Cerebellar Function in Autism: Functional Magnetic Resonance Image Activation During a Simple Motor Task

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Background: *The cerebellum is one of the most consistent sites of neuroanatomic abnormality in autism, yet it is still unclear how such pathology impacts cerebellar function. In normal subjects, we previously demonstrated with functional magnetic resonance imaging (fMRI) a dissociation between cerebellar regions involved in attention and those involved in a simple motor task, with motor activation localized to the anterior cerebellum ipsilateral to the moving hand. The purpose of the present investigation was to examine activation in the cerebella of autistic patients and normal control subjects performing this motor task.*

Methods: *We studied eight autistic patients and eight matched normal subjects, using fMRI. An anatomic region-of-interest approach was used, allowing a detailed examination of cerebellar function.*

Results: *Autistic individuals showed significantly increased motor activation in the ipsilateral anterior cerebellar hemisphere relative to normal subjects, in addition to atypical activation in contralateral and posterior cerebellar regions. Moreover, increased activation was correlated with the degree of cerebellar structural abnormality.*

Conclusions: *These findings strongly suggest dysfunction of the autistic cerebellum that is a reflection of cerebellar anatomic abnormality. This neurofunctional deficit might be a key contributor to the development of certain diagnostic features of autism (e.g., impaired communication and social interaction, restricted interests, and stereotyped behaviors).*

Key Words: Autism, brain development, cerebellum, magnetic resonance imaging, motor, pervasive developmental disorders

Autism is a pervasive developmental disorder characterized by impaired social interaction and communication, behavioral stereotypes, and a range of cognitive deficits (American Psychiatric Association 1994). Abnormalities in nearly every brain system have been proposed to underlie this condition (e.g., Bachevalier 1996; Bailey et al 1996; Baron-Cohen et al 2000; Ciaranello and Ciaranello 1995; Courchesne 1997; DeLong 1992; Minshew 1994); however, autopsy and structural magnetic resonance imaging (MRI) studies have demonstrated that one of the most consistent sites of neuroanatomic abnormality is the cerebellum (for reviews, see Courchesne 1997; Courchesne and Pierce 2002). For example, more than 95% of autistic cases examined at autopsy show cerebellar pathology. The most common is a reduction of Purkinje neurons (Bailey et al 1998; Fehlow et al 1993; Kemper and Bauman 1998; Ritvo et al 1986; Williams et al 1980), though molecular and receptor abnormalities have also been reported (Fatemi et al 2001; Purcell et al 2001; Fatemi et al 2002b; Lee et al 2002), as has reduced Purkinje cell size (Fatemi et al 2002a). Nonetheless, cerebellar involvement in autism remains a controversial topic. This controversy seems to be fueled largely by the traditional view that the cerebellum is exclusively a motor structure, causing many to question the relevance of cerebellar abnormality to a disorder characterized by cognitive, social, and emotional deficits; however, recent data showing cerebellar involvement in a variety of cognitive, social, and emotional functions (e.g., Allen et al 1997; Courchesne et al 1994d; Fiez et al 1992; Gao et al 1996; Gottwald et al 2003; Ivry et al 2002; Le et al 1998; Paradiso et al 1997; Sacchetti et al 2002; Schmahmann and Sherman 1998; Townsend et al 1999; Trillenberg et al 2004; Xiang et al 2003) have significantly revised the traditional view. Thus, it is in fact not unreasonable to consider the potential role of cerebellar dysfunction in autism.

Neurobehavioral studies have shown associations between cerebellar anatomic abnormality and certain motor, cognitive, and social deficits (Haas et al 1996; Harris et al 1999; Pierce and Courchesne 2001; Townsend et al 1999); however, functional neuroimaging data on the autistic cerebellum are relatively limited (Table 1), with only two studies (Allen and Courchesne 2003; Heh et al 1989) designed specifically to address cerebellar function. The overall picture from these investigations is equivocal; several reported reduced cerebellar activity relative to normal, some showed relative increases, whereas still others showed no difference. Together, these studies highlight the need for further investigation of cerebellar function in autism, with a closer examination of the association between anatomic and functional abnormalities.

The goal of the present study was to examine the dynamics of simple motor activation in the autistic cerebellum, with particular attention to the relationship between structural volume and functional activation within cerebellar subregions. We used the same motor task from our previous functional (f)MRI investigations (i.e., self-paced button press with the dominant thumb; Allen et al 1997; Allen and Courchesne 2003). Self-paced movements were chosen because imposed pacing adds an attentional component, which can confound the study of a population known for its attentional deficits (Allen and Courchesne 2001). We took an anatomic region-of-interest (ROI) approach to analyzing functional data. This approach had two stages. In the primary analysis, activation was examined in cerebellar regions normally involved in the motor task. In the secondary stage, we explored beyond these areas. In this manner, we were able to investigate possible functional abnormalities in cerebellar motor areas, in addition to potential abnormal involvement of cerebellar tissue outside of these regions.

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Table 1. Functional Neuroimaging Studies Reporting Cerebellar Activation in Autistic Individuals Relative to Normal Control Subjects

Study	Modality	Task	Reported Location
No Difference from Normal			
Hashimoto et al 2000	SPECT	N/A	Vermis and hemispheres
Rumsey et al 1985	PET (rCMRglc)	N/A	Cerebellum
Heh et al 1989	PET (rCMRglc)	N/A	Vermis and hemispheres
Baron-Cohen et al 1999	fMRI	Theory of mind	Cerebellum
Luna et al 2002	fMRI	Working memory	Lateral cerebellum
Less Activity than Normal			
George et al 1992	SPECT	N/A	Cerebellum
Ryu et al 1999	SPECT	N/A	Cerebellar hemisphere
Müller et al 1998	PET (^{15}O)	Listen to sentences	Right dentate nucleus
Müller et al 1999	PET (^{15}O)	Listen to tones	Vermis and hemispheres
Critchley et al 2000	fMRI	Judge facial expressions	Left cerebellum
Allen and Courchesne 2003	fMRI	Selective attention	Posterior hemispheres
Müller et al 2003	fMRI	Motor learning	Left anterior cerebellum
Greater Activity than Normal			
Müller et al 1998	PET (^{15}O)	Repeat sentences	Right dentate nucleus
Müller et al 2001	fMRI	Finger movements	Vermis
Allen and Courchesne 2003	fMRI	Thumb movement	Posterior hemispheres

Locations are reported as they were described in the original studies. SPECT, single photon emission computed tomography; PET, positron emission tomography; rCMRglc, regional cerebral metabolic rate for glucose; fMRI, functional magnetic resonance imaging.

Methods and Materials

Subjects

Participants (Table 2) were eight patients with autism (aged 14.4–38.2 years) and eight normal control subjects (aged 14.0–39.7 years). Patients were diagnosed with autistic disorder as defined by the DSM-IV (American Psychiatric Association 1994). They also fulfilled Autism Diagnostic Interview-Revised (Lord et al 1994) and Autism Diagnostic Observation Schedule (ADOS; Lord et al 1989) criteria for autism. None met criteria for Asperger's syndrome. Diagnoses were made by clinical psychologists within our laboratory and not by referring clinicians. None of the patients were positive for fragile X, as determined by deoxyribonucleic acid or chromosomal analyses; none had a history of seizure or seizure-like episodes; none had additional

Table 2. Description of Autistic and Normal Subjects

Subject No.	Gender	Hand	Age (years)	BD	OA	IQ
Autistic Subjects						
1	M	R	14.43	19	9	87
2	M	R	20.34	9	10	74
3	F	R	20.73	8	10	73
4	M	L	21.56	15	9	79
5	M	R	32.19	12	13	76
6	M	R	33.73	18	10	103
7	M	L	33.94	13	10	102
8	M	L	38.16	6	10	86
Mean			26.89	12.50	10.13	85.00
SD			8.59	4.69	1.25	11.95
Normal Subjects						
1	M	R	13.97	14	14	106
2	M	R	21.36	12	11	115
3	F	R	20.92	13	6	115
4	M	L	24.53	15	14	128
5	M	R	34.05	11	10	100
6	M	R	30.68	15	16	120
7	M	L	28.90	14	10	120
8	M	L	39.74	13	11	106
Mean			26.77	13.38	11.50	113.75
SD			8.22	1.41	3.12	9.21

BD, WAIS-R/WISC-R Block Design subtest, age-scaled score; OA, WAIS-R/WISC-R Object Assembly subtest, age-scaled score. Subtest scores are scaled to a mean of 10 and a standard deviation of 3. IQ, WAIS-R/WISC-R full-scale intelligence quotient. For normal subjects, IQ was estimated with a short form of the WAIS-R/WISC-R consisting of the Vocabulary and Block Design subtests (Brooker and Cyr 1986). WAIS-R, Wechsler Adult Intelligence Scale-Revised; WISC-R, Wechsler Intelligence Scale for Children-Revised. M, male; F, female; R, right; L, left.

psychiatric or neurologic diagnoses; and none used psychotropic medication. Intelligence quotient (IQ) was evaluated with the Wechsler Adult Intelligence Scale-Revised (WAIS-R; Wechsler 1981) or the Wechsler Intelligence Scale for Children-Revised (WISC-R; Wechsler 1974), and all subjects were nonretarded (i.e., full-scale IQ > 70; Table 2).

Normal control subjects, recruited through advertisements in the community, had no history of developmental, psychiatric, or neurologic disorders. Autistic and normal subjects were matched for age, gender, and handedness but not IQ. Groups are often matched for IQ to control for differences in general cognitive functioning; however, in autism, IQ is not a valid measure of such functioning owing to the atypical profile of subtest performance (Lincoln et al 1988). Moreover, for studies with anatomic or physiologic dependent variables, ability measures are not always appropriate matching variables, because they can in turn be influenced by the dependent variables. Despite the implications of this practice (i.e., removing true effects and injecting spurious ones), it is often done. As an alternative, groups were matched for scores on the Wechsler Block Design (BD) and Object Assembly (OA) subtests, which measure abilities typically spared in autism. Matched-pair t tests (two-tailed) demonstrated that the groups did not differ significantly in age [$t(7) = .12$; $p = .91$], BD score [$t(7) = -.62$; $p = .56$], or OA score [$t(7) = -1.04$; $p = .33$].

The complete protocol was approved by the institutional review boards of San Diego Children's Hospital Research Center, the University of California, San Diego, and San Diego State University. After complete description of the study to the subjects and before their participation, written informed consent was obtained. Parents provided written consent for the two subjects aged <18 years, who also provided verbal assent.

The Task

Each subject held a joystick in the dominant hand and pressed a button with the thumb repeatedly "at a comfortable pace." A rear-projection screen mounted at subjects' feet was viewed through a mirror attached to the radiofrequency (RF) coil. Every 40 sec over the course of 320 sec, a one-word instruction appeared on the otherwise blank screen for 2 sec, cueing subjects to switch between the task ("GO") and rest ("STOP"). The mean number of button presses across the four motor task blocks was used as an index of button press frequency.

MRI

Images were acquired on a GE Signa 1.5-T system (General Electric Medical Systems, Milwaukee, Wisconsin) with a local head gradient coil and an asymmetrical circular endcapped RF coil (Medical Advances, Milwaukee, Wisconsin) designed to provide extended coverage of the posterior–inferior portions of the brain. To obtain data from anatomically comparable coronal slices across subjects, we first acquired localizer images in the axial and sagittal planes; axial images ensured limited head rotation, whereas sagittal images were used to designate the coronal slice locations (Figure 1).

After manual shimming to reduce inhomogeneities in the magnetic field, images were acquired with a single-shot gradient-recalled echo-planar imaging (EPI) pulse sequence (interleaved slice acquisition; repetition time [TR] = 2500 msec; echo time [TE] = 40 msec; flip angle = 90°; matrix = 64 × 64; field of view [FOV] = 24 cm; slice thickness = 5 mm; slice gap = 1 mm). While subjects alternately rested and performed the task, a time series of 130 EPI images was acquired at five coronal slice locations through the cerebellum. Subsequent to functional imaging, 20 EPI phase map images were acquired at each slice location. Finally, high-resolution whole-brain images (three-dimensional magnetization prepared rapid gradient echo [MPRAGE] pulse sequence: TR = 30 msec; TE = 5 msec; flip angle = 45°; matrix = 256 × 192 × 128; FOV = 24 cm; slice thickness = 1.5–1.7 mm) were acquired during the same scan session for each subject.

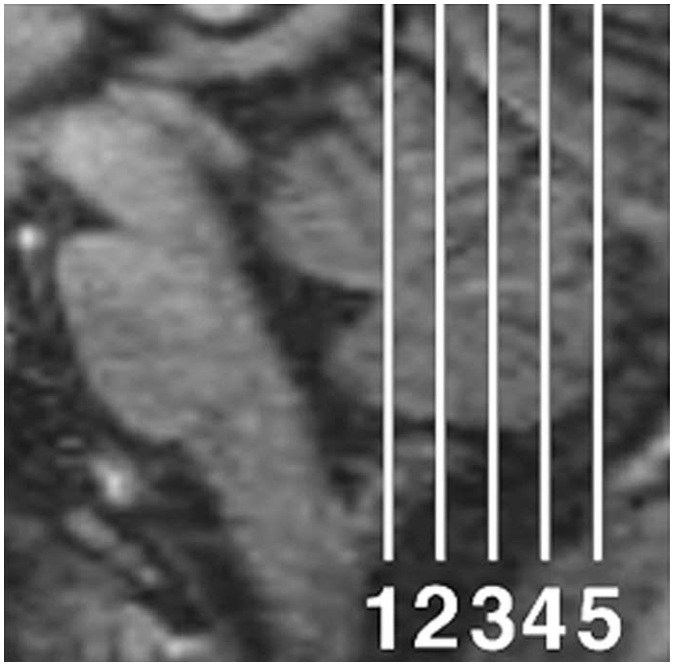

Figure 1. Coronal slice locations, used for the acquisition of functional data, shown on a midsagittal anatomic magnetic resonance image of the brainstem and cerebellum from a single subject. The most anterior slice (slice 1) was located immediately posterior to the apex of the fourth ventricle, constraining the most posterior slice (slice 5) to a position at or near the caudal limit of the vermis.

Measurement of Cerebellar Volume

To investigate possible group differences in cerebellar anatomy, the full cortical volume of the cerebellum was estimated for each subject. Cerebellar gray matter (GM, excluding cerebrospinal fluid [CSF] and deep white matter [WM]) was traced manually on every other MPRAGE image, beginning with the most posterior slice in which the cerebellum appeared and continuing anteriorly until it no longer appeared. The total number of voxels within all tracings was then multiplied by twice the single voxel volume to arrive at an estimate of total cerebellar GM volume. The mean number of slices used to estimate volume was 19, indicating a coefficient of error of less than 1% (Mayhew and Olsen 1991).

Anatomic Identification of ROIs

Before the analysis of functional activation, anatomic ROIs were traced on the coronal MPRAGE image corresponding to each EPI slice location (Figure 2). All ROIs were located in cerebellar cortex (i.e., tracing excluded CSF and deep WM), including the vermis and hemispheres. Two major bands of WM that cross the vermis were landmarks for identifying vermis subregions. Tissue superior to the upper band was identified as anterior vermis (AVe), whereas posterior vermis (PVe) was inferior to the lower band, and tissue between the two bands was termed anterior/posterior vermis (A/PVe). In the hemispheres,

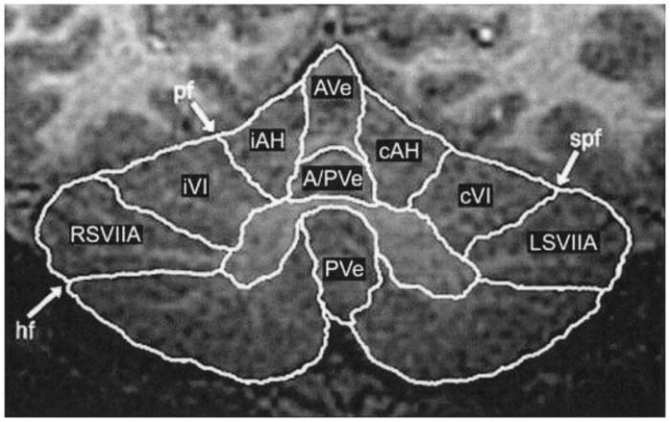

Figure 2. Locations of regions of interest shown on a coronal anatomic magnetic resonance image of the cerebellum from a single subject. pf, primary fissure, the boundary between anterior and posterior portions of the cerebellum; spf, superior posterior fissure, the boundary between lobule VI and superior lobule VIIA (superior semilunar lobule); hf, horizontal fissure, the inferior boundary of superior lobule VIIA; A/PVe, tissue between AVe and PVe; AVe, anterior vermis; PVe, posterior vermis; iAH, anterior hemisphere (central and anterior quadrangular lobules) ipsilateral to the moving hand; cAH, anterior hemisphere (central and anterior quadrangular lobules) contralateral to the moving hand; iVI, lobule VI (posterior quadrangular lobule) ipsilateral to the moving hand; cVI, lobule VI (posterior quadrangular lobule) contralateral to the moving hand; RSVIIA, right superior lobule VIIA; LSVIIA, left superior lobule VIIA.

cortices bounded medially by the vermis and laterally by the primary fissure were identified as anterior hemisphere (central and anterior quadrangular lobules) ipsilateral (iAH) and contralateral (cAH) to the moving hand. Lobules VI (posterior quadrangular lobule) ipsilateral (iVI) and contralateral (cVI) to the moving hand were bounded medially by the primary fissure and laterally by the superior posterior fissure. Finally, right and left superior lobules VIIA (RSVIIA and LSVIIA; superior semilunar lobules) were inferior to the superior posterior fissure and superior to the horizontal fissure. Primary ROIs were AVe, A/PVe, iAH, and iVI. The choice of these ROIs was based on previous studies that have shown activation in these regions during simple hand movements (Allen et al 1997; Desmond et al 1997; Stephan et al 1995) and on studies showing that these regions receive input from the ipsilateral upper extremity (Altman and Bayer 1997) and the hand area of motor cortex (Middleton and Strick 1997). Note that for these same reasons, primary ROIs were analyzed according to whether they were ipsilateral or contralateral to the moving hand, rather than right or left. Secondary ROIs were PVe, cAH, cVI, RSVIIA, and LSVIIA. Despite our use of a specialized RF coil (Medical Advances), signal loss in the inferior cerebellum did not allow complete imaging of the posterior–inferior cerebellar hemispheres (inferior lobule VIIA-lobule IX) in all subjects. Therefore, these regions were not included in our analyses. Each of the ROIs was traced on each of the slices in which it appeared. Region of interest identification was guided by human cerebellar atlases (Courchesne et al 1989; Press et al 1989, 1990).

Identification of Functional Activity

To correct for image distortion resulting from magnetic field inhomogeneities, an unwarping algorithm using the phase map images was applied to each EPI data set (Reber 1998). Next, to correct for subject motion, a three-dimensional volume registration algorithm (Cox and Jesmanowicz 1999) was applied. Two separate indices of functional activity, the correlation coefficient and percent signal change, were then calculated with AFNI software (Cox 1996). Before these calculations, the first two repetitions of each EPI slice, acquired before magnetization had reached equilibrium, were eliminated, and the global drift of the time course MRI signal data from each voxel was orthogonally projected out of the data. The data were then correlated (Bandettini et al 1993) with a set of nine hemodynamic model response functions, each one being a box-car wave with sloped sides approximating the delay in hemodynamic response onset (0, 2.5, or 5 sec) and the delay between this onset and maximum signal change (5, 7.5, or 10 sec). The output of the correlation was the result of a voxel-by-voxel best fit with these models. Significantly activated voxels were those that exceeded a threshold r value equivalent to one-tailed $p < .05$ with Bonferroni correction for multiple comparisons. Here, the number of comparisons equaled the total number of voxels within all ROIs across all five slices (i.e., approximately 500 voxels). The resulting threshold was an r value of .33 ($p < 10^{-5}$).

ROI Analyses

First, the anatomic area of each ROI was measured in each of the five slices in which it appeared. Then, the activation area (i.e., the total area of all significantly active voxels) within each ROI was calculated. Anatomic and activation area values were collapsed across slices to create anatomic and activation "volumes." For each ROI in each subject, anatomic and activation volumes were compared to yield a percent volume active, an index of activation "extent." We also examined the mean percent signal change across the entire ROI volume, an index of activation "magnitude." In the primary, hypothesis-driven analysis, Bonferroni correction protected against Type I error (i.e., α of .05 adjusted for four ROIs = .05/4 = .0125). In the secondary stage of analysis, such protection procedures were not used. The relationship between cerebellar structure and function was also examined by correlating activation extent and magnitude with anatomic volume in each ROI in which significant group differences were identified.

Results

Data Screening

The extreme studentized deviate method (Iglewicz and Hoaglin 1993) was used to screen for outliers. This method adjusts the critical value for excluding outliers according to sample size. Here, the critical z was 2.13. Thus, if a subject produced ROI activation greater than 2.13 standard deviations (SDs) from the sample mean, he was considered an outlier. With this approach, one autistic subject (#6) and one normal subject (#8) were identified as outliers and excluded from further analyses. Exclusion did not bring about group differences in the matching variables age [$t(12) = .24$; $p = .82$], BD score [$t(12) = -.96$; $p = .36$], or OA score [$t(12) = -1.04$; $p = .32$].

Cerebellar and ROI Anatomy

Cerebellar GM volume in cubic centimeters was 103.9 ± 23.2 (mean ± SD) for the autistic subjects and 108.3 ± 13.1 for the normal control subjects. This difference of approximately 4% was not statistically significant [$t(12) = -.44$; $p = .34$] but was similar in magnitude to significant differences seen in larger-sample studies (e.g., Courchesne et al 2001; Hashimoto et al 1995). Figure 3 shows the mean autistic and normal anatomic measures for each ROI. In all but two regions (RSVIIA and A/PVe), autistic measures were smaller. The degree of difference ranged from 1%

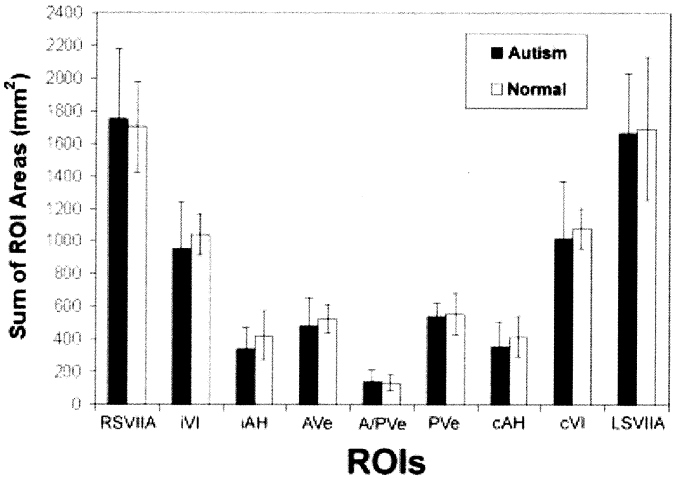

Figure 3. Region of interest (ROI) anatomic areas summed across slices for the autistic and normal subjects. Bars represent group means. Error bars represent the standard deviation. A/PVe, tissue between AVe and PVe; AVe, anterior vermis; PVe, posterior vermis; iAH, anterior hemisphere (central and anterior quadrangular lobules) ipsilateral to the moving hand; cAH, anterior hemisphere (central and anterior quadrangular lobules) contralateral to the moving hand; iVI, lobule VI (posterior quadrangular lobule) ipsilateral to the moving hand; cVI, lobule VI (posterior quadrangular lobule) contralateral to the moving hand; RSVIIA, right superior lobule VIIA (superior semilunar lobule); LSVIIA, left superior lobule VIIA.

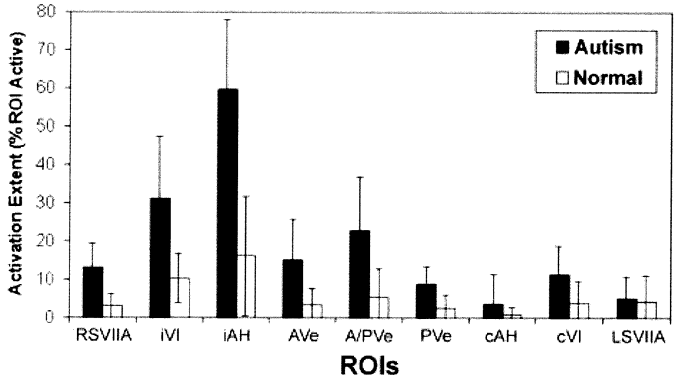

Figure 5. Mean activation extent in each region of interest for autistic and normal right-handed subjects. Error bars represent the standard deviation. A/PVe, tissue between AVe and PVe; AVe, anterior vermis; PVe, posterior vermis; iAH, anterior hemisphere (central and anterior quadrangular lobules) ipsilateral to the moving hand; cAH, anterior hemisphere (central and anterior quadrangular lobules) contralateral to the moving hand; iVI, lobule VI (posterior quadrangular lobule) ipsilateral to the moving hand; cVI, lobule VI (posterior quadrangular lobule) contralateral to the moving hand; RSVIIA, right superior lobule VIIA (superior semilunar lobule); LSVIIA, left superior lobule VIIA.

(LSVIIA) to 29% (iAH). The iAH difference was statistically significant [$t(12) = -1.8$; $p < .05$], and cAH approached significance [$t(12) = -1.55$; $p < .07$].

ROI Activation: Autism Versus Normal

Figure 4 demonstrates that both groups showed activation in predicted regions of the cerebellum; however, ROI analyses revealed important group differences. Analysis of variance (ANOVA) showed a significant ROI × Diagnosis (DX) × Handedness interaction for both extent [$F(3,30) = 7.22$; $p < .05$] and magnitude [$F(3,30) = 3.43$; $p < .05$]. There were too few left-handed subjects to carry any statistical power, but follow-up analyses in the right-handed subjects showed a significant ROI × DX interaction for extent [$F(3,21) = 9.84$; $p < .05$] and magnitude [$F(3,21) = 4.66$; $p < .05$]. For extent (Figure 5), one-way ANOVAs examining main effects of DX within the four primary ROIs showed that autistic subjects had significantly more activity in iAH [$F(1,7) = 14.71$; $p < .0125$], with the differences in iVI [$F(1,7) = 7.16$; $p = .03$], A/PVe [$F(1,7) = 5.89$; $p = .05$], and AVe [$F(1,7) = 5.21$; $p = .06$] approaching significance. Similarly, for magnitude (Figure 6), autistic subjects showed significantly more activation in iAH [$F(1,7) = 20.83$, $p < .0125$], with iVI [$F(1,7) = 11.1$; $p = .013$] and A/PVe [$F(1,7) = 6.43$, $p = .04$] approaching significance. Secondary analyses showed that for autistic subjects, activation extent was significantly greater than normal within RSVIIA [$F(1,7) = 10.13$, $p < .05$] and PVe [$F(1,7) = 5.64$, $p < .05$], whereas the difference in activation magnitude in RSVIIA approached significance [$F(1,7) = 5.37$, $p = .05$].

In considering the basis for these differences between autistic and normal right-handed subjects, it was first necessary to consider possible differences in movement rate. As described above, the mean number of button presses across the four motor task blocks was our index of button press frequency. No subject pressed the button during rest, and no other extraneous movements were observed. The frequency of button pressing (Table 3) did not differ significantly between the groups [$t(7) = .72$, $p = .50$]. Thus, movement rate is unlikely to have been a factor in the

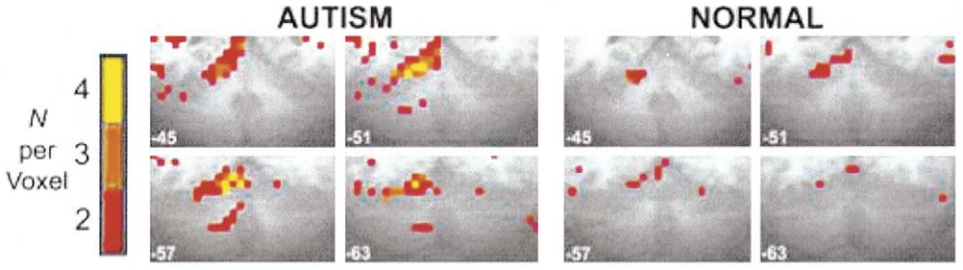

Figure 4. Cerebellar activation in right-handed autistic and normal subjects overlaid on averaged coronal anatomic images of slices 1–4 through the cerebellum. (The ipsilateral cerebellum is to the reader's left.) To create these maps, each brain was spatially normalized according to the system of Talairach and Tournoux (1988). All active voxels were then superimposed across subjects, thus displaying common sites of activation within the two groups. Anterior–posterior (i.e., y) Talairach coordinates are in the lower left of each panel. Images show the greater expanse of motor activation in the autistic cerebellum relative to normal. Red represents activation by any two individuals, orange by any three, and yellow by any four. Comparison of autistic and normal subjects demonstrates that autistic subjects showed an increased extent of activation in the ipsilateral anterior cerebellar hemisphere in addition to vermis and posterior cerebellar activation not seen in normal control subjects. Although individual autistic subjects also showed contralateral anterior activation, these activations were spatially less extensive and nonoverlapping.

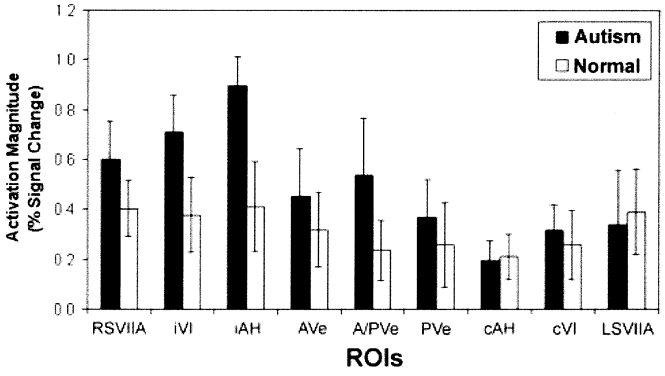

Figure 6. Mean activation magnitude in each region of interest for autistic and normal right-handed subjects. Error bars represent the standard deviation. A/PVe, tissue between AVe and PVe; AVe, anterior vermis; PVe, posterior vermis; iAH, anterior hemisphere (central and anterior quadrangular lobules) ipsilateral to the moving hand; cAH, anterior hemisphere (central and anterior quadrangular lobules) contralateral to the moving hand; iVI, lobule VI (posterior quadrangular lobule) ipsilateral to the moving hand; cVI, lobule VI (posterior quadrangular lobule) contralateral to the moving hand; RSVIIA, right superior lobule VIIA (superior semilunar lobule); LSVIIA, left superior lobule VIIA.

activation differences, especially in light of findings that cerebellar activation is relatively insensitive to changes in movement rate during such tasks (Jäncke et al 1999).

Association Between Structure and Function in Cerebellar ROIs

Group differences in ROI anatomy were much more pronounced within the right-handed subjects than they were when handedness groups were combined. For instance, autistic AVe size was 16% smaller than normal in these subjects, and iAH was 38% smaller. Such differences highlighted the need for a more detailed investigation of the association between regional cerebellar anatomy and functional activation. Although the sample size was small, these associations were nonetheless examined. In terms of activation extent, in regions in which autistic subjects showed significantly greater activation, they also showed strong inverse correlations between anatomy and function (i.e., $r = -.74$ for iAH and $r = -.88$ for RSVIIA). The corresponding associations in the normal group were .15, and $-.44$ (Figure 7). Given the small number of subjects, these correlations were not significantly different between groups by one-tailed comparison of Fisher's z' ($p > .05$). Similar associations were not observed when correlating ROI anatomy with measures of activation magnitude.

Table 3. Frequency of Button Pressing in Autistic and Normal Right-Handed Subjects

Pair	Autism	Normal
1	58.00	60.00
2	74.00	96.75
3	74.25	48.75
5	61.00	53.00
6		28.25
Mean	66.81	57.35
SD	8.5	25.0

Pair numbers correspond to subject numbers in Table 2. Frequency values represent the mean number of button presses across the four blocks of the motor task. Note that the autistic member of pair 6 was deemed an outlier based on extreme region of interest activation effects and excluded from further analyses.

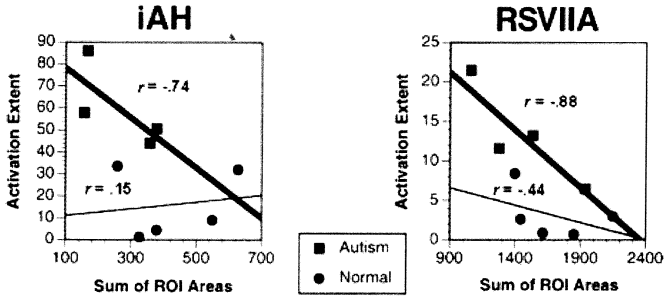

Figure 7. Correlation between anatomy and function in autistic and normal right-handed subjects. Percent region of interest (ROI) active in anterior hemisphere (central and anterior quadrangular lobules) ipsilateral to the moving hand (iAH), and right superior lobule VII (RSVIIA) plotted against summed anatomic areas in those same regions.

Discussion

The cerebellum is one of the most commonly reported sites of neural abnormality in autism. Autopsy studies of this disorder have consistently reported cerebellar anomalies (Bailey et al 1998; Fatemi et al 2001, 2002a, 2002b; Fehlow et al 1993; Kemper and Bauman 1998; Lee et al 2002; Purcell et al 2001; Ritvo et al 1986; Williams et al 1980), the most common being a reduction of Purkinje neurons. Furthermore, multiple structural MRI studies have demonstrated hypoplasia of one or more regions in the cerebellar vermis (Courchesne et al 1987, 1988, 1994a, 1994b, 1994d, 2001; Ciesielski et al 1997; Hashimoto et al 1995; Kaufmann et al 2003; Kleiman et al 1992; Levitt et al 1999; Saitoh et al 1995; Zilbovicius et al, unpublished data) and hemispheres (Courchesne et al 2001; Murakami et al 1989). A crucial question, then, is how such anatomic abnormalities impact cerebellar function, and in turn how cerebellar dysfunction might impact the behaviors and symptoms of individuals with autism.

In the present study, we examined cerebellar function during a simple motor task in autistic and normal subjects. Both groups showed activation in the anterior cerebellar hemisphere and in hemisphere lobule VI ipsilateral to the moving hand. This is consistent with previous studies that have shown activation in these regions during simple hand movements in normal adults (Allen et al 1997; Desmond et al 1997; Stephan et al 1995). Nevertheless, autistic and normal groups also showed important structural and functional differences. In terms of structure, anatomic ROI measures in the autistic cerebellum were on average 12% smaller than normal. Functionally, in the main predicted region of cerebellar motor activation (i.e., ipsilateral anterior cerebellum), both the spatial extent and magnitude of activation were significantly greater than normal in autism. Also, in autistic subjects, contralateral and posterior cerebellar regions not typically associated with such simple motor tasks were abnormally active. In addition, there were significant negative correlations between ROI anatomy and activation extent in autistic subjects but not normal control subjects, strongly suggesting that the functional differences observed were a reflection of cerebellar anatomic abnormality.

While linking anatomic and functional abnormalities in the cerebellum, these findings also point to a potential neurofunctional link between abnormal cerebellar anatomy and motor deficits that have been observed in autism. The earliest published

account of autism described children who were "clumsy in gait and gross motor performances" (Kanner 1943). Later investigations of autistic individuals' motor functioning on standard neurologic measures revealed abnormalities on a variety of cerebellar tests (e.g., gait, alternating and sequential movements, balance) (Haas et al 1996; Hallett et al 1993), with an overall picture "indicative more of cerebellar dysfunction than of any other definable central nervous system disorder" (Hallett et al 1993, p. 1306). Now, abnormal patterning of cerebellar activation during a motor task provides added support for the notion that the motor deficiencies observed in many autistic individuals are related, at least in part, to cerebellar dysfunction.

Motor impairments are not part of the formal diagnosis of autism; however, they are among the earliest distinguishing features of individuals with autism, because they are observable long before most social or language deficits become evident (Dawson et al 2000; Teitelbaum et al 1998). These motor impairments likely have an effect that goes beyond hampering locomotion and other forms of coordinated movement, because a child with such early problems of motor coordination will be at a great disadvantage in exploring, interacting with, and learning about his environment; however, there is a more central reason that cerebellar dysfunction might have broader consequences for autism, and that is that the cerebellum is simply more than just a motor structure.

In recent years, the cerebellum has been shown to play a role in multiple functional domains (e.g., Allen et al 1997; Gao et al 1996; Le et al 1998; Paradiso et al 1997; Xiang et al 2003), and cerebellar damage has been associated with an array of cognitive deficits and affective changes (e.g., Courchesne et al 1994c; Fiez et al 1992; Gottwald et al 2003; Sacchetti et al 2002; Schmahmann and Sherman 1998; Townsend et al 1999; Trillenberg et al 2004. For instance, in adults with acquired cerebellar lesions, Schmahmann and Sherman (1998) have outlined a "cerebellar cognitive affective syndrome" characterized by language, visuospatial, and executive function deficits in addition to personality changes (e.g., inappropriate behavior and flattening of affect). A similar syndrome has been reported in children after surgical resection of cerebellar tumors (Levisohn et al 2000; Riva and Giorgi 2000), and in at least one of these pediatric cases, the behavioral changes actually resembled classic symptoms of autism (e.g., gaze aversion, social withdrawal, stereotyped movements) (Riva and Giorgi 2000). These findings indicate that cerebellar pathology can bring about a wide range of cognitive, affective, and motor deficits (Allen and Courchesne 1998).

The mechanism through which cerebellar dysfunction impacts these various functional domains is unknown, because the fundamental function of the cerebellum is itself unknown; however, motor functioning in individuals with autism provides a useful model for how cerebellar pathology might impact other domains. By characterizing the quality of motor impairments in autism as they might relate to cerebellar dysfunction, a greater understanding of the potential impact of such dysfunction in other domains should emerge. In fact, in several recent investigations novel motor paradigms have been used to explore how motor control is affected in autism. For instance, using a "reach, grasp, and place task," Hughes (1996) showed that autistic children had difficulty executing simple, goal-directed movements thought to involve "anticipatory monitoring." Similarly, when performing a serial choice reaction time task, autistic subjects showed deficient movement preparation, and their deficit was characterized as a "lack of anticipation" (Rinehart et al 2001). And more recently, autistic children were found to be deficient at making anticipatory postural adjustments during a load-lifting task, such that their adjustments were reactive rather than predictive (Schmitz et al 2003). The theme here is clear: motor performance in these individuals with autism was impaired because it lacked the anticipatory advantage that normally facilitates coordinated movement.

The neuroanatomic basis for anticipatory motor deficits in autism has not been established, but such findings fit nicely with several theories that ascribe an anticipatory or predictive role to the cerebellum (e.g., Courchesne and Allen 1997; Coenen et al 2001; Darlot 1993; Miall et al 1993; Nixon 2003; Paulin 1993). It is well known that the cerebellum is involved in learning (for review, see Courchesne and Allen 1997). Furthermore, the cerebellum seems to have a special role in detecting signals in temporal sequences (Braitenberg et al 1997) that arrive at the cerebellum as both exogenous (e.g., sensory events) and endogenous (e.g., from frontal cortex, hippocampus, and hypothalamus) neural activities. We have previously proposed that when presented with such sequences, the cerebellum predicts—on the basis of prior learning—what is about to happen and initiates preparatory actions that alter neural responsiveness in whichever neural systems are to be needed in upcoming moments (Akshoomoff et al 1997; Allen et al 1997; Courchesne and Allen 1997; Courchesne et al 1994c) The cerebellum is thought to perform this fundamental function for all systems with which it maintains connections (e.g., sensory, motor, autonomic, memory, attention, affect, and language systems). When this function is impaired due to congenital or acquired pathology, other neural systems can continue to perform but will do so suboptimally in situations in which prediction and preparation might aid performance. So, in the motor context, cerebellar damage certainly does not abolish movements, but it does cause them to be uncoordinated (Holmes 1939). This leads to a simple analogy for the effects of cerebellar pathology in other domains; function is not abolished, but it lacks coordination due to a preparatory deficit.

This general effect of cerebellar pathology applies to any context in which successful performance requires the individual to process or produce coordinated sequences of events or actions. Thus, in the context of attention, which we have studied at length, cerebellar pathology does not eliminate the ability to orient or shift attention but instead makes attentional adjustments slow and inaccurate (Akshoomoff and Courchesne 1992, 1994; Courchesne et al 1994c; Townsend et al 1999). Likewise, cerebellar dysfunction is thought to be at play in many of the behavioral disturbances that define autism (e.g., difficulty following the natural sequential flow of conversations and other social interactions and problems understanding the causal relationship between behaviors and their consequences). Furthermore, other classic symptoms (e.g., restricted interests and behaviors, insistence on sameness, resistance to change) might in fact develop as attempts to compensate for cerebellar dysfunction, for in a world where the ability to prepare for change is impaired, repetition and the status quo might be particularly reinforcing. Therefore, through its proposed role in preparatory functioning, cerebellar abnormality might not only be a common feature of autism, but a key contributor to many of its hallmark symptoms.

Several recent findings support the notion that cerebellar dysfunction plays a more central role in autism than previously thought. For instance, in a study of autistic children exploring a structured environment (Pierce and Courchesne 2001), reduced exploration (a manifestation of "restricted interests") was significantly correlated with the midsagittal area of cerebellar vermis

lobules VI–VII but not with total brain volume or frontal lobe volume. Moreover, autistic children were more likely to engage in repetitive behaviors, which was also associated with reduced vermis size. Recently, discriminant function analysis was used to examine the ability of various cerebral and cerebellar MRI measures to predict diagnosis in a large group of normal children and children with autism spectrum disorders (Akshoomoff et al 2004). In that investigation, cerebellar WM volume was the strongest single predictor of diagnosis. Cerebellar WM also emerged as a particularly important variable in an MRI investigation in which monozygotic twin pairs clinically concordant for autism were compared with clinically discordant pairs (Kates et al 2004). In this study, both the concordant and discordant pairs showed concordance in cerebral GM and WM, but only the clinically concordant pairs showed concordance in cerebellar GM and WM volumes. Furthermore, within-pair differences in ADOS communication and social scores were not associated with cerebral measures but were significantly associated with cerebellar measures. These findings suggest that given the genetic predisposition to develop autism, cerebellar status might be crucial to the emergence of certain diagnostic features; however, two studies suggest a more direct connection between genetics, cerebellar anatomy, and autism. In these studies, significant associations were found between *Engrailed 2*, a gene that plays an essential role in the development of cerebellar cortex, and diagnosis in the autism spectrum (Gharani et al 2004; Petit et al 1995). Together, these investigations indicate that abnormalities of structure and function in the cerebellum, which are arguably the most consistent findings in autism neuroscience, might in fact be central to the diagnoses.

By design, this investigation focused on the autistic cerebellum to the exclusion of other brain regions; however, in another investigation, we found abnormal variability of cerebral motor activation maps in autistic individuals (Müller et al 2001). An important goal for future studies will be to examine how cerebellar dysfunction relates to such abnormal activation in extracerebellar regions. A crucial question for such investigations will be how functional changes in the cerebrum influence patterns of cerebellar activation, and vice versa. Of course, future investigations will also be required to replicate the present findings and address certain limitations of our study (e.g., the relatively small number of subjects and their heterogeneity with regard to handedness).

In sum, we demonstrated atypical patterning of cerebellar activation in a sample of autistic subjects, suggesting that the cerebellum is functionally abnormal in autism. These findings might help to explain the cerebellar motor abnormalities (e.g., clumsiness and poor motor coordination) that have been observed in persons with autism (Haas et al 1996; Hallett et al 1993); however, it is known from previous functional neuroimaging studies (Table 1) that cerebellar dysfunction in autism extends beyond the motor domain. In fact, given what we know about functional diversity in the cerebellum, coupled with the diffuse nature of Purkinje neuron reduction in autism, cerebellar function in this disorder is likely to be generally deficient. Although much more work is needed in this area, our hypothesis is that by interfering with the fundamental function of the cerebellum and its interaction with diverse brain systems, cerebellar pathology is an important contributor to many of the defining features of autism.

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