the subjects with ADHD had been diagnosed with any other chronic neurologic illness.

Seven of the patients with ADHD had been previously diagnosed with that disorder and had received methylphenidate in the past. One of these seven individuals had also received dextroamphetamine and pemoline; another had received clonidine. One patient had a history of a single febrile seizure at less than 2 years of age, for which he received a single dose of phenobarbital.

The control group was selected from our database archive, and consisted of 23 males with a mean age of 11.3 years (range 6.6–24.6), and a mean Wechsler Full-Scale IQ of 112 (range 101–139). IQ testing was available in 12 of the males in the control group. Of the 11 untested males in the control group, eight were normal controls in an MRI study of Tourette syndrome, one had a clinical scan for headaches, and two were normal volunteers. All of these subjects had clinical histories and/or evaluations consistent with at least normal intelligence. None of the control subjects had a history of ADHD, learning disability, or other chronic neurologic or psychiatric disorders.

Four of the subjects with ADHD and nine of the control subjects were siblings of patients with neurofibromatosis-1. In all of these cases, the diagnosis of neurofibromatosis-1 was ruled out after extensive evaluation, which included an MRI and examinations by an experienced neurologist, geneticist, and ophthalmologist.

None of the subjects with ADHD or individuals from the control group had clinical evidence of cerebellar disease.

MRI Measurements

All MRI scans were acquired on a 1.5T GE Signa scanner. The head was aligned with laser cross-hairs referenced to the nasion and the midsagittal plane. T_1-weighted images were obtained with a T_R of 600 msec, a T_E of 20 msec, and nex = 2. Studies were performed with images that were 3 mm thick except in two subjects, in one of whom images were 5 mm thick and in the other images were 6 mm thick. All studies were performed with a gap of 0 mm to 1.5 mm, a 20 cm to 24 cm field of view, and a 256 × 256 matrix.

Midline neuroanatomic structures were manually delineated using the Brainimage program.[32] Operational definitions of regions of interest were based on guidelines determined by an experienced neuroradiologist and with reference to standard neuroanatomic landmarks.[33] Area measurements of the cerebellar vermis, fourth ventricle, and intracranium were made on midsagittal magnetic resonance images, which were identified by choosing the sagittal image that most clearly showed the cerebral aqueduct and the lobular anatomy of the vermis. Care was taken to distinguish the lobules of the vermis from the cerebellar tonsil and hemispheres (Figure 1).

Quantitative analyses were performed by five raters who were blinded to the identification and diagnosis of the subject whose image was being analyzed. Intraclass correlation coefficient was used to analyze interrater reliability for the neuroanatomic measurements used in this study. The means for the interrater combinations were as follows: intracranial = 0.948, anterior vermis = 0.912, lobules VI/VII = 0.873, lobules VIII–X = 0.843, fourth ventricle = 0.92. Analysis of scans common to all raters revealed no systematic differences between raters.

Statistical Analysis

Area measurements in the group of 12 patients with ADHD and in the group of controls were not normally distributed; therefore,

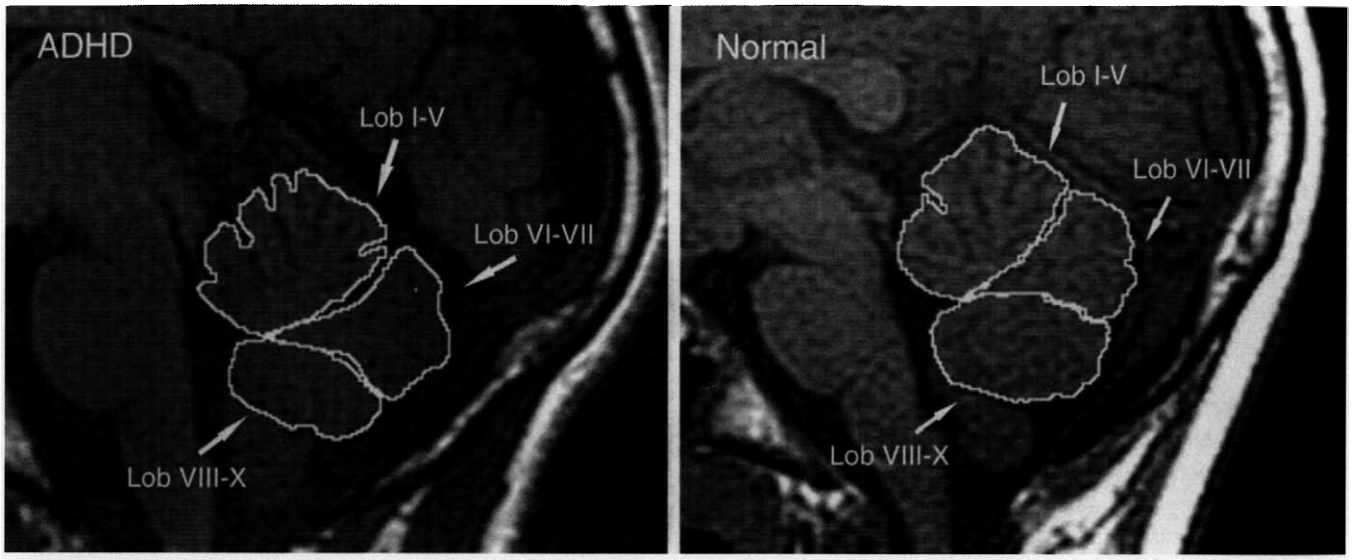

Figure 1. Midsagittal magnetic resonance images of a male with ADHD and a normal male control patient. Borders are drawn around the anterior cerebellar vermis (lobules I–V); and lobules VI–VII and lobules VIII–X of the posterior cerebellar vermis. The area of the inferior posterior cerebellar vermis (lobules VIII–X) appears to be smaller in the male with ADHD.

nonparametric statistics were used. Mann-Whitney tests were used in the assessment of group differences for specified neuroanatomic regions. Wilcoxon signed rank statistics were used to analyze differences between the matched pairs of subjects with ADHD and those without ADHD. Z values were corrected for ties in instances of tied rankings. Critical values of P (two-tailed) were set at 0.05 for both the Mann-Whitney and Wilcoxon signed rank analyses.

RESULTS

Preliminary analyses revealed no significant differences in age or Wechsler Full-Scale IQ between the group of males with ADHD and the large comparison group. Intracranial area was smaller in the group of males with ADHD, but not at a significant level.

The results of area measurement taken from the midsagittal plane are listed in Table 1. To correct for overall brain size on an individual basis, ratios of vermal area measurements to intracranial area were calculated. Mann-Whitney analyses revealed that the ratio of posterior vermis (lobules VI–X) area to intracranial area was significantly smaller in the group of males with ADHD compared with the control group ($U = 77$, $P < .05$). There was no significant difference between the two groups in the ratio of anterior vermis (lobules I–V) area to intracranial area. Within the posterior vermis, the ratio of inferior posterior vermis (lobules VIII–X) area to intracranial area was significantly smaller in the group of males with ADHD ($U = 80$, $P < .05$); there was no significant difference between the two groups in the ratio of superior posterior vermis (lobules VI–VII) area to intracranial area.

The results of area measurements in the midsagittal plane were also analyzed using Wilcoxon signed rank, which compared area measurements in the group of 12 males with ADHD with a group of 12 male controls individually matched for age (and Wechsler Full-Scale IQ if available). Preliminary analyses revealed no significant differences in age or Wechsler Full-Scale IQ between the two groups.

The results of area measurements, which are listed in Table 2, revealed findings similar to those observed when Mann-Whitney statistics were used to compare the group of males with ADHD to the larger control group. Intracranial area was not significantly different between the two groups. The ratio of posterior vermis area to intracranial area ($Z = -2.51$, $P < .05$) was significantly smaller in the group of males with ADHD, with no significant difference in the ratio of anterior vermis area to intracranial area between the two groups. Within the posterior vermis, the ratio of inferior posterior vermis area to intracranial area ($Z = -2.824$,

Table 1. Midsagittal Area Measurements and Ratios for Groups of Subjects with ADHD and Controls

	ADHD (n = 12)		*Controls (n = 23)*	
Areas and Ratios	*Mean*	*SD*	*Mean*	*SD*
Brain region (cm^2)				
Intracranial	158.11	11.27	162.87	8.23
Fourth ventricle	1.00	0.24	1.02	0.26
Vermis (total)	11.21	1.01	12.26	1.21
Anterior vermis (lob I–V)	4.81	0.72	5.12	0.64
Posterior vermis (lob VI–X)	6.40	0.53	7.16	0.79
Lobules VI and VII	2.99	0.32	3.26	0.33
Lobules VIII–X	3.41	0.38	3.89	0.61
Ratios				
Vermis (total)/intracranial	0.071	0.007	0.075	0.007
Posterior vermis/intracranial*	0.041	0.004	0.044	0.005
Anterior vermis/intracranial	0.030	0.005	0.031	0.004
Lobules VI and VII/intracranial	0.019	0.002	0.020	0.002
Lobules VIII–X/intracranial*	0.022	0.003	0.024	0.004

ADHD = attention-deficit hyperactivity disorder; *ADHD less than control ($P < .05$).

Table 2. Midsagittal Area Measurements and Ratios for Groups of Subjects with ADHD and Matched Pair Controls

	ADHD (n = 12)		Controls (n = 12)	
Areas and Ratios	*Mean*	*SD*	*Mean*	*SD*
Brain region (cm^2)				
Intracranial	158.11	11.27	162.57	6.73
Fourth ventricle	1.00	0.24	1.00	0.17
Vermis (total)	11.21	1.01	12.72	0.83
Anterior vermis (lob I–V)	4.81	0.72	5.36	0.57
Posterior vermis (lob VI–X)	6.40	0.53	7.36	0.61
Lobules VI and VII	2.99	0.32	3.35	0.32
Lobules VIII–X	3.41	0.38	4.01	0.46
Ratios				
Vermis (total)/intracranial†	0.071	0.007	0.078	0.004
Posterior vermis/intracranial*	0.041	0.004	0.045	0.003
Anterior vermis/intracranial	0.030	0.005	0.033	0.001
Lobules VI and VII/intracranial	0.019	0.002	0.021	0.002
Lobules VIII-X/intracranial‡	0.022	0.003	0.025	0.003

ADHD = attention-deficit hyperactivity disorder.
*ADHD < controls ($P < .05$).
†ADHD < controls ($P < .01$).
‡ADHD < controls ($P < .005$).

$P < .005$) was significantly smaller in the group of males with ADHD, while the ratio of superior posterior vermis area to intracranial area was not. Total vermis area to intracranial area ratio was also significantly smaller in the group of males with ADHD ($Z = -2.589$, $P < .01$), which was not observed in the previous analyses.

DISCUSSION

In this study, midsagittal vermal measurements in a group of males with ADHD were compared with those of a control group matched for sex, age, and IQ. Statistical analyses were conducted comparing the group of 12 males with ADHD to a group of 23 controls, and in pairs to 12 matched controls. Common to both analyses was the finding that posterior vermis size was significantly decreased in males with ADHD. Within the posterior vermis, after correcting for overall brain size, the area of the inferior posterior vermis (lobules VIII–X) was significantly decreased in males with ADHD, while the area of the superior posterior vermis (lobules VI/VII) was not.

Conclusions from this study are limited by small sample size as well as the inclusion of only male subjects. In addition, the presence of comorbid diagnoses was not closely examined, raising the possibility that the observed reduction in inferior posterior vermis size may be associated with neuropsychiatric abnormalities other than ADHD. Furthermore, because patients with ADHD were limited in number and age range, age-by-structure correlations could not be performed. Therefore, it is unclear whether the inferior posterior vermis is hypoplastic, or if it is small as a result of abnormal prenatal development, or because of atrophy later in childhood.

The mean vermal measurements for the male control group in this study were greater than those previously reported for a normal development male control group in a study of individuals with fragile-X syndrome.[23] The differences are most likely due to the fact that the normal development group from the aforementioned study included individuals with neurologic and neuropsychiatric diagnoses including seizures, chronic headache, depression, bipolar disorder, oppositional defiant disorder, learning disabilities, and ADHD. Therefore, the means from the current study are probably a better reflection of normative data.

The primary finding in this study—that the size of the inferior posterior vermis of the cerebellum is reduced in males with ADHD—is not unprecedented. The only previous study to use MRI morphometry to examine the vermis in patients with ADHD also found a decrease in size of the inferior posterior vermis with sparing of the superior portion.[19] The agreement between the two studies certainly suggests that a specific anomaly of the inferior posterior vermis is associated with ADHD.

Most researchers suggest that ADHD is the result of dysfunction within frontal-striatal intentional networks, manifesting as deficits in executive function, including decreased ability to inhibit off-task behavior, difficulty sustaining attention and difficulties with planning, organizing, and sequencing movement and behavior.[4,6,34] Several investigations of subjects with ADHD have found neuropsychological deficits in executive functioning that are similar to those seen in patients with a history of prefrontal lesions.[4,6,35–37] Structural and functional imaging studies have revealed abnormalities in frontal and prefrontal regions in individuals with ADHD, as well as abnormalities in closely related structures such as the caudate and anterior portions of the corpus callosum.[8–11,14–18,38]

The presence of cerebellar abnormalities in patients with ADHD is not inconsistent with a frontal-striatal hypothesis. Recent findings of projections from the dentate nucleus to the dorsolateral prefrontal cortex (Brodmann's areas 46 and 9) suggest that the cerebellum may be part of a larger distributed network in the intentional system. In support of this hypothesis, several studies have reported executive function abnormalities in patients with cerebellar lesions, including deficits in error detection, sequencing, and planning.[26–31] Furthermore, in a recent study, PET was used to evaluate the effects of methylphenidate, a medication widely used to treat executive function deficits associated with ADHD, on brain metabolism in 15 healthy subjects. The administration of methylphenidate induced a significant increase in metabolism only in the cerebellum; it induced a significant reduction in metabolism in the basal ganglia.[39]

Cerebellar dysfunction may contribute to problems involving timing that are often associated with the syndrome of ADHD, including impaired time management, inability to judge durations needed to complete tasks, and inability to keep in mind future consequences of present actions. A number of investigators have reported that, compared to controls, children with ADHD perform worse on time estimation and time production tasks.[6,40,41] Ivry et al have found that the cerebellum may be critical for motor and perceptual timing.

Compared to individuals with cerebral cortical lesions and those with Parkinson's disease, adults with cerebellar lesions perform worse on tasks involving motor and perceptual timing.[42,43] A PET study of perceptual timing supported these findings, revealing cerebellar activation that included the vermis.[44]

Although the preponderance of existing evidence is consistent with frontal-network dysfunction, there are findings suggestive of a parietal contribution to the ADHD phenotype as well. A functional imaging study found bilateral posterior periventricular hypoperfusion in children with ADHD.[7] Recently, Filipek et al[11] reported that, compared to controls, males with ADHD had significantly smaller volumes of bilateral retrocallosal (parietal-occipital) white matter. Two groups, Semrud-Clikeman et al[18] and Hynd et al,[45] found that the splenium of the corpus callosum was smaller in children and adolescents with ADHD. Interestingly, in both the Filipek et al and Semrud-Clikeman et al studies, a medication-response effect was noted, with stimulant non-responders having the smallest measurements for these posterior brain regions.

Cerebellar projections to the parietal lobe have also been recently identified.[25] In addition, Courchesne et al have reported abnormalities in orienting and shifting attention in patients with cerebellar lesions, reminiscent of deficits reported in patients with lesions of the parietal lobe.[46] This deficit was noted particularly in patients with autism identified as having abnormalities of the *superior* portion of the posterior vermis (lobules VI/VII).[20,47]

In this study, we found that males with ADHD had decreased *inferior* posterior vermis area, with no reduction in the size of the superior portion. It may be that patients who have difficulty in orienting and shifting attention have dysfunction within a network involving the parietal lobe and the superior posterior vermis, while the preponderance of patients with ADHD, who typically have more difficulty with executive aspects of attention (as well as broader executive functions), have abnormalities in a frontal-subcortical network that includes the inferior posterior vermis. Further work would need to be done to support this hypothesis, including mapping of specific cerebellar cortical projections to areas of the cerebral cortex.

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