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An MRI Study of the Cerebellar Vermis in Chronically-Treated and Treatment-Naïve Children with ADHD-Combined Type

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Abstract

Background—Because of its dense connections to the prefrontal cortex and basal ganglia, the cerebellum is thought to play an important role in cognition. Numerous MRI studies have found abnormalities in the cerebellum in children with ADHD. While some studies in animal and human models suggest that the certain brain structures are affected by chronic stimulant medication, it is unclear whether the cerebellum is also affected. The purpose of the current study was to determine if cerebellar morphology was different in treatment-naïve vs. chronically-treated children with ADHD.

Methods—There were 32 boys and 15 girls total ($N = 47$) that comprised three groups: ADHD-C children with no history of stimulant medication treatment ($n = 14$), ADHD-C children chronically treated with stimulant medication ($n = 18$), and typically developing control children ($n = 15$).

Results—Treatment-naïve children with ADHD had significantly smaller area in the posterior inferior vermis (lobules VIII-X) than both chronically-treated children with ADHD ($p = .004$) and typically developing controls ($p = .001$). No differences were observed between chronically-treated children with ADHD and controls.

Conclusions—The results from this study suggest that chronic stimulant treatment may normalize the development of important areas of the cerebellar vermis in children with ADHD.

Keywords

ADHD; cerebellum; MRI; medication treatment; vermis

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Introduction

Attention-Deficit/Hyperactivity Disorder (ADHD) is thought to affect approximately 5-10% of all school-age children and nearly 5% of adults (1). Cardinal symptoms of ADHD include inattention, impulsivity, and hyperactivity. The DSM-IV-TR categorizes ADHD into three subtypes: ADHD-Predominantly Hyperactive/Impulsive (ADHD-H/I), ADHD-Predominantly Inattentive (ADHD-PI), and ADHD-Combined Type (ADHD-C; i.e., meeting criteria for both ADHD-H/I and ADHD-PI).

Foundational theories connect the symptoms of ADHD to impairments in executive functioning (EF) (2). Based on this work, meta-analytic reviews representing approximately 109 studies on EF in children with ADHD found significant impairments in planning ability, response inhibition, and in particular, working memory (3-4). Furthermore, EF tasks are thought to be modulated by the prefrontal cortex and the associated neural networks of the basal ganglia and cerebellum (5). These neural networks are thought to be altered in children with ADHD.

The cause of ADHD is unknown. Current etiological theories of ADHD, however, suggest impairments in fronto-striatal neurocircuitry are at the core of ADHD symptomatology (2, 6-10). Support for this hypothesis comes from both neuropsychological and neuroimaging studies of ADHD.

Investigations using magnetic resonance imaging (MRI) and functional MRI (fMRI), implicate fronto-striatal-cerebellar neural circuit deficits in ADHD. Specifically, research has found that abnormalities in brain structure and function are key components of the ADHD phenotype. For example, Castellanos, Giedd, Hamburger, Marsh, & Rapoport, (1996; 11) reported that the volume of the frontal cortex was significantly smaller in boys with ADHD compared to boys without. Similarly, it appears that caudate volume (9,12-13) as well as cerebellar volume and area are smaller in children with ADHD (14-19). For example, numerous studies observed smaller cerebellar volume and area with a particular reduction in the posterior inferior vermis (Lobules XIII-V) (14-19). Other studies, using fMRI, found dysfunctions (i.e., hypoactivation) in the anterior cingulate cortex (ACC; 20). This finding is significant given the importance of the ACC in the monitoring of attention and in error processing. The prefrontal cortex (PFC), an area responsible for a host of executive functions, has also been found to be impaired in children with ADHD (21-23). Thus, many neural systems are impaired in children with ADHD, which likely contributes to the vast heterogeneity of the disorder.

Stimulant medication is often prescribed for children with ADHD given its effects on the fronto-striatal dopaminergic system (24-25). Stimulants, such as methylphenidate, block the re-uptake of dopamine and norepinephrine, allowing for improved neurochemical transmission between neurons. In animal studies, chronic stimulant use has been linked to changes in the density of dopamine transporters (26). For this reason researchers have also been interested in the effects of stimulant medication on the development of brain structures in humans.

A 5-year longitudinal study looking at the effects of stimulant medication on brain development found that unmedicated ADHD children (compared to medicated) had smaller total white matter volume (7). Thus, it appears that stimulant medication may normalize white matter development. Researchers have also observed volumetric differences in the ACC in medicated versus unmedicated children with ADHD (27). The right ACC was significantly smaller in unmedicated children compared to both chronically medicated ADHD children and typically developing control children. Therefore, it is hypothesized that chronic medication may also normalize ACC development.

These studies collectively suggest that chronic medication treatment is related to the normalization of brain structures associated with symptoms of ADHD. The results of only two studies, however, should be interpreted with caution given inconsistent findings, limited sample sizes and decision to control or not control for comorbid disorders or ADHD subtypes which may reflect qualitatively different populations. Further, while these studies provide important information about the effects of chronic stimulant treatment on the development of cerebral white matter and the ACC, it is unclear how/if stimulant medication affects the development of the cerebellum. Because numerous studies found differences in cerebellar volume and area in ADHD children (14-19), the question regarding chronic treatment and cerebellar development remains.

The current study looked at the effects of chronic medication on the development of the cerebellar vermis in children with ADHD. We hypothesized that reductions in vermal area would be found in treatment-naïve children with ADHD but not chronically-treated ADHD or typically developing controls. Further, we hypothesized that chronically-treated children with ADHD would have similar vermal area as controls.

Methods and Materials

All subjects (N=47) were right-handed and consisted of 15 girls and 32 boys with a mean age of (11.34 years $\pm$ 2.42). There were three groups: ADHD-C children with no history of stimulant medication treatment (n = 14), ADHD-C children chronically treated with stimulant medication (n = 18), and typically developing control children (n = 15). Chronically-treated children with ADHD-C had taken medication for at least one year (range of 2.3 - 5 years). The treatment-naïve ADHD-C group had never received medication for any psychiatric illness including ADHD.

Inclusion Criteria

Using a comprehensive evaluation, ADHD subjects were diagnosed with ADHD-Combined Type according to DSM-IV-TR (28) criteria using the Diagnostic Interview Schedule for Children – IV – Parent Edition (DISC-IV-P; 29). Subjects did not meet criteria for any other disorder including Oppositional Defiant Disorder (ODD), Conduct Disorder (CD), tic, or other affective illness. The typically developing control group did not meet criteria for any psychiatric disorder nor have a history of treatment for psychiatric illness. No child in this study met criteria for a learning disability. In addition, medical history was reviewed for all subjects. Subjects had no current or past history of alcohol or substance abuse or dependence.

To ensure a careful diagnosis of ADHD, the Conners' Global Index was used for all subjects enrolled in the study (30). Subjects in the treatment-naïve ADHD group all had baseline Restless/Impulsive indices (RI) that fell 1.5 standard deviations above average for their age and gender according to parent ratings. Typically developing control subjects all had RI ratings that fell within one standard deviation for their age and gender on both parent and teacher reports. In addition to Conners', the Behavioral Assessment Scale for Children (BASC-P, 31) was used to assess concentration and attention. On the BASC, chronically-treated ADHD children were rated by their parents while off medication in the past six months. All chronically-treated ADHD children fell within 1.5 standard deviations above the mean for age and gender. Finally, chronically-treated ADHD children had received stimulant medication continuously for at least one year according to their primary caregiver.

Global Conceptual Ability (GCA) scores from the Differential Ability Scales (DAS, 32) were used to assess subjects' current level of cognitive ability. To be included in the study, all subjects had GCA scores that fell at or above 85. In addition, the Wechsler Individual Achievement

Test (WIAT-II, 33) was used to assess reading and mathematical skills. Subjects that met criteria for a learning disability were excluded from the study.

Image Acquisition

MRI scans were obtained on a GE/Elscint 2T Prestige scanner. All MRI's were performed in the Research Imaging Center at the University of Texas Health Science Center in San Antonio, Texas. Structural MRI images were obtained using three-dimensional gradient recalled acquisitions (3-D GRASS) with a repetition time (RT) 33ms, echo time (TE) = 12ms, and a flip angle of 60 degrees, with a volume of data of 256 X 192 X 192 and a spatial resolution of 1mm X 1mm X 1mm.

Raw data was analyzed on Silicon Graphics workstations and brains were oriented along the anterior and posterior commissures to account for differences in head orientation during scanning. Images were also spatially normalized to a standard brain template in order to accurately control for developmental differences in brain size and volume between subjects. Images were then converted to MINC (Medical Image NetCDF) files. Area analysis of MINC images was carried out using a PC version of DISPLAY software (Montreal Neurologic Institute) at the Center for Neurodevelopmental Study at Michigan State University.

Image Analysis

Analysis of all vermal and cerebrum area measurements was done in the midsagittal plane. The midsagittal plane was identified via careful inspection of the cerebral aqueduct, connection between cerebral aqueduct and the 4th ventricle, and anatomy of the vermis. Given that the midline of the cerebellar vermis is not consistently equidistant to the midline of the cerebrum, the mid-sagittal plane of the vermis was used for determining the midsagittal plane. The midsagittal plane was also confirmed and double checked in the coronal plane. This method has been found to be useful in other studies measuring the cerebellar vermis (19). Parcellation of vermal structures was divided up into three areas: lobules I-V (anterior vermis), lobules VI-VII (posterior superior vermis), and lobules VIII-X (posterior inferior vermis) (34). Intracranial area was also measured in the midsagittal plane. Area measurements were hand traced and started at the apex of the fourth ventricle in the order of lobules I-V, lobules VI-VII, and VIII-X for all subjects. Midsagittal images of each group as well as the designated lobules of the vermis are presented in Figures 2.

The operational definitions for all anatomic landmarks were adapted from other studies on the cerebellar vermis (14,19) and confirmed with a detailed MRI atlas of the cerebellum (34).

During area measurements, DISPLAY paint opacity was consistent for all subjects (0.2) in order to control for discrepancies between vermal tissue and cerebrospinal fluid (CSF). The authors also took care in distinguishing the cerebellar lobules from the cerebellar peduncles (see Figure 1). DISPLAY paint brush size was also consistent for all subjects (1 voxel, 1mm). Brain area measurements were highlighted, double checked in all three planes, and calculated in DISPLAY. All measurements were done blind to diagnosis and over 1/3 of the brains were re-measured to establish reliability and consistency. Intrarater reliability for the anterior vermis was .927, posterior superior vermis was .963, and posterior inferior vermis was .944.

Statistical Analysis

Demographic data was analyzed with multivariate analysis of variance (MANOVA), and follow-up pairwise comparisons were carried out with a Tukey least significant difference (LSD) test. For vermal and intracranial area analyses, a 3 group (ADHD-Treatment Naive, ADHD-Chronically Treated, and Control) X 4 measure (anterior vermis, posterior superior, posterior inferior, and total vermis) multivariate analysis of covariance (MANCOVA) was

used. Intracranial area was used as a covariate in order to control for individual and developmental differences in brain size. Follow-up ANOVAs and Fisher's PLSD post-hoc tests were used to determine differences between the three groups.

Results

Initial analysis of Conners' RI indicated, as expected, group differences in both ADHD groups versus controls ($F = 7.648$, $df = 2, 43$, $p = .001$), but no differences between the ADHD groups ($p = .742$). This suggests that the ADHD groups did not differ on the level of symptom severity. Demographic and clinical variables are presented in Table 1.

Results for Cerebellar Vermis

Consistent with our hypothesis, groups differed on measurements of area in the cerebellar vermis. Analyses revealed a statistically significant group X vermal area interaction, Wilks' Lambda yielded ($F = 4.202$, $df = 6, 82$, $p = .001$, $\eta^2 = .235$). Follow-up ANOVA's resulted in statistically significant group differences in the posterior inferior vermis (lobules VIII-X), ($F = 10.354$, $df = 2, 47$, $p < .001$, $\eta^2 = .325$). No other vermal structure (anterior vermis, $F = 2.532$, $df = 2, 47$, $p = .091$, $\eta^2 = .105$; posterior superior vermis, $F = 1.065$, $df = 2, 47$, $p = .354$, $\eta^2 = .047$), nor total vermis ($F = 2.596$, $df = 2, 47$, $p = .086$, $\eta^2 = .108$) or intracranial area, differed between any of the three groups. Post-hoc analyses (Fisher's PLSD) found that the treatment-naïve ADHD group had significantly smaller area in the posterior inferior vermis than both chronically-treated ADHD ($p = .004$) and typically developing controls ($p = .001$). No differences were observed between chronically-treated ADHD and control children ($p = .462$). The means and standard deviations for all cerebellar measurements are presented in Table 2.

Discussion

As hypothesized, treatment-naïve children with ADHD had significantly smaller area measures in the posterior inferior vermis (lobules VIII-X) than either the chronically-treated children with ADHD and controls. No differences were observed between chronically-treated and typically developing controls in any vermal area measurement. This finding is important given recent accounts of cerebellar abnormalities in children with ADHD.

Numerous studies have reported that children with ADHD have smaller volumes and areas in the cerebellar vermis than children without ADHD (14-19). In particular, the posterior inferior vermis appears to account for much of the reduction in volume and area (14,17,19). It was unclear, however, if the reductions in volume and area of the vermis were related to having a history of treatment with stimulant medication. In light of previous work, the current study suggests that a reduction in the posterior inferior vermis may be a structural abnormality specific to ADHD children who do not have a history of treatment with stimulant medication. Additionally, this study found that chronically-treated children with ADHD had similar vermal area compared to children without ADHD. Therefore, it appears that chronic treatment with stimulant medication may have normalizing effects on the developing cerebellum, especially for the posterior inferior vermis. While the results of this study provide important information regarding the effects of treatment with stimulant medication for children with ADHD, several limitations are worth mentioning.

Because many children with ADHD also meet criteria for another psychiatric disorder, our sample is limited in that we recruited children with a sole diagnosis of ADHD. Ecological validity in future studies could be improved by recruiting subjects with comorbid disorders such as Oppositional Defiant Disorder and Mood Disorders. However, because past studies have used mixed samples, it was unclear if ADHD or another comorbid disorder accounted for the observed structural differences. The results of this study suggest that ADHD is related to

volumetric abnormalities in the cerebellum. In addition, future studies should connect structural data and behavioral data in order to provide more information regarding the brain-behavior relationships in ADHD. Lastly, longitudinal studies using a similar sample of ADHD children are needed in order to determine whether morphometric changes in the posterior inferior vermis can be explained by the use of stimulant medication.

The cerebellum contains more neurons than the entire central nervous system, with projections to the basal ganglia, prefrontal cortex, and parietal lobe (35). These connections make the cerebellum an integral structure for many important aspects of cognition. Because studies have found abnormalities in the cerebellum in children with ADHD, new theories have implicated this structure in ADHD pathology. Until recently little was known about the effect of stimulant medication on the structural anatomy of the brain. This is one of the first studies to report abnormalities in the cerebellum in treatment-naïve children with ADHD. These results suggest that treatment with a stimulant medication may normalize development of key cerebellar structures that influence executive functioning ability. More studies are needed, however, in order to determine what, if any, relationship exists between cerebellar development and executive functioning ability in children with ADHD.

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Figure 1.

Mean Area Measurements of the Cerebellar Vermis.

Note: ADHD_{Tn} = ADHD-treatment naïve; ADHD_{Rx} = ADHD-chronically treated; Anterior Vermis = Lobules I-V; Posterior Superior = Lobules VI-VII; Posterior Inferior = Lobules VIII-X.

* This structure was significantly smaller in ADHD_{Tn} compared to ADHD_{Rx} and Controls.

Figure 2.
Midsagittal image representing vermal structures.

Table 1
Clinical and Demographic Characteristics of Subjects.

	ADHD _{Tn}		ADHD _{Rx}		Controls	
	Mean	SD	Mean	SD	Mean	SD
N		14		18		15
Age, years	12.01	2.13	11.47	1.51	11.10	3.32
Ability (DAS-GCA)	101.10	10.65	105.66	14.10	113.86 α	12.20
WIAT - Reading	96.00	6.86	104.88 ϕ	9.87	107.20 ϕ	10.34
Parent Conners' R-I	75.00 τ	16.95	76.89 τ	15.72	56.07	15.39

Note: ADHD_{Tn} = ADHD-treatment naïve; ADHD_{Rx} = ADHD-chronically treated; GCA = General Conceptual Ability; WIAT = Wechsler Individual Achievement Test; R-I = Restless Impulsive Index.
 α This group's performance significantly differed from the ADHD_{Tn} group. ϕ These groups significantly differed from the ADHD_{Tn} group. τ These groups significantly differed from the control group

Table 2
Cerebellar Vermis Measurements for ADHD_{Tn}, ADHD_{Rx}, Controls.

Brain Areas (cm ²)	ADHD _{Tn}		ADHD _{Rx}		Controls	
	Mean	SD	Mean	SD	Mean	SD
Intracranial	127.94	8.36	125.63	8.65	125.10	8.54
Anterior Vermis Lobules I-V	3.74	.40	3.89	.50	3.59	.31
Posterior Superior Vermis Lobules VI-II	2.45	.46	2.35	.38	2.22	.23
Posterior Inferior Vermis Lobules VIII-X	2.40 [*]	.25	2.77	.33	2.86	.41
Total Vermis	8.60	.73	9.01	.89	8.68	.62

Note: ADHD_{Tn} = ADHD-treatment naïve; ADHD_{Rx} = ADHD-chronically treated.

^{*} This group was significantly different from the ADHD_{Rx} and Control group.