Cerebellar vermal volumes and behavioral correlates in children with autism spectrum disorder

Sara Jane Webb[a,b,*], Bobbi-Faun Sparks[c], Seth D. Friedman[c], Dennis W.W. Shaw [c,d], Jay Giedd[e], Geraldine Dawson[a,b,f], Stephen R. Dager[c]

[a]Department of Psychiatry and Behavioral Sciences, University of Washington, Seattle, WA, United States
[b]Center on Human Development and Disabilities, University of Washington, Seattle, WA, United States
[c]Department of Radiology, University of Washington, Seattle, WA, United States
[d]Seattle Children's Hospital & Regional Medical Center, Seattle, WA, United States
[e]National Institute of Mental Health, Bethesda, MD, United States
[f]Department of Psychology, University of Washington, Seattle, WA, United States

ARTICLE INFO

ABSTRACT

Cerebellar histopathological abnormalities have been well documented in autism, although findings of structural differences, as determined by magnetic resonance imaging, have been less consistent. This report explores specific cerebellar vermal structures and their relation with severity of symptoms and cognitive functioning in young children with autism spectrum disorder (ASD). Children with ASD aged 3 to 4 years were compared with typically developing children (TD) matched to the ASD children on chronological age, and children with developmental delay (DD) matched to the ASD children on both chronological and mental age. Volumes of the cerebellum and midsagittal vermal areas were measured from 3-D T1-weighted magnetic resonance images. Children with ASD had reduced total vermis volumes compared with children with TD after controlling for age, sex, and overall cerebral volume or cerebellum volume. In particular, the vermis lobe VI–VII area was reduced in children ASD compared with TD children. Children with DD had smaller total vermis areas compared with children with ASD and TD. Within the ASD group, cerebellar measurements were not correlated with symptom severity, or verbal, non-verbal or full scale IQ. Within the DD group, larger cerebellar measurements were correlated with fewer impairments. The specific relation between altered cerebellar structure and symptom expression in autism remains unclear.

© 2008 Elsevier Ireland Ltd. All rights reserved.

1. Introduction

Autism spectrum disorder (ASD) is characterized by impaired social functioning and communication, and a restricted range of activities. A number of neurobiological hypotheses have been put forward to account for autism behaviors that implicate neural and network abnormalities in the cerebellum, frontal cortex, medial temporal lobe, in general, and the amygdala and/or hippocampus, superior temporal lobe/sulcus, and brainstem, specifically. While this list is not exhaustive in its scope, it illustrates the pervasive impact of this disorder on neural functioning, the likelihood that multiple brain regions are affected, and the potential for heterogeneity in etiology.

Post-mortem histopathological studies have consistently demonstrated cellular alterations of the cerebellum in individuals with autism. In 21 of 29 autopsy cases reviewed by Palmen et al. (2004), there were decreased numbers of Purkinje cells, the main efferent system for the cerebellum. For a subset of cases, morphological

alterations were also present. Histopathological findings suggest that cell loss occurs more consistently in the lateral hemispheres and the vermis, particularly posterior regions (Williams et al., 1980; Ritvo et al., 1986; Fehlow et al., 1993; Bauman and Kemper, 1994; Bailey et al., 1998; Kemper and Bauman, 1998, 2002; Purcell et al., 2001; Lee et al., 2002).

Structural MRI investigations of cerebellum morphometry in ASD have generally demonstrated increases in total cerebellar volume and posterior vermis volume, but reports have been less consistent in direction of effects in other areas. Herbert et al. (2003), Sparks et al. (2002), and Palmen et al. (2005) all found increased cerebellar volume in young children with autism spectrum disorder; however, overall cerebellar volumes were proportional to total enlarged cerebral volume, rather than specific to the cerebellum. Posterior midsagittal vermis areas VI–VII have been found to be decreased (Kates et al., 1998; Carper and Courchesne, 2000; Courchesne et al., 2001; Kaufmann et al., 2003; Akshoomoff et al., 2004). In contrast, anterior vermis has been found to be both normal and increased (Courchesne et al., 2001; Akshoomoff et al., 2004); and the pyramis/uvula/nodulus (vermis volume VIII–X) has been found to be both decreased and normal (Levitt et al., 1999; Courchesne et al., 2001).

For this report, we evaluated cerebellar structural abnormalities and examined the correlation between structural differences and symptom severity and cognitive functioning in children with ASD. Children with ASD aged 3 to 4 years were compared with age-matched children with typical development, as well as with children with developmental delay, who were matched to the ASD children on both chronological and mental age. Brain-imaging findings, including overall cerebral and substructure volume relations, and tissue-based chemical alterations for this sample have been previously reported (Sparks et al., 2002; Friedman et al., 2003, 2006; Munson et al., 2006; Petropoulos et al., 2006; Boger-Megiddo et al., 2006). Based on the existing literature, we hypothesized that ASD children would demonstrate significantly smaller vermal areas and that these changes would be associated with more severe autism symptom expression and lower IQ.

2. Methods

2.1. Participants

The study sample consisted of three groups of children 3–4 years of age: 45 children with ASD, 14 children with developmental delay (DD), and 26 children with typical development (TD). In addition, two children with ASD and one TD child had magnetic resonaance imaging (MRI) scans with poorly defined cerebellar sub-regions that could not be accurately measured, and these children were excluded from all analyses. Children having significant motor or sensory impairment (e.g., blindness, deafness), major physical abnormalities, seizures, history of serious head injury, identifiable neurological disorder, prenatal or perinatal difficulties, metal implants such as prostheses, or treatment with psychoactive medications on a regular basis were not included. Further, children with developmental delay (without autism) had no known genetic syndrome (e.g., Fragile X, Down syndrome), prenatal or postnatal brain trauma, or a defined disease. Children studied at the University of Washington (UW) were recruited from local parent advocacy groups, preschools, the Center on Human Development and Disabilities, clinics and hospitals in the greater Seattle area, and the UW Infant and Child Subject Pool.

As shown in Table 1, there were no significant age differences between groups. Group differences in sex were demonstrated using Pearson χ^2 analysis. There were more girls in the DD (57.1%) group relative to the ASD (15.6%) and TD (30.7%) groups.

The TD group included 13 children studied at the UW and 13 studied at the NIH. Children recruited for the UW TD group were included if they scored within one standard deviation of normal on the Vineland Adaptive Behavior Scales, and had no parental report of language, social, motor or cognitive delay, emotional or psychiatric disturbances or had not received special services for learning problems or speech. Children in the NIH TD group were assessed via a telephone screen and an on-site structured psychiatric evaluation; children were excluded if they had a history of psychiatric illness,

neurological disorder, or developmental delay (Giedd et al., 1996). Written parental/guardian informed consent, approved by the UW Internal Review Board or the NIH Internal Review Board, was obtained for each child participating in the study.

Children with ASD were administered a diagnostic evaluation consisting of the Autism Diagnostic Interview — Revised (ADI-R; Lord et al., 1994) and the Autism Diagnostic Observation Schedule — Generic (ADOS-G; Lord et al; 2000). In addition, experienced clinicians made a clinical judgment of diagnosis based on presence/absence of autism symptoms as defined in the DSM-IV (American Psychiatric Association, 1994) using all available information. Diagnosis of autism was defined as meeting criteria for Autistic Disorder on the ADOS-G and ADI-R (within 2-points) and meeting DSM-IV criteria for Autistic Disorder based on clinical judgment ($n=30$). Diagnosis of PDD was defined as meeting criteria for ASD on the ADOS-G, meeting criteria for Autistic Disorder on the ADI-R (within 5 points), and meeting DSM-IV criteria for Autistic Disorder or PDD based on clinical judgment ($n=15$). Comparison children (DD or TD) did not meet DSM-IV criteria for Autistic Disorder or PDD based on clinical judgment. IQ for the children with ASD or DD was evaluated using the Mullen Scales of Early Learning. Children with ASD and DD were also administered the Vineland Adaptive Behavior Scales including the subscales: Adaptive Behavior, Communication, Daily Living, Motor, and Socialization. Participant descriptive demographic information is presented in Table 1. ADOS and IQ scores were not available on the TD group. The ASD group had significantly higher ADOS total scores than the DD group. The ASD and DD groups did not differ in IQ.

2.2. MRI scans

Children with ASD and DD were imaged at the UW during the daytime using continuous intravenous infusion of propofol at 180 to 220 µg/kg per minute, as previously described (Amundsen et al., 2005). TD children, scanned both at the UW and at NIH, were scanned late at night during normal sleep. For the UW TD sample, children were sedated on an optional basis with parentally administered Benadryl if the child previously had experienced sedation when given this agent ($n=8$, 25-mg PO). No sedation was used for the NIH TD sample. As prior work has established scanner compatibility between sites and previous published comparisons of cerebral volume and discrete sub-region structures were not different between the UW and NIH TD samples, the TD samples were combined for all analyses (Sparks et al., 2002).

Imaging studies at the UW and NIH were performed on a 1.5 T GE Signa Scanner. A 3-D SPGR imaging sequence (TR=33 ms, TE=3 ms, flip angle=30 degrees, 22-cm field of view (FOV) and 256×256 matrix) acquired in the coronal plane was used for volume determinations. During acquisition, the effective slice thickness of the 3-mm slice acquisition was reduced to 1.5 mm through zero-filling in the third phase encoding direction to improve spatial resolution (i.e., the effective partition thickness) with a small loss in contrast (i.e., signal-to-noise ratio). Scanning of TD children at the NIH used an identical GE scanner and similar acquisition parameters with the exception that coronal slice thickness was 2 mm (no zero-filling) at a 24-cm FOV.

2.3. Structural measurements

Volumetric measurements of total cerebrum and cerebellum, and midline area measurements of the vermal lobules I–V, VI–VII and VIII–X were performed by a single rater blinded to diagnosis (BFS) using MEASURE, a semi-automated imaging analysis program developed at Johns Hopkins University, which allows simultaneous data visualization and interaction within multiple planes (coronal, axial, sagittal). In previously reported work (Sparks et al., 2002), cerebral and cerebellum volumes were obtained using a stereotaxic grid

Table 1
Descriptive information on participants (mean, standard deviation in parentheses and range)

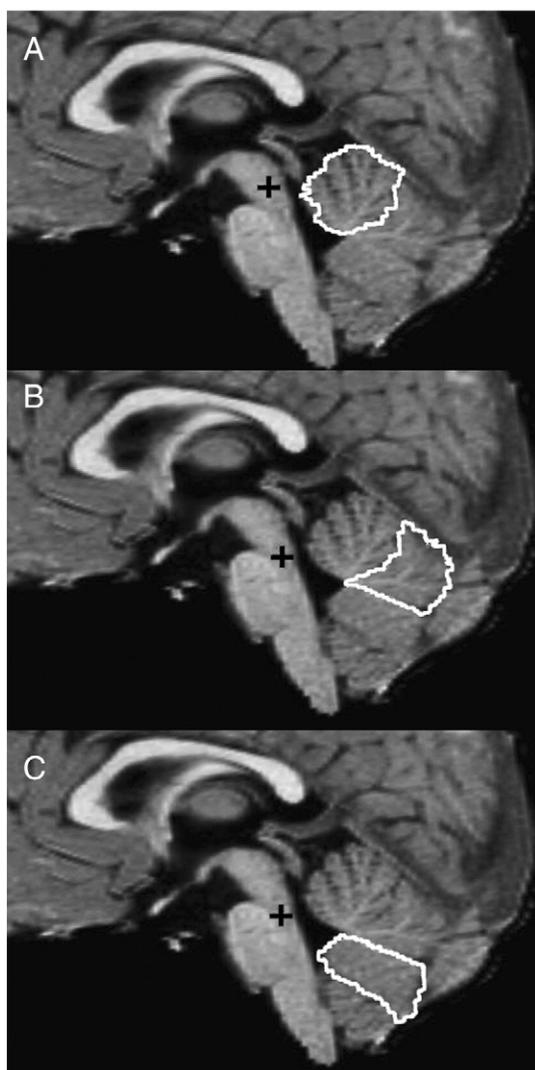|	ASD	DD	TYP	
Subjects	45	14	26	$\chi^2=9.6$, $df=2$,
	(38 males)	(6 males)	(18 males)	$P<0.008$
Age at MRI (mo.)	47.33 (4)	47.5 (6)	46.9 (6)	$F_{(2,82)}=1.0$,
	38 to 54 mo.	40 to 58 mo.	36 to 56 mo.	$P=0.91$
ADOS total	14.8 (4)	2.8 (2)	NA	$F_{(1,57)}=132$,
(Social+communication)	8 to 21	1 to 8		$P<0.001$
Mullen	59.0 (21)	56.9 (14)	NA	$F_{(1,56)}=0.13$,
IQ	30 to 104	29 to 79		$P=0.72$
Mullen	53.2 (25)	54.4 (16)	NA	$F_{(1,56)}=0.03$,
Verbal IQ	18 to 108	20 to 82		$P=0.87$
Mullen	64.8 (18)	59.8 (15)	NA	$F_{(1,57)}=0.91$,
Non-verbal IQ	36 to 104	38 to 93		$P=0.34$

Fig. 1. Representative midsagittal MRI of a subject with ASD showing vermal sub-regions: Fig. 1A depicts vermal lobules I–V; Fig. 1B depicts vermal lobules VI–VII; Fig. 1C depicts vermal lobules VIII–X.

(Gunderson and Jensen, 1987). In the current study, cerebral and cerebellar measurements were obtained using a semi-automated histogram approach to improve measurement sensitivity for small volume differences (Friedman et al., 2006; Petropoulos et al., 2006). Cerebral volume included the basal ganglia and corpus callosum, and excluded the ventricles, brain stem and cerebellum. At the level of the cerebellar peduncles, the cerebellum and brain stem were separated from the cerebrum by drawing a straight line from the most antero-lateral point of the fourth ventricle to the "notch" that is created by the junction of the brainstem and cerebellum (Fig. 1). The cerebellum was segmented using rules previously described in an article by Aylward and Reiss (1991). The approach used by previous researchers (Aylward and Reiss, 1991; Courchesne et al., 1994) for measuring vermal lobules was employed. The vermian segmentation was performed by an experienced analyst (BFS) supervised by a pediatric neuroradiologist (DWWS). Briefly, a midsaggital slice was reconstructed where the apex of the fourth ventricle, the cerebral aqueduct and the obex were all visible. Divisions between lobes I–V, VI–VII, and VIII–X were traced on this slice, as illustrated in Fig. 1a, b and c. Interrater reliability (DWWS vs. BFS) on 10 scans produced the following correlation values: vermal lobes I–V=0.97, vermal lobes VI–VII=0.94, and vermal lobes VIII–X=0.89.

2.4. Data analysis

Because both age and gender are known to affect brain size, data were analyzed with covariance for age and sex to account for any potential influences on comparisons. In addition, in order to account for the influence of brain volume on sub-regional analyses, we undertook an additional set of analyses using cerebral volume or cerebellum volume as a covariate in addition to gender and age.

For those measures showing group differences, additional analyses were performed to evaluate the distribution of measurements. Courchesne et al. (1994) suggest that the variability in vermal areas found in ASD represents two distinct subpopulations of ASD individuals: those with vermal hypoplasia and those with vermal hyperplasia. To replicate those findings, data were plotted as a probability plot in which observed vermis area values for each subject were plotted against the expected normal distribution. In this type of plot, a unimodal Gaussian distribution would appear as a straight line; whereas a significant Shapiro and Wilk's W statistic would reject the assumption of a normal distribution.

To examine whether individual differences in cerebellar volume or sub-region volumes were correlated with symptom severity (ADOS, ADI), IQ (Mullen Scales), or general functioning (Vineland Adaptive Behavior Scales) (e.g., Paradiso et al., 1997; Mostofsky et al., 1998), structural measures were examined separately for the ASD subgroups, which differed in terms of severity of symptoms (Autism Disorder vs. PDD). Correlations with ADOS, ADI, Mullen Scales of Early Learning, and the Vineland Adaptive Behavioral Scales were conducted separately for the ASD and DD groups for total vermis area and cerebellum volume. Relations with behavioral measures were considered exploratory.

3. Results

3.1. Structural measures

Structural measures for the three groups are shown in Table 2 and statistical comparisons are shown in Table 3. Vermal areas are plotted in Fig. 2.

3.1.1. Total vermis

Covarying for age and gender, total vermal area in the ASD group was marginally smaller (at the trend level) compared with the TD group. However, when either controlling for cerebral volume or cerebellar volume, total vermal area was disproportionately smaller in children with ASD (see Tables 2 and 3). Compared with the ASD and TD groups, the children with DD exhibited significantly smaller total vermal area with scaling for age and gender. This finding persisted when using cerebral volume as a covariate. In contrast, the total vermis area did not differ between DD and ASD groups when cerebellum volume was added as a covariate.

3.1.2. Vermal sub-regions

Results of analyses of the vermal sub-regions are shown in Table 3. Covarying for age and gender, vermal segments VI–VII in the ASD group

Table 2
Raw group means (±S.D.) for brain regions in children with autism spectrum disorder (ASD), typical development (TD), and developmental delay (DD)

	Total vermis (mm^2)	Vermis I–V (mm^2)	Vermis VI–VII (mm^2)	Vermis VIII–X (mm^2)	Cerebellum (ml)	Cerebrum (ml)
ASD	1023 (114)	426 (54)	284 (53)	312 (48)	1377.71 (129.9)	11,730.19 (937.3)
TD	1087 (134)	452 (58)	319 (68)	316 (45)	1289.17 (138.8)	10,872.60 (1020.8)
DD	820 (246)	343 (104)	235 (76)	242 (83)	1020.77 (353.9)	10,492.86 (1289.2)

Table 3

Group comparison of brain regions for children with autism spectrum disorder (ASD), typical development (TD), and delayed development (DD)

	Group comparisons[a]	ANCOVA (Age and sex)	ANCOVA (Age, sex, cerebral volume)	ANCOVA (Age, sex, cerebellum volume)
Total vermis		$F_{(2,80)}=12.8$, $P<0.0001$	$F_{(2,79)}=15.0$, $P<0.0001$	$F_{(2,79)}=10.1$, $P<0.0001$
	ASD vs. TD	$P=0.064$	$P=0.001$	$P<0.001$
	ASD vs. DD	$P<0.001$	$P=0.010$	$P=0.879$
	TD vs. DD	$P<0.001$	$P<0.001$	$P=0.004$
Vermis I–V		$F_{(2,80)}=11.1$, $P<0.0001$	$F_{(2,79)}=12.8$, $P<0.0001$	$F_{(2,79)}=8.7$, $P<0.0001$
	ASD vs. TD	$P=0.096$	$P=0.003$	$P<0.001$
	ASD vs. DD	$P=0.001$	$P=0.018$	$P=0.861$
	TD vs. DD	$P<0.001$	$P<0.001$	$P=0.014$
Vermis VI–VII		$F_{(2,80)}=7.7$, $P=0.001$	$F_{(2,79)}=9.4$, $P<0.0001$	$F_{(2,79)}=6.3$, $P=0.003$
	ASD vs. TD	$P=0.020$	$P=0.001$	$P=0.001$
	ASD vs. DD	$P=0.032$	$P=0.023$	$P=0.946$
	TD vs. DD	$P<0.001$	$P<0.001$	$P=0.030$
Vermis VIII–X		$F_{(2,80)}=8.0$, $P=0.001$	$F_{(2,79)}=7.0$, $P=0.002$	$F_{(2,79)}=2.1$, $P=0.129$
	ASD vs. TD	$P=0.690$	$P=0.179$	$P=0.119$
	ASD vs. DD	$P=0.001$	$P=0.010$	$P=0.527$
	TD vs. DD	$P<0.001$	$P<0.001$	$P=0.086$
Cerebellum		$F_{(2,80)}=14.0$, $P<0.0001$	$F_{(2,79)}=10.8$, $P<0.0001$	
	ASD vs. TD	$P=0.105$	$P=0.755$	
	ASD vs. DD	$P<0.001$	$P<0.001$	
	TD vs. DD	$P<0.001$	$P<0.001$	
Cerebrum		$F_{(2,80)}=6.9$, $P=0.002$		
	ASD vs. TD	$P=0.003$		
	ASD vs. DD	$P=0.004$		
	TD vs. DD	$P=0.526$		

[a] Post hoc adjustment for multiple comparison using least significant differences.

Fig. 2. Adjusted means and standard deviations (bars) for vermal areas when age, sex, and cerebrum or age, sex and cerebellum were used as covariates.

were smaller than corresponding segments in the TD group. Significantly smaller areas in the ASD group compared with the TD group were accentuated with the additional covariates of either cerebral volume or cerebellar volume and included both sub-regions I–V and VI–VII. No differences were found for sub-regions VIII–X when comparing ASD and TD groups.

Compared with the ASD and TD groups, the DD group exhibited significantly reduced volume for regions I–V, VI–VII, and VIII–X when covarying for age and gender. A similar direction of results for both sub-regions was demonstrated when adding cerebral volume as a covariate. In contrast, adding cerebellum as a covariate resulted in a lack of statistical differences for both sub-regions between DD and ASD groups but not between DD and TD groups.

3.2. Distribution of measurements

Using the approach of Courchesne et al. (1994), we examined the distribution of vermal areas within each diagnostic group to assess the occurrence of a bimodal distribution of measurements. There were no deviations from the normal distribution for any of the groups for vermis I–V area (all Shapiro–Wilk's $W>0.95$, all Ps=ns) or vermis VIII–X area (all Shapiro–Wilk's $W>0.9595$ Ps=ns). For vermis VI–VII area, both the ASD and TD group deviated from the normality assumption (Shapiro–Wilk's W ASD=0.92, $P<0.01$, DD=0.93, P=ns; TD=0.91, $P=0.03$).

To further explore the distribution across and within groups, we categorized each sub-region in relation to the mean of the TD sample. That is, based on the raw means and S.D. presented in Table 2, individuals were recoded as having a value greater than +1 S.D. from the mean, within 1 S.D. of the mean, or −1 S.D. or more from the TD mean. Presented in Table 4 and Fig. 3, the overall distribution differed across the three groups. In all three sub-regions, the DD group compared with the ASD and TD group had a larger proportion of individuals below 1 S.D.
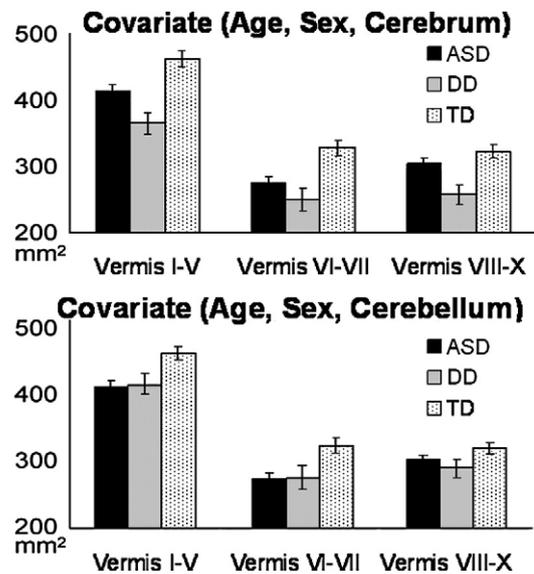
3.3. Relation of cerebellum structure to behavior

To evaluate whether individual differences in cerebellar structure were correlated with behavioral differences, we first assessed differences in cerebellar structure between ASD subgroups (AUT vs. PDD) differing in symptom severity. There were no significant differences between ASD subgroups for cerebellar volume, total vermal area, sub-regional areas vermis I–V, VI–VII, or VIII–X when including age, gender, and total cerebral volume or age, gender, and cerebellum volume as covariates: cerebellar volume (AUT: M=1380, S.D.=134; PDD: M=1373, S.D.=126), total vermal area (AUT: M=1016, S.D.=112; PDD: M=1037, S.D.=123), sub-regional areas vermis I–V (AUT: M=426, S.D.=54; PDD: M=428, S.D.=57), vermis VI–VII (AUT: M=281, S.D.=49; PDD: M=290, S.D.=v61), or vermis VIII–X (AUT: M=308, S.D.=48; PDD: M=319, S.D.=50).

Second, we examined the relation between symptom severity, IQ and adaptive functioning in the ASD group. There were no significant correlations between total vermis area or cerebellum volume and symptom severity, IQ or adaptive functioning.

Third, we examined the relation between IQ and adaptive functioning in the DD group. The Vineland Communication Standard Score, Daily Living Standard Score, and Motor Standard Score were correlated with total vermal area (rs=0.59 to 0.64, Ps<0.05). The Social Standard Score was not correlated. Motor Standard Score was also correlated with cerebellum volume (r=0.58, $P<0.05$). Larger

Table 4

Distribution of individual area measurements relative to the mean of the typically developing group

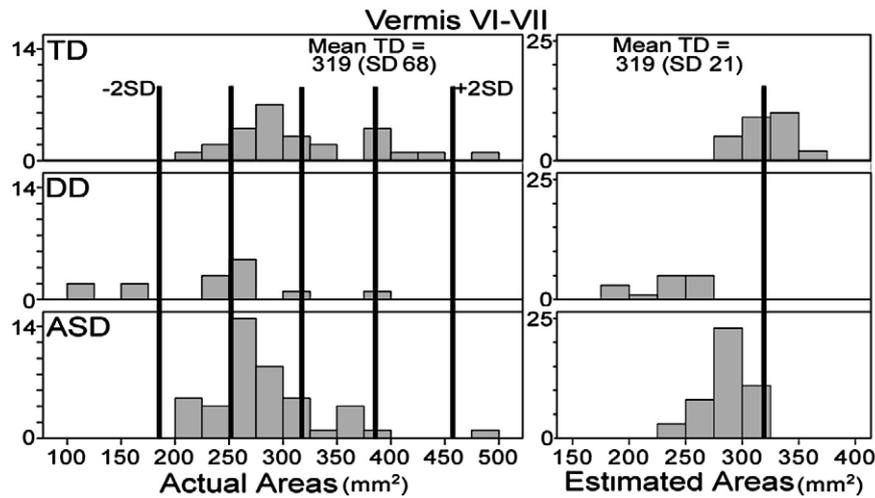|	−1 S.D.	−0.99 to 0.99 S.D.	+1 S.D.
Vermis I–V	$\chi^2=17.4$, $df=4$, $P=ß0.002$		
ASD	12	30	3
DD	10	4	0
TD	3	19	4
Vermis VI–VII	$\chi^2=20.26$, $df=4$, $P<0.001$		
ASD	10	34	1
DD	8	5	1
TD	3	16	7
Vermis VIII–X	$\chi^2=11.2$, $df=4$, $P=0.02$		
ASD	9	29	7
DD	8	5	1
TD	3	19	4

Fig. 3. Distribution of actual and estimated areas for vermis VI–VII. Black vertical bars represent 1 S.D. of TD mean. The DD group compared with the ASD and TD groups had a larger proportion of individuals below 1 S.D.

vermis total area (or cerebellum volume) was correlated with better scores (i.e., fewer impairments).

4. Discussion

The primary finding of this study was a significant reduction in midsagittal vermian area, vermal lobes I–V, and vermal lobes VI–VII when adjusted for increases in total cerebral or cerebellum volume in the children with ASD as compared to the children with typical development. Children with developmental delay exhibited cerebellar volumes that were persistently smaller compared to children with typical development and ASD, after controlling for age, gender, and total cerebral volume. These findings are similar to previous reports suggesting hypoplasia of vermis VI–VII in children with autism and children with PDD aged 1.9 to 5.2 years (Akshoomoff et al., 2004) and an overlapping sample of children with autism compared with typical controls aged 2 to 16 years (Courchesne et al., 2001). This pattern of decreased vermal midsagittal area may be a general anatomical finding associated with ASD, consistent with the results of a meta analysis which noted that between 84% and 92% of individuals with ASD exhibited vermal hypoplasia (Courchesne et al., 1994).

As well, we examined whether there existed a bimodal distribution for vermal areas and whether the distributions for the volume of the vermal lobules VI–VII for both the ASD and TD groups deviated from normal. Thus, while we did find evidence of a non-normal distribution, this pattern does not appear to be specific to the ASD sample. As seen in Fig. 3, the ASD and TD groups have extreme overlap in absolute (raw) values (Fig. 3a) and some overlap in volumes that are corrected for age, gender and cerebrum volume (Fig. 3b). Furthermore, while the mean value of the ASD group significantly differed from the TD group, only a small number of individuals had volumes that were beyond 1 S.D. of the mean.

Our findings are in contrast with Akshoomoff's report of increased anterior vermis areas (Akshoomoff et al., 2004). Specifically, we found smaller anterior vermis I–V areas in children with ASD compared with TD (Fig. 2). Examining the variability in vermis I–V areas, as compared with the TD mean, 34% of the ASD sample and 71% of the DD sample had values 1 S.D. below the mean of the TD group, while 6% of the ASD sample and 0% of the DD sample had values 1 S.D. above the mean of the TD group. There are several demographic differences as well between the Akshoomoff sample and ours. Akshoomoff included only *male* children between 1.9 and 5.2 years of age. Our sample included both male and female children

between 3.0 and 4.8 years of age. More importantly, our analyses used gender, age, and total cerebral volume or cerebellum volume as covariates, whereas Akshoomoff et al. did not. Given that Akshoomoff et al. also found enlarged total brain volume in children with low ($P<0.05$) and high ($P=0.08$) functioning autism vs. controls, it is possible that their pattern of findings would change if scaled for total cerebral volume.

In this study, we found no relation between cerebellar measures and measures of symptom severity and verbal or non-verbal IQ in the ASD group. However, there was a relation within the DD group with larger vermal area and cerebellum volume being correlated with better daily living skills, better communication, and more typical motor skills. It is unclear why these skills would be correlated within the DD group but not the ASD group. (Scores were not available for the TD sample.) One possibility is that children in the DD group represented the lower end of the normal distribution and thus demonstrate the same relation found in neurotypicals. In neurologically typical individuals, larger cerebellum size has been shown to be correlated with better neurophysiological functioning, including memory, fine motor dexterity, and IQ (Andreasen et al., 1993; Paradiso et al., 1997).

There have been some structural correlations with neurophysiological findings in ASD. Of note, in a recent report with the same group of children with ASD, we found that larger right amygdala volume, but not hippocampal volume, was predictive of poorer social and communication abilities (Munson et al., 2006). There are several possible explanations to account for the absence of a relation between cerebellar measures and measures of autism symptom severity. First, it is possible that measures that more directly relate to cerebellar function are needed to fully explore the functional significance of these anatomical findings (e.g., manual dexterity such as finger tapping, verbal memory). Second, the cerebellum may mediate general behaviors (such as attention, exploration) that are reflective of the autism phenotype but not directly assessed by the measures in this study.

In contrast to autism, individuals with Williams Syndrome (WMS) show conserved cerebellar volume and disproportional enlargement of VI–VII and VIII–X despite reduced cerebral volumes (Jernigan and Bellugi, 1990; Reiss et al., 2000; Schmitt et al., 2001). Individuals with WMS are socially motivated, although the disorders share characteristics of abnormalities in motor coordination and gait. Of note, Schaefer et al. (1996) have observed that hypoplasia of cerebellar vermal lobules VI and VII is a diagnostically non-specific finding that occurs in a number of other developmental disorders. For example,

decreases in vermal size have been reported in association with ADHD, fragile X, schizophrenia, velo-cardio-facial syndrome, and Joubert syndrome (e.g., Holroyd et al., 1991; Mostofsky et al., 1998; Nopoulos et al., 1999; Eliez et al., 2001; Campbell et al., 2006). Thus, cerebellum structures may be genetically unstable, environmentally susceptible, or sensitive to downstream alterations by other affected regions.

What might cause relative decreases in vermal area? It has been suggested that there are two types of cerebellar pathology in autism. First, there may be structural hypoplasia of posterior vermal lobes VI–VII and cerebellar hemispheres related to severe Purkinje neuron loss. Second, hypoplasia may result from a failure to develop appropriate prefrontal–neocerebellar circuitry. The posterior vermis has a long postnatal development period and develops in parallel with frontal and prefrontal structures (Schmahmann, 1991; Ciesielski et al., 1997). Deficits at any levels of the circuitry may result in eventual neuronal loss in the cerebellum.

Although the cerebellar system it has consistently been identified as a region of abnormality in histopathological postmortem studies of autism, the link between anatomical measurements and the autism phenotype is unclear. Future investigations of cerebellar dysmorphology that include targeted functional assessments, are appropriate for across species use, and allow for the assessment of developmental stages of the disorder will provide valuable evidence about the role cerebellar circuitry plays in ASD.

Acknowledgements

References

Akshoomoff, N., Lord, C., Lincoln, A.J., Courchesne, R.Y., Carper, R.A., Townsend, J., Courchesne, E., 2004. Outcome classification of preschool children with autism spectrum disorders using MRI brain measures. Journal of the American Academy of Child and Adolescent Psychiatry 43, 349–357.

American Psychiatric Association, 1994. Diagnostic and Statistical Manual of Mental Disorders, 4th ed. American Psychiatric Association, Washington, DC.

Amundsen, L.B., Artru, A.A., Dager, S.R., Shaw, D.W., Friedman, S., Sparks, B., Dawson, G., 2005. Propofol sedation for longitudinal pediatric neuroimaging research. Journal of Neurosurgical Anesthesiology 17 (4), 180–192.

Andreasen, N.C., Flaum, M., Swayze II, V., O'Leary, D.S., Alliger, R., Cohen, G., Ehrhardt, J., Yuh, W.T., 1993. Intelligence and brain structure in normal individuals. The American Journal of Psychiatry 150 (1), 130–134.

Aylward, E.H., Reiss, A., 1991. Area and volume measurement of posterior fossa structures in MRI. Journal of Psychiatric Research 25, 159–168.

Bailey, A., Luthert, P., Dean, A., Harding, B., Janota, I., Montgomery, M., Rutter, M., Lantos, P., 1998. A clinicopathological study of autism. Brain 121, 889–905.

Bauman, M.L., Kemper, T.L., 1994. Neuroanatomic observations of the brain in autism. In: Bauman, M.L., Kemper, T.L. (Eds.), The Neurobiology of Autism. Johns Hopkins University Press, Baltimore, pp. 119–145.

Boger-Megiddo, I., Shaw, D.W., Friedman, S.D., Sparks, B.F., Artru, A.A., Giedd, J.N., Dawson, G., Dager, S.R., 2006. Corpus callosum morphometrics in young children with autism spectrum disorder. Journal of Autism and Developmental Disorders 36 (6), 733–739.

Campbell, L.E., Daly, E., Toal, F., Stevens, A., Azuma, R., Catani, M., Ng, V., van Amelsvoort, T., Chitnis, X., Cutterm, W., Murphy, D.G., Murphy, K.C., 2006. Brain and behaviour in children with 22q11.2 deletion syndrome: a volumetric and voxel-based morphometry MRI study. Brain 129 (Pt 5), 1218–1228.

Carper, R., Courchesne, C., 2000. Inverse correlation between frontal lobe and cerebellum sizes in children with autism. Brain 123 (4), 836–844.

Ciesielski, K.T., Harris, R.J., Hart, B.L., Pabst, H.F., 1997. Cerebellar hypoplasia and frontal lobe cognitive deficits in disorders of early childhood. Neuropsychologia 35, 643–655.

Courchesne, E., Townsend, J., Saitoh, O., 1994. The brain in infantile autism: posterior fossa structures are abnormal. Neurology 44, 214–223.

Courchesne, E., Karns, C.M., Davis, H.R., Ziccardi, R., Carper, R.A., Tigue, Z.D., Chisum, H.J., Moses, P., Pierce, K., Lord, C., Lincoln, A.J., Pizzo, S., Schreibman, L., Haas, R.H., Akshoomoff, N.A., Courchesne, R.Y., 2001. Unusual brain growth patterns in early life in patients with autistic disorder. An MRI study. Neurology 57, 245–254.

Eliez, S., Schmitt, J.E., White, C.D., Wellis, V.G., Reiss, A.L., 2001. A quantitative MRI study of posterior fossa development in velocardiofacial syndrome. Biological Psychiatry 49 (6), 540–546.

Fehlow, P., Bernstein, K., Tennstedt, A., Walther, F., 1993. Early infantile autism and excessive aerophagy with symptomatic megacolon and ileus in a case of Ehlers–Danlos syndrome. Padiatrie und Grenzgebiete 31 (4), 259–267.

Friedman, S.D., Shaw, D.W., Artru, A.A., Richards, T.L., Gardner, J., Dawson, G., Posse, S., Dager, S.R., 2003. Regional brain chemical alterations in young children with autism spectrum disorder. Neurology 60, 100–107.

Friedman, S.D., Shaw, D.W., Artru, A.A., Dawson, G., Petropoulos, H., Dager, S.R., 2006. Gray and white matter brain chemistry in young children with autism. Archives of General Psychiatry 63 (7), 786–794.

Giedd, J.N., Snell, J.W., Lange, N., Rajapakse, J.C., Casey, B.J., Kozuch, P.L., Vaituzis, A.C., Vauss, Y.C., Hamburger, S.D., Kaysen, D., Rapoport, J.L., 1996. Quantitative magnetic resonance imaging of human brain development: ages 4–18. Cerebral Cortex 6 (4), 551–560.

Gunderson, H., Jensen, E., 1987. The efficiency of systematic sampling in stereology and its prediction. Journal of Microscopy 147, 229–263.

Herbert, M., Ziegler, D., Deutsch, C., O'Brien, L., Lange, N., Bakardjiev, A., Hodgson, J., Adrien, K., Steele, S., Makris, N., Kennedy, D., Harris, G., Caviness, V., 2003. Dissociations of cerebral cortex, subcortical and cerebral white matter volumes in autistic boys. Brain 126, 1182–1192.

Holroyd, S., Reiss, A.L., Bryan, R.N., 1991. Autistic features in Joubert syndrome: a genetic disorder with agenesis of the cerebellar vermis. Biological Psychiatry 29 (3), 287–294.

Jernigan, T.L., Bellugi, U., 1990. Anomalous brain morphology on magnetic resonance images in Williams syndrome and Down syndrome. Archives of Neurology 47 (5), 529–533.

Kates, W.R., Mostofsky, S.H., Zimmerman, A.W., Mazzocco, M.M., Landa, R., Warsofsky, I.S., Kaufmann, W.E., Reiss, A.L., 1998. Neuroanatomical and neurocognitive differences in a pair of monozygous twins discordant for strictly defined autism. American Neurologic Association 43, 782–791.

Kaufmann, W.E., Cooper, K.L., Mostofsky, S.H., Capone, G.T., Kates, W.R., Newschaffer, C.J., Bukelis, I., Stump, M.H., Jann, A.E., Lanham, D.C., 2003. Specificity of cerebellar vermian abnormalities in autism: a quantitative magnetic resonance imaging study. Journal of Child Neurology 18, 463–470.

Kemper, T.L., Bauman, M., 1998. Neuropathology of infantile autism. Journal of Neuropathology and Experimental Neurology 57, 645–652.

Kemper, T.L., Bauman, M.L., 2002. Neuropathology of infantile autism. Molecular Psychiatry 7 (2), S12–S13.

Lee, M., Martin-Ruiz, C., Graham, A., Court, J., Jaros, E., Perry, R., Iversen, P., Bauman, M., Perry, E., 2002. Nicotinic receptor abnormalities in the cerebellar cortex in autism. Brain 127, 1483–1495.

Levitt, J.G., Blanton, R., Capetillo-Cunliffe, L., Guthrie, D., Toga, A., Cracken, J.T., 1999. Cerebellar vermis lobules VIII–X in autism. Progress in Neuro-Psychopharmacology and Biology Psychiatry 23, 625–633.

Lord, C., Rutter, M., Le Couteur, A., 1994. Autism Diagnostic Interview — Revised. A revised version of a diagnostic interview for caregivers of individuals with possible pervasive developmental disorders. Journal of Autism and Developmental Disorders 24, 659–685.

Lord, C., Risi, S., Lambrecht, L., Cook Jr, E.H., Leventhal, B.L., DiLavore, P.C., Pickles, A., Rutter, M., 2000. The Autism Diagnostic Observation Schedule — Generic. A standard measure of social and communication deficits associated with the spectrum of autism. Journal of Autism and Developmental Disorders 30, 205–223.

Mostofsky, S.H., Reiss, A.L., Lockhart, P., Denckla, M.B., 1998. Evaluation of cerebellar size in attention-deficit hyperactivity disorder. Journal of Child Neurology 13 (9), 434–439.

Munson, J., Dawson, G., Abbott, R., Faja, S., Webb, S.J., Friedman, S.D., Shaw, D., Artru, A., Dager, S.R., 2006. Amygdalar volume and behavioral development in autism. Archives of General Psychiatry 63 (6), 686–693.

Nopoulos, P.C., Ceilley, J.W., Gailis, E.A., Andreasen, N.C., 1999. An MRI study of cerebellar vermis morphology in patients with schizophrenia: evidence in support of the cognitive dysmetria concept. Biological Psychiatry 46 (5), 703–711.

Palmen, S.J., van Engeland, H., Hof, P.R., Schmitz, C., 2004. Neuropathological findings in autism. Brain 127 (Pt 12), 2572–2583.

Palmen, S.J., Hulshoff Pol, H.E., Kemner, C., Schnack, H.G., Durston, S., Lahuis, B.E., Kahn, R.S., Van Engeland, H., 2005. Increased gray-matter volume in medication-naive high-functioning children with autism spectrum disorder. Psychological Medicine 35 (4), 561–570.

Paradiso, S., Andreasen, N.C., O'Leary, D.S., Arndt, S., Robinson, R.G., 1997. Cerebellar size and cognition: correlations with IQ, verbal memory and motor dexterity. Neuropsychiatry, Neuropsychology, and Behavior Neurology 10 (1), 1–8.

Petropoulos, H., Friedman, S.D., Shaw, D.W., Artru, A.A., Dawson, G., Dager, S.R., 2006. Gray matter abnormalities in autism spectrum disorder revealed by T2 relaxation. Neurology 67 (4), 632–636.

Purcell, A.E., Jeon, O.H., Zimmerman, A.W., Blue, M.E., Pevsner, J., 2001. Postmortem brain abnormalities of the glutamate neurotransmitter system in autism. Neurology 57, 1618–1628.

Reiss, A.L., Eliez, S., Schmitt, J.E., Straus, E., Lai, Z., Jones, W., Bellugi, U., 2000. IV. Neuroanatomy of Williams syndrome: a high-resolution MRI study. Journal of Cognitive Neuroscience 12 (Supplement 1), 65–73.

Ritvo, E.R., Freeman, B.J., Scheibel, A.B., Duong, T., Robinson, H., Guthrie, D., Ritvo, A., 1986. Lower Purkinje cell counts in the cerebella of four autistic subjects. Initial findings of the UCLA-NSAC autopsy research report. The American Journal of Psychiatry 143, 862–866.

Schaefer, G., Thompson, J., Bodensteiner, J., McConnell, J., Kimberling, W., Gay, C., Dutton, W., Hutchings, D., Gray, S., 1996. Hypoplasia of the cerebellar vermis in neurogenetic syndromes. Annals of Neurology 39, 382–385.

Schmahmann, J.D., 1991. An emerging concept. The cerebellar contribution to higher function. Archives of Neurology 48 (11), 1178–1187.

Schmitt, J.E., Eliez, S., Warsofsky, I.S., Bellugi, U., Reiss, A.L., 2001. Enlarged cerebellar vermis in Williams syndrome. Journal of Psychiatric Research 35 (4), 225–229.

Sparks, B.F., Friedman, S.D., Shaw, D.W., Aylward, E.H., Echelard, D., Artru, A.A., Maravilla, K.R., Giedd, J.N., Munson, J., Dawson, G., Dager, S.R., 2002. Brain structural abnormalities in young children with autism spectrum disorder. Neurology 59, 184–192.

Williams, R.S., Hauser, S.L., Purpura, D.P., DeLong, G.R., Swisher, C.N., 1980. Autism and mental retardation: neuropathologic studies performed in four retarded persons with autistic behavior. Archives of Neurology 37 (12), 749–753.