Specificity of Cerebellar Vermian Abnormalities in Autism: A Quantitative Magnetic Resonance Imaging Study

Walter E. Kaufmann, MD; Karen L. Cooper, BA; Stewart H. Mostofsky, MD; George T. Capone, MD; Wendy R. Kates, PhD; Craig J. Newschaffer, PhD; Irena Bukeliis, MD; Mariah H. Stump, BS; Adelene E. Jann, BS; Diane C. Lanham, MA

ABSTRACT

To gain insight into the specificity of cerebellar vermic abnormalities reported in autism, we conducted a magnetic resonance imaging (MRI) study of boys with either of two conditions associated with autism, Down syndrome and fragile X syndrome, compared with boys with idiopathic autism and controls. The subjects, ranging in age from 3 to 9 years, included 16 boys with Down syndrome + autism and 11 boys with Down syndrome only; 13 boys with fragile X syndrome + autism and 9 boys with fragile X syndrome only; 10 boys with idiopathic autism; and 22 controls. Diagnosis of autism was based on DSM-IV criteria, confirmed primarily by the Autism Diagnostic Interview. T1-weighted midsagittal MRIs were used to measure midline structures. Intracranial area, reflecting brain size, was significantly smaller in subjects with Down syndrome. Therefore, all vermian measures were expressed as ratios to intracranial area. Analysis of covariance (covarying for age and IQ) demonstrated that posterior vermis (lobules VI–VII and VIII–X) were markedly smaller in both Down syndrome groups and those with fragile X syndrome only, whereas only lobules VI–VII were reduced in idiopathic autism. Factorial analyses of variance tested interactions between autism factor and the diagnosis of Down syndrome or fragile X syndrome. The size of lobules VI–VII/intracranial area was dependent on autism status only in fragile X syndrome, with ratios significantly larger in fragile X syndrome with autism with respect to fragile X syndrome only. We conclude that selective posterior vermis hypoplasia is seen not only in idiopathic autism but also in Down syndrome and some individuals with fragile X syndrome. However, reductions in vermian lobules VI and VII appear to be specific to idiopathic autism, whereas increased size of lobules VI and VII is associated with autism in fragile X syndrome. The latter results are consistent with MRI studies showing lobules VI–VII hyperplasia in a subset of subjects with idiopathic autism and cerebral and hippocampal enlargements in fragile X syndrome. (J Child Neurol 2003;18:463–470).

Neuropathologic and morphometric imaging studies of individuals with idiopathic autism have consistently reported abnormalities in the cerebellum.1-4 Microscopic cerebellar abnormalities include decreases in the number of Purkinje cells and, in some instances, pallor of the granule cell layer that mainly affects the posterolateral neocerebellum.1,2 A postmortem examination of the vermis in 11 patients with idiopathic autism also revealed increased variability in lobule size and widening of the space between folia in several subjects.2 The cellular correlates of these macroscopic vermian abnormalities remain uncertain because an initial report on reductions in Purkinje cell numbers1 was not con-
firmed in a subsequent study. Several magnetic resonance imaging (MRI) studies have also demonstrated abnormalities in the size of this cerebellar region; most of them have shown reductions in vermillon size (cross-sectional area), affecting predominantly lobules VI–VII (posterosuperior vermis). A report also found selective decreases in the size of the postero-inferior portion of the vermis (ie, lobules VIII–X). Enlargement (hyperplasia) of lobules VI–VII has also been reported in a small fraction of a wide range sample of autistic subjects. Despite the lasting controversy about the etiologic and topographic selectivity of the autism-associated vermian hypoplasia, recent studies have shown associations between vermian size and deficits in attention-orienting and reduced exploration and stereotypic behavior in children and adults with idiopathic autism.

Down syndrome is the most common genetic disorder associated with mental retardation. Patients with Down syndrome may also exhibit severe behavioral problems, including autistic features. Depending on the criteria used and the method of ascertainment, the prevalence of autism among individuals with Down syndrome is estimated to be 5 to 10%. In contrast to the aforementioned data on idiopathic autism, indicating relatively selective or subtle anatomic abnormalities, neuropathologic studies have shown widespread developmental anomalies in Down syndrome. As expected of such a wide distribution, several of the neural systems implicated in idiopathic autism are also abnormal in Down syndrome. Cerebellar size is particularly reduced, in proportion to the overall decrease in brain size, but in correspondence to lower granule cell density in both patients with Down syndrome and a trisomic mouse model. Neuroimaging investigations have further documented selective vermian hypoplasia in Down syndrome. One study found that, in adults with Down syndrome, there is a relative reduction in the size of vermian lobules VI–VII after adjusting for the shorter stature of the Down syndrome group. Despite these data, no studies have directly examined the relationship between cerebellar or vermian size and autistic features in Down syndrome.

Fragile X syndrome is the most common form of inherited cognitive impairment. As expected from an X-linked disorder, male individuals are more affected. In addition to mental retardation, a high proportion of boys with fragile X syndrome displays severe behavioral disturbances that include autistic features. Little is known about the neurobiologic basis of autistic features in fragile X syndrome; nevertheless, as in Down syndrome and idiopathic autism, there is neuroanatomic (ie, MRI) evidence of vermian anomalies. In contrast to other brain regions (ie, hippocampus) that tend to be larger, the cerebellar vermis is selectively hypoplastic. Whether the reductions in vermian size in fragile X syndrome affect the entire posterior vermis (ie, lobules VI–X) or only lobules VI–VII is still unclear and appears to depend on the sample under study. To our knowledge, the only available study addressing the relationship between autism and vermian size in fragile X syndrome was conducted in females with this condition and found a negative correlation between the area of lobules VI–VII and the frequency and severity of autistic behaviors. Despite these findings, at present, no study has directly examined whether vermian hypoplasia is associated with autism in fragile X syndrome.

Based on the data mentioned above, we postulate that selective posterior vermian changes, in particular hypoplasia, may be associated with an autistic phenotype not only in idiopathic autism but also in other developmental disorders presenting with autistic features. Down syndrome and fragile X syndrome are among the most likely conditions for such an association because of the relatively high frequency of individuals with autism comorbidity and their distinctive whole cerebellar or vermian hypoplasia (‘risk factor’), respectively. Selective vermian changes in Down syndrome and fragile X syndrome resembling idiopathic autism would suggest common neural pathways and pathogenetic mechanisms to many individuals with developmental disorders and autistic features. Alternatively, unique differences between autistic and nonautistic subjects within either the Down syndrome or fragile X syndrome groups would indicate condition-specific pathologic mechanisms. For these purposes, we conducted an MRI morphometric evaluation of the cerebellar vermis cross-sectional area of young males with Down syndrome and fragile X syndrome, with (Down syndrome + autism, fragile X syndrome + autism) and without (Down syndrome only, fragile X syndrome only) autistic features. They were compared with gender-matched subjects with idiopathic autism and normal controls. We chose to study only young males because the association between mental retardation and autism in Down syndrome and fragile X syndrome involves predominantly this gender. An additional advantage of the restriction in age and gender is the comparison of relatively homogeneous samples, a factor typically absent from many previous MRI studies that could contribute to discrepancies in the literature on idiopathic autism. We expected (1) to confirm the selective hypoplasia of lobules VI–VII in idiopathic autism; (2) to demonstrate that, in correspondence with the cerebellar hemispheres, the vermis is markedly hypoplastic in Down syndrome; and (3) to show that both genetic autistic groups, Down syndrome + autism and fragile X syndrome + autism, have reductions in posterior vermian size disproportionate to global cerebral and cerebellar changes.

METHOD

Subjects

The participants included boys with idiopathic autism, Down syndrome, fragile X syndrome, and controls. The Down syndrome and fragile X syndrome groups included subjects with (Down syndrome + autism, fragile X syndrome + autism) and without (Down syndrome only, fragile X syndrome only) autistic features. There were 10 boys with idiopathic autism (mean age 7.0 ± 2.4 years, mean IQ 60.1 ± 14.4), 27 boys with Down syndrome, 16 boys with Down syndrome + autism (mean age 7.0 ± 1.8 years, mean IQ 20.1 ± 6.9), and 11 boys with Down syndrome only (mean age 7.2 ± 2.1 years, mean IQ 41.3 ± 9.1), and 22 boys with fragile X syndrome, 13 boys
Table 1. Characteristics of the Subjects Under Study

<table>
<thead>
<tr>
<th></th>
<th>Control</th>
<th>Idiopathic Autism</th>
<th>DS Only</th>
<th>DS + AUT</th>
<th>FRAX Only</th>
<th>FRAX + AUT</th>
</tr>
</thead>
<tbody>
<tr>
<td>(n = 22)</td>
<td>(n = 10)</td>
<td>(n = 11)</td>
<td>(n = 11)</td>
<td>(n = 16)</td>
<td>(n = 9)</td>
<td>(n = 13)</td>
</tr>
<tr>
<td>Age (yr)</td>
<td>8.3 ± 1.9</td>
<td>6.9 ± 2.4</td>
<td>7.2 ± 2.1</td>
<td>7.0 ± 1.8</td>
<td>5.3 ± 1.1</td>
<td>5.7 ± 2.1</td>
</tr>
<tr>
<td>IQ</td>
<td>120.8 ± 9.2</td>
<td>66.1 ± 14.4</td>
<td>41.3 ± 9.1</td>
<td>20.1 ± 6.9</td>
<td>56.0 ± 15.2</td>
<td>46.0 ± 15.0</td>
</tr>
<tr>
<td>ICA (sq cm)</td>
<td>167.7 ± 11.5</td>
<td>165.8 ± 10.9</td>
<td>139.8 ± 8.6</td>
<td>142.4 ± 9.2</td>
<td>161.3 ± 9.7</td>
<td>164.9 ± 15.7</td>
</tr>
<tr>
<td>Lobules I-V</td>
<td>4.8 ± 0.82</td>
<td>4.9 ± 0.53</td>
<td>3.8 ± 0.57</td>
<td>3.6 ± 0.41</td>
<td>4.7 ± 0.45</td>
<td>4.9 ± 0.61</td>
</tr>
<tr>
<td>Lobules VI-VII</td>
<td>3.3 ± 0.55</td>
<td>2.8 ± 0.52</td>
<td>2.3 ± 0.37</td>
<td>2.3 ± 0.39</td>
<td>2.5 ± 0.49</td>
<td>2.9 ± 0.51</td>
</tr>
<tr>
<td>Lobules VII-X</td>
<td>3.4 ± 0.65</td>
<td>3.6 ± 0.55</td>
<td>2.3 ± 0.37</td>
<td>2.3 ± 0.41</td>
<td>2.6 ± 0.57</td>
<td>3.0 ± 0.58</td>
</tr>
<tr>
<td>Lobules I-VICA</td>
<td>0.029 ± 0.004</td>
<td>0.030 ± 0.004</td>
<td>0.027 ± 0.003</td>
<td>0.025 ± 0.003</td>
<td>0.029 ± 0.004</td>
<td>0.030 ± 0.004</td>
</tr>
<tr>
<td>Lobules VI-VIIICA</td>
<td>0.020 ± 0.003</td>
<td>0.017 ± 0.003</td>
<td>0.016 ± 0.003</td>
<td>0.017 ± 0.003</td>
<td>0.015 ± 0.003</td>
<td>0.018 ± 0.003</td>
</tr>
<tr>
<td>Lobules VII-XICA</td>
<td>0.020 ± 0.004</td>
<td>0.022 ± 0.004</td>
<td>0.016 ± 0.002</td>
<td>0.016 ± 0.003</td>
<td>0.018 ± 0.004</td>
<td>0.019 ± 0.004</td>
</tr>
</tbody>
</table>

†Values correspond to mean ± 1 SD.
AUT = autism; DS = Down syndrome; FRAX = fragile X syndrome; ICA = intracranial area.

with fragile X syndrome + autism (mean age 5.7 ± 2.1 years, mean IQ 46.0 ± 15.0) and 9 boys with fragile X syndrome only (mean age 5.3 ± 1.1 years, mean IQ 56.0 ± 15.2). The contrast group included 22 gender-matched controls (mean age 8.3 ± 1.9 years, mean IQ 120.9 ± 9.2). All cases of idiopathic autism, Down syndrome + autism, and fragile X syndrome + autism fulfilled Diagnostic and Statistical Manual of Mental Disorders—IV (DSM-IV) diagnostic criteria for autism.47 Four of the 16 boys with Down syndrome + autism were also diagnosed with childhood disintegrative disorder (mean age 7.5 ± 1.1 years, mean IQ 25.3 ± 8.4) based on an additional decline in functioning after 3.5 years of age.

Subjects in the idiopathic autism group were recruited as part of studies of neuroanatomic variation in monozygotic twins discordant for autism and for procedural learning in autism, primarily through the Autism Society of America; the psychiatry, neurology, and developmental pediatrics clinics at the Kennedy Krieger Institute; and by word of mouth. DSM-IV diagnosis of autism was confirmed by the Autism Diagnostic Interview-Revised48 and the Autism Diagnostic Observation Scale.49 Children were included regardless of the level of cognitive functioning, which was assessed by the Stanford-Binet-IV.48

Subjects with Down syndrome only and Down syndrome + autism were recruited through the Down syndrome clinic at the Kennedy Krieger Institute. The diagnosis of Down syndrome was determined by clinical examination by one of the authors (G.T.C.) and was confirmed by karyotype. All subjects with Down syndrome had trisomy 21; none were mosaic. DSM-IV diagnosis of autism in the Down syndrome + autism group was confirmed by a score > 60 (mean = 78.5 ± 15.6 years, range 63–107 years) on the Autism Behavior Checklist.50 Subjects with Down syndrome with severe sensory impairment, socioenvironmental deprivation, or a DSM-IV diagnosis of stereotypic movement disorder, depression, obsessive-compulsive disorder, attention-deficit hyperactivity disorder (ADHD), tic disorder, or disruptive disorder were excluded from the study. Subjects with fragile X syndrome only and fragile X syndrome + autism were recruited as part of a study of the development of cognition and social behavior in young males with fragile X syndrome at the Kennedy Krieger Institute. The diagnosis of fragile X syndrome was established by the standard FMR1 Southern blot test.50 All subjects with fragile X syndrome had the full mutation; none were mosaic. DSM-IV diagnosis in the fragile X syndrome + autism group was confirmed by the Autism Diagnostic Interview-Revised using the same criteria applied to the subjects with idiopathic autism.

To assess the cognitive ability of the subjects with Down syndrome and fragile X syndrome, one of the following tests was administered: the Bayley Scales of Infant Development—II—Mental Scales51 or the Stanford Binet-IV. The Bayley Scales of Infant Development II was administered to all boys with Down syndrome and fragile X syndrome whose abilities fell below the 2-year level. The Stanford Binet-IV was used in children who exceeded the mental age ceiling (> 2 years) on the Bayley Scales of Infant Development II. Level of cognitive impairment (ie, severe to profound mental retardation) was not used to exclude subjects.

Healthy control subjects were recruited through the offices of a local pediatrician. The pediatrician sent letters to the parents of patients who, according to their medical records, did not have emotional problems or learning disabilities. The parents then contacted the Kennedy Krieger Institute if they were interested in participating in the study and were screened initially by telephone. Subjects receiving (or having had received) special education services or mental health treatment were excluded. Children who met the telephone screening criteria were then brought in for testing. To further rule out the presence of emotional and behavioral problems, the Achenbach Child Behavior Checklist52 and the Revised Behavior Problem Checklist53 were administered. The Wechsler Intelligence Scale for Children, Third Edition (WISC-III),54 was administered to determine intellectual ability and to rule out the presence of cognitive disability. The test composite scores from the Stanford-Binet-IV, WISC-III, Mental Development Index (MDI), and Bayley Scales of Infant Development II estimated IQ, representing levels of overall cognitive abilities, were labeled as “IQ” for data analysis purposes. Table 1 displays the basic features of each group of subjects under analysis.

The study was explained to all participants in language appropriate to their level of cognitive functioning. Each parent signed consent forms, and, if appropriate, participants also signed assent forms, which were approved by the institutional review board of the Johns Hopkins Medical Institutions (the Joint Committee on Clinical Investigation).

Magnetic Resonance Imaging
All MRIs were acquired using a 1.5-Tesla Signa MRI scanner (General Electric, Milwaukee, WI). The head was aligned with laser crosshairs referenced to the nasion and midsagittal plane.
T1-weighted sagittal images were obtained with a TR of 600 milliseconds, a TE of 20 milliseconds, and a NEX = 2. Most of the scans contained images with a 3 mm thickness, one scan contained images that were 4 mm thick, and four scans contained images of 5 mm thickness. The gap between the slices ranged from 0 to 1.0 mm, with a 24 cm field of view and a 256 × 256 matrix. T1-weighted, three-dimensional volumetric radiofrequency spoiled gradient images, acquired in the coronal plane with scan parameters previously reported,23,24 were used for one subject with Down syndrome + autism because of motion on the T1-weighted sagittal data.

**Image Analyses**

Midline neuroanatomic structures were manually delineated on the midsagittal images and measured using the BrainImage program.27 Operational definitions of regions of interest were based on specified guidelines determined by an experienced neuroradiologist and with reference to standard neuroanatomic landmarks,28 as described in previous publications assessing the size of the cerebellar vermis in several developmental disorders.25,26 Area measurements of the cerebellar vermis and intracranium (used as a surrogate of brain size) were made on the midsagittal MRIs, which were identified by choosing the sagittal image that most clearly showed the cerebral aqueduct and the lobular anatomy of the vermis. Care was taken to distinguish the lobules of the vermis from the cerebellar tonsil and hemispheres. The measurement of the cerebellar vermis included the anterior vermis (lobules I–V), the posterior superior vermis (lobules VI–VII), and the posterior inferior vermis (lobules VIII–X). Raters who were blind to the diagnosis of the subject whose brain image was being measured performed quantitative image analyses independently. Interrater reliability for all measures, as determined by intraclass correlation coefficients, was 0.90 or above.

**Statistical Analysis**

The distributions of measures of the vermician area, as well as intracranial area, within each group were plotted and examined visually, with normality tested by the Kolmogorov-Smirnov test. Preliminary analyses of variance (ANOVA, Games-Howell post hoc tests), detailed in the next section, examined differences in age, IQ, and intracranial area between the groups under study. Findings from these preliminary analyses, as discussed in more detail below, informed subsequent decisions to (1) evaluate ratio measures of the vermician area to the intracranial area rather than absolute vermician area values to control for differences in intracranial area between the groups and (2) to control for age differences when comparing these measures across the developmental disorder groups. Because the main question is whether autistic features biologically delineate distinctive subphenotypes, most analyses were conducted using the Down syndrome and fragile X syndrome subgroups (ie, Down syndrome only, Down syndrome + autism, fragile X syndrome only, fragile X syndrome + autism) rather than the combined, autistic and nonautistic, Down syndrome and fragile X syndrome cohorts.

Analyses of ratios of vermician to intracranial area followed a two-step approach. First, analysis of covariance (covarying for age and/or IQ), with Games-Howell post hoc tests, was used to test differences between the five groups with developmental disorders (ie, idiopathic autism, Down syndrome only, Down syndrome + autism, fragile X syndrome only, fragile X syndrome + autism) and controls for each one of the three vermician ratios. Second, based on approaches used in previous neuroimaging studies, in which we examined the influence of ADHD on frontal lobe volumes in Tourette syndrome,49 we conducted analyses of the effect of the autism factor on vermic size in both Down syndrome and fragile X syndrome using two separate multivariate factorial ANOVA (ie, controls, idiopathic autism, Down syndrome only, Down syndrome + autism and control, idiopathic autism, fragile X syndrome only, fragile X syndrome + autism) of vermician ratios.

**RESULTS**

**Preliminary Analyses**

There were significant differences in age between the groups, with the fragile X syndrome only and fragile X syndrome + autism groups significantly younger than the control group. As expected, significant differences were also found in IQ between the controls and all of the groups of subjects with developmental disorders, as well as between the two Down syndrome groups (ie, Down syndrome only, Down syndrome + autism). Although we conducted all appropriate analyses covarying for IQ, we report here the results before and after introducing the covariate because it is possible that differences in IQ could be determined by the same molecular and cellular mechanisms leading to the neuroanatomic abnormalities under investigation (in a previous study, we showed that vermician measures predicted IQ28). Consequently, adjustment for IQ might inappropriately mask biologically important differences in the structures under study.50 Nonetheless, as can be observed in the following section, covarying for IQ did not substantially affect the outcome of our group comparisons. The ANOVA for intracranial area showed significant reductions in the Down syndrome only and Down syndrome + autism groups compared with the control group (P < .0001). The intracranial areas of the Down syndrome only and Down syndrome + autism groups were 16.6% and 15.4%, respectively, smaller than that of the control group. Based on these results, areas of cerebellar vermis lobules I–V (anterior vermis), VI–VII (posterosuperior vermis), and VIII–X (posteroinferior vermis) were analyzed as ratios to individual intracranial area rather than absolute values using individual analyses of covariance (age as covariate). Table 1 and Figure 1 summarize the absolute values and their distribution for the brain structures under evaluation. Table 1 also displays the ratios of vermician to intracranial area.

**Main Analyses**

Comparisons between each group of developmental disorders with the control group revealed specific differences. The idiopathic autism group showed a borderline significantly lower ratio of lobules VI–VII to intracranial area than the control group (ANOVA P = .046; analysis of covariance, covarying for IQ, P = .052). In contrast, comparisons between both Down syndrome groups and control subjects, with and without covarying for IQ, showed multiple differences. The relative size of the vermis was particularly reduced in the Down syndrome + autism group, with all three vermician ratios significantly lower as follows: anterior vermis to intracranial
Figure 1. Box plots depicting ratios of vermian posterosuperior (lobules VI–VII) to intracranial cross-sectional areas for all of the groups under study. The central line corresponds to the median and the points to the subjects with values above the 90th percentile and below the 10th percentile, respectively. The diamonds represent the mean for each group. AUT = autism; CNT = control group; DS = Down syndrome; FRAX = fragile X syndrome; IA = idiopathic autism group.

The present MRI study intended to test the hypothesis that selective posterior vermian changes (i.e., hypoplasia) may be associated not only with idiopathic autism but also with other developmental disorders that present with autistic features and cerebellar hypoplasia. Consequently, our study design contrasted boys with idiopathic autism, Down syndrome with and without autism, and fragile X syndrome with and without autism with normal gender-matched controls. We also compared the Down syndrome and fragile X syndrome autistic subphenotypes with their nonautistic counterparts. MRI morphometric analyses included the three main components of the vermian: anterior vermis (lobules I–V), the posterosuperior vermis (lobules VI–VII), and the posteroinferior vermis (lobules VIII–X). Our preliminary analyses showed a marked reduction in brain size affecting the subjects with Down syndrome; therefore, comparisons of vermian size were done after correction for intracranial area (surrogate measure of brain size). In correspondence with earlier studies, the ratio of lobules VI–VII to intracranial area was reduced (at a borderline significant level) in the idiopathic autism group with respect to controls. Comparisons with controls also indicated that both Down syndrome groups had a decrease in the size of the two components of the posterior vermis, whereas both fragile X syndrome groups showed smaller ratios of lobules VI–VII to intracranial area, although these differences were

<table>
<thead>
<tr>
<th>Table 2. Statistical Comparisons Between Groups (P Values)</th>
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<tr>
<td>Control vs</td>
</tr>
<tr>
<td>Idiopathic Autism</td>
</tr>
<tr>
<td>Age*</td>
</tr>
<tr>
<td>IQ*</td>
</tr>
<tr>
<td>ACA</td>
</tr>
<tr>
<td>Lobules I–V:ICA*</td>
</tr>
<tr>
<td>Lobules VI–VII:ICA*</td>
</tr>
<tr>
<td>Lobules VIII–X:ICA*</td>
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</tbody>
</table>

*Analysis of variance.

P values in the trend-significant range.

Analysis of covariance (covarying for age or IQ).
significant only in the fragile X syndrome only group. The Down syndrome + autism group also had a lower ratio of anterior vermis to intracranial area than the control group. Factorial ANOVA of the “autism” factor demonstrated an interaction effect only in the fragile X syndrome cohort, with the fragile X syndrome + autism group showing significantly higher ratios of lobules VI–VII to intracranial area than its nonautistic counterpart.

Cerebellar abnormalities are among the most common findings reported in neuropathologic and neuroimaging studies of idiopathic autism.1–12 Despite a recent study reporting proportional increases in cerebellar volumes in young children with idiopathic autism,8,9 most MRI investigations have shown reductions in the size of the cerebellar vermis, particularly of lobules VI–VII.5–12 Our data confirm, to some extent, these previous observations; we found a slight but selective reduction in the ratio of lobules VI–VII to intracranial area in our idiopathic autism group. Data distribution, depicted in Figure 1, demonstrates that the borderline statistical significance of the hypoplasia of lobules VI–VII in the idiopathic autism group was not attributable to a bimodal distribution, as suggested by earlier studies showing a subgroup of autistic individuals with hyperplasia of this vermic region.7 We did not find decreases in lobules VIII–X, as reported in two studies of children with idiopathic autism8,11 and one investigation on boys with ADHD.9,12 Because the methodology employed for assessing vermic area is similar in most investigations, discrepant results between this and other published studies could be explained mainly on the basis of subject selection. For instance, the report by Levitt and colleagues on posteriorinferior vermic hypoplasia was on a cohort of high-functioning autistic children.11 In our analyses, IQ was markedly and significantly lower in the idiopathic autism group than in the control group (see Table 1). Although covarying for IQ slightly reduced the difference in the ratio of lobules VI–VII to intracranial area between the idiopathic autism and control groups, the regional selectivity of the findings was not modified (see Table 2). Recent publications on cerebrial13,14 and cerebellar15 abnormalities in individuals with idiopathic autism suggest that some abnormalities are independent of cognitive status. This is an issue that deserves further examination; however, it is beyond the scope of the present study.

Down syndrome and fragile X syndrome are among the most common genetic disorders associated with mental retardation.17 Both conditions are also characterized by cerebellar hypoplasia, at least involving the vermis, and subsets of patients fulfilling DSM-IV diagnostic criteria for autism.18–20,28–31 Nevertheless, the relationship between cerebellar hypoplasia and autistic behavior, generally accepted in idiopathic autism, has not been directly examined in either Down syndrome or fragile X syndrome. Our original hypothesis that those individuals with extreme levels of posterior vermis reduction, within the Down syndrome and fragile X syndrome cohorts, will be clustered in the Down syndrome + autism and fragile X syndrome + autism groups was not confirmed. We found that global vermic hypoplasia is marked, even after correcting for overall brain hypoplasia, in both groups with Down syndrome. In fact, if any vermic component appears to be linked to autism status in Down syndrome, it is the anterior vermis that is selectively decreased in Down syndrome + autism but not in Down syndrome only (see Table 2). In the case of fragile X syndrome, the previously reported posterior vermis hypoplasia34,35 affects both components and is characteristic of the nonautistic subgroup (see Table 2). However, the fragile X syndrome only versus fragile X syndrome + autism comparison revealed a significant relative enlargement of lobules VI–VII in the autistic subgroup (if one considers the nonautistic fragile X syndrome subset as the reference group). Consequently, discrepancies with regard to regional
selectivity of vermal hypoplasia in fragile X syndrome might be explained by different proportions of autistic subjects in the studied samples.

Our data, altogether, suggest that anatomic abnormalities of the posterosuperior vermis are, indeed, characteristic of genetic disorders associated with severe developmental disability. Nonetheless, reductions in the size of the vermis are both regionally selective and linked to autistic features only in autistic individuals. Mild changes, of opposite direction, in the size of vermal lobules VI–VII are associated with autism status in males with idiopathic autism and boys with fragile X syndrome. The fact that this association is present in a relatively homogeneous genetic disorder (i.e., fragile X syndrome) further emphasizes the possible role that the postero superior vermis plays in the pathogenesis of some of the characteristic features of autistic behavior. A recent study showed that, in children with idiopathic autism, decreased white matter was significantly correlated with hypoplasia of lobules VI–VII. Additional investigations have linked, in idiopathic autism, cerebellar vermis abnormalities with both aberrant behavior and disrupted frontocerebellar connections. Although our findings do not rule out the involvement of the cerebellum in the pathophysiology of autism in Down syndrome, they indicate that abnormal cerebellar circuitry is more likely a mechanism for autistic behavior in fragile X syndrome than in the former disorder. Selective enlargement of brain structures is not a surprising finding in fragile X syndrome because relatively larger hippocampi, caudate nuclei, and parietal lobes have been reported by us and others in this condition. Our study was limited by sample size, lack of uniformity in behavioral instruments, and restricted focus on vermis size cross-sectional area. Despite these shortcomings, we considered this an initial attempt to address the role of the cerebellum in the pathogenesis of autism in the context of disorders associated with autistic features. Our findings could also be valuable for planning investigations on fragile X syndrome’s behavioral phenotype and mechanisms of abnormal brain development.

Acknowledgment
We thank Alice Kau for assistance in review of behavioral diagnoses.

References


