Title

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Journal

New England Journal of Medicine, 318(21)

ISSN

0028-4793

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Publication Date

1988-05-26

DOI

10.1056/nejm198805263182102

Peer reviewed

HYPOPLASIA OF CEREBELLAR VERMAL LOBULES VI AND VII IN AUTISM

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Abstract Autism is a neurologic disorder that severely impairs social, language, and cognitive development. Whether autism involves maldevelopment of neuroanatomical structures is not known.

The size of the cerebellar vermis in patients with autism was measured on magnetic resonance scans and compared with its size in controls. The neocerebellar vermal lobules VI and VII were found to be significantly smaller in the patients. This appeared to be a result of developmental hypoplasia rather than shrinkage or deterioration after full development had been achieved. In contrast, the adjacent vermal lobules I to V, which are ontogenetically, developmentally, and anatomically distinct from lobules VI and VII, were found to be of normal size. Maldevelopment of the vermal neocerebellum had occurred in both retarded and nonretarded patients with autism. This localized maldevelopment may serve as a temporal marker to identify the events that damage the brain in autism, as well as other neural structures that may be concomitantly damaged.

Our findings suggest that in patients with autism, neocerebellar abnormality may directly impair cognitive functions that some investigators have attributed to the neocerebellum; may indirectly affect, through its connections to the brain stem, hypothalamus, and thalamus, the development and functioning of one or more systems involved in cognitive, sensory, autonomic, and motor activities; or may occur concomitantly with damage to other neural sites whose dysfunction directly underlies the cognitive deficits in autism. (N Engl J Med 1988; 318:1349-54.)

AUTISM is a developmental disorder that results in severe deficits in social, language, and cognitive functioning.[1-4] In 1943, Kanner[1] suggested that autism is a biologic rather than a psychological disorder. Nonetheless, the cause of autism remains unknown, and the possibility that the disorder involves abnormal development of neuroanatomical structures remains unconfirmed.

Several studies[5,6] have reported that lateral ventricles are enlarged in some patients with autism. Enlarged ventricles do not serve as markers of damage to specific neuroanatomical regions, however, nor do they specifically point to an abnormality in early neuroanatomical development, since ventriculomegaly may be the result of a variety of congenital and acquired diseases. CT and postmortem studies of patients have found no appreciable abnormalities in the cerebral cortex.[7-11] However, postmortem studies of patients in whom autism was complicated by seizures, severe mental retardation, or the use of medication showed that the numbers of Purkinje cells in the cerebellum were reduced.[9,10,12] Moreover, we recently reported results of in vivo magnetic resonance scanning in a patient with autism uncomplicated by severe mental retardation, epilepsy, or a history of drug use or neurologic disease,[13] which demonstrated developmental hypoplasia of the neocerebellar hemispheres and vermal lobules VI and VII (i.e., declive, folium, and tuber in the superior posterior vermis). Neighboring paleocerebellar regions of the hemispheres and vermis (anterior vermal lobules I to V and inferior posterior vermal lobules VIII to X) were relatively unaffected.

To clarify further the relation between cerebellar abnormality and autism, the following questions need to be answered about the cerebellar abnormalities: Are they more closely associated with autism or with the concomitant medical histories? Are they due to maldevelopment or to tissue loss occurring later in life, after the development of the brain is complete? Are they frequently present in the general population with autism, or only in rare cases? To answer these questions, we obtained magnetic resonance scans of 18 patients with autism without superimposed disorders.

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Supported by funds from Children's Hospital Research Center, San Diego, by a grant (5-R01-NS-19855) from the National Institute of Neurological and Communicative Disorders and Stroke, and by a grant (1-R01-MH-36840) from the National Institute of Mental Health to Dr. E. Courchesne.

METHODS

Study Groups

Patients with Autism

The patient group consisted of 18 subjects with autism that was not complicated by severe mental retardation, cerebral palsy, epilepsy, genetic abnormality, other neurologic disease, or the use of anticonvulsant or antipsychotic medication. The criteria for infantile autism as defined by the *Diagnostic and Statistical Manual of Mental Disorders*[14] were used to identify autistic subjects. Their ages ranged from 6 to 30 years (mean, 20.9); 2 patients were female and 16 male. These 18 subjects were all the patients with autism in whom our laboratory has conducted behavioral and neurophysiologic studies for five years.[15-20]

The verbal IQ of the 18 subjects ranged from 45 to 111 on the Wechsler scale (mean, 77); the Wechsler performance IQ ranged from 70 to 112 (mean, 88). Thirteen subjects had full-scale Wechsler IQs between 73 and 108, of whom 7 held jobs (e.g., gardener's aide, assembler in a bicycle shop, and secretarial aide), attended college, or did both. The other five subjects had full-scale IQs between 55 and 70. They had a much lower level of function and required constant custodial care; three of them could not read or solve simple mathematical problems.

Normal Controls

The control group consisted of 12 subjects whose ages ranged from 9 to 37 years (mean, 24.8), of whom 3 were female and 9 male.

Three subjects had volunteered (all men). The other nine had been selected from patients who had undergone magnetic resonance scanning of the brain at the University of California–San Diego Magnetic Resonance Institute according to the following method. The entire file of scans available at the institute was searched for brain scans that included axial and sagittal images; 90 such scans were found. From the patients represented by these scans, normal controls were selected by using the following criteria: age between 6 and 36 years, no symptoms of cerebellar dysfunction, and no evidence of central nervous system abnormalities on the scan, as reviewed independently by two of us who are neuroradiologists. Among the reasons for referral were head and neck pain, depression, headaches, and neurogenic bladder. Nine patients were identified who satisfied all these criteria.

Although an ideal normal control group would have consisted entirely of normal volunteers, limitations on funding dictated the use of existing scans of nine patients found to be normal. Since the central point of this study was to compare the neuroanatomy of persons with autism with that of persons without autism, the controls selected represent a sample of nonautistic persons with normal magnetic resonance scans.

Patients with Other Neurologic Disorders

We also analyzed the scans of patients with various abnormalities of the hindbrain, including developmental malformations and atrophy with onset in childhood or adulthood. This group comprised six patients with cerebellar atrophy associated with metabolic or seizure disorders, two patients with olivopontocerebellar dysgenesis, six patients with Arnold–Chiari Type I malformation of the cerebellum, one patient with agenesis of the corpus callosum, and one patient with Dandy–Walker malformation.

The scans of seven patients with focal lesions of the cerebral white matter were also evaluated.

Protocol for Magnetic Resonance Scanning

After appropriate informed consent was obtained, magnetic resonance scanning was performed in each patient with autism, by means of a 1.5-tesla imaging system (G.E. Signa). A multisection spin-echo sequence (TR [repetition time], 2000 msec; TE [echo time], 25, 70 msec) was conducted in the axial and coronal planes, and a multisection T_1-weighted sequence (TR, 600; TE, 25) in the sagittal plane centered at the midline. The sections were 5 mm thick, with a gap of 2.5 mm between adjacent sections.

Quantification Procedures

Figure 1 (top panel) shows the location of vermal lobules I to V (the anterior vermis), vermal lobules VI and VII (the superior posterior vermis), and vermal lobule VIII (the inferior posterior vermis). In the midline sagittal plane, the boundary between the anterior vermis (i.e., lobules I to V) and vermal lobules VI and VII was defined as the line joining the anterior aspect of the primary fissure to the apex of the fourth ventricle. The boundary between vermal lobules VI and VII and vermal lobule VIII was defined as the line joining the anterior aspect of the prepyramidal fissure to the apex of the fourth ventricle. The boundary between vermal lobule VIII and lobule IX was defined as the line joining the anterior aspect of the secondary fissure and the apex of the fourth ventricle.

Magnetic resonance images for the group with autism, the control group, and the group with nonautistic neurologic disorders were coded and mixed at random before evaluation by the investigators, who were blinded to the identity and group membership of each subject. Quantification of vermal cross-sectional areas was performed on the sagittal image that showed most clearly the aqueduct of Sylvius and the deepest extent of the primary and prepyramidal fissures. On the midsagittal scan of every subject, the boundaries of vermal lobules I to V, VI and VII, and VIII were independently traced twice, once by one of us who is a neuroradiologist and once by a graduate student in our neurosciences department. Next, four investigators measured the areas of these traced regions planimetrically: two measured the set of tracings from the neuroradiologist, and two measured the set from the student. All tracings and measurements were done on coded images so that the identities and group memberships of the subjects were unknown to the investigators. The four measures of each of the three regions of interest in each subject were highly correlated with one another. For example, correlations between any two of the four measurements of vermal lobules VI and VII ranged from a low of 0.855 to a high of 0.986. The four planimetric measures were averaged, and the results were used in the statistical analyses.

Vermal lobules IX and X were not measured, because the scans used in this study did not show clearly defined boundaries for them. Furthermore, these lobules are classified as the paleocerebellum and the archicerebellum, respectively, and did not have prime relevance to this study. These regions and the cerebellar hemispheres were intended to be measured in later investigations.

Results

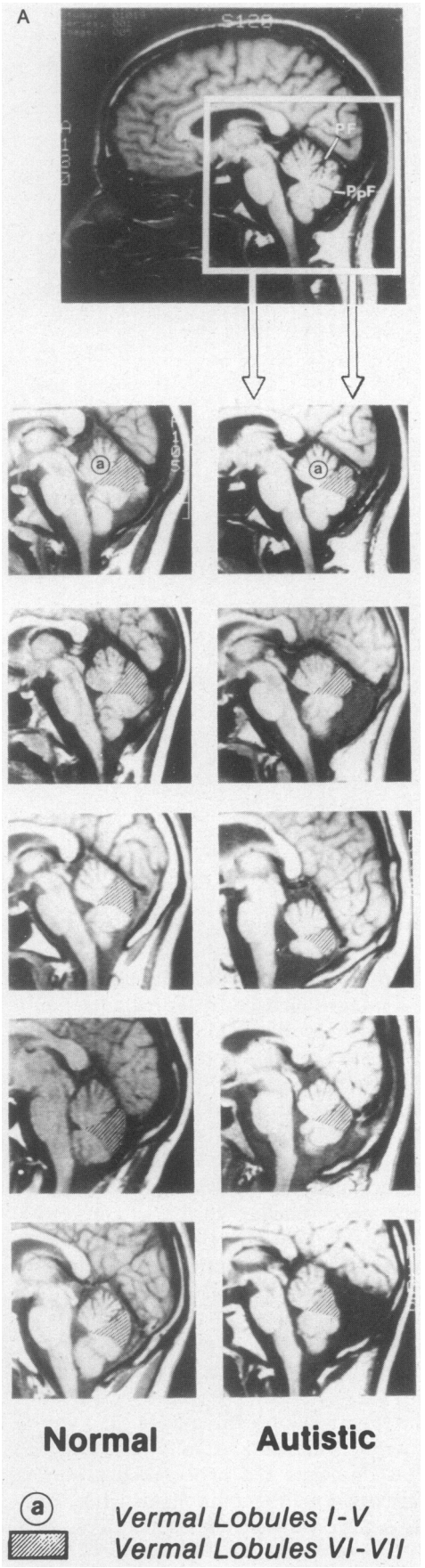
The vermal lobules VI and VII of the patients with autism were found to be significantly smaller than those of the controls ($F(1,28) = 10.83$, $P = 0.003$) (Fig. 1). Of the 18 autistic subjects, 14 had lobule areas that fell between 1.1 and 4.33 SD below normal (Table 1). In these 14 subjects, vermal lobules VI and VII were 25 percent smaller than in the control subjects (mean, 229 vs. 305 mm^2). Both the patients with lower functioning and those with higher functioning were among those with the severest vermal hypoplasia.

Figure 1A shows five examples of a normal vermis and five examples of a vermis with hypoplasia. Figure 1B shows superimposed contours of lobules I to V and of lobules VI and VII in the same subjects represented in Figure 1A. Vermal lobules I to V (the anterior vermis) were similar in size in the autistic and normal groups (421 vs. 423 mm^2), as was vermal lobule VIII (118 vs. 127 mm^2) ($P>0.55$ for both comparisons) (Fig. 1 and Table 1).

In one patient with autism, lobule VIII also appeared to have developmental hypoplasia (2.58 SD below normal) (Fig. 1A). In other respects, the image of this patient matched the pattern of the patients with autism as a whole: vermal lobules VI and VII had pronounced hypoplasia (4.33 SD below normal), and the anterior vermis was of normal size.

To confirm that the smaller size of vermal lobules VI and VII was regionally localized in the patients with autism and was not due to a possibly smaller brain overall, we created a simple index of regionally localized vermal hypoplasia. This index was the ratio of the total of the combined areas of vermal lobules VI and VII to the total of the combined areas of lobules I to V in each subject, expressed as a percentage. It was 72.4±6.5 percent in the control group, but only 59.1±9.2 percent in the autistic group ($F(1,28) = 18.8$, $P<0.001$). In the patients with autism, the reduction in the area of vermal lobules VI and VII relative to the anterior vermis is shown in Figure 1, and the index of regionally localized vermal hypoplasia shown in Figure 2. In 14 of the patients, the index of hypoplasia was 1.40 to 4.92 SD below that of the control group (Table 1).

The diminished size of vermal lobules VI and VII did not appear to be the result of parenchymal atro-



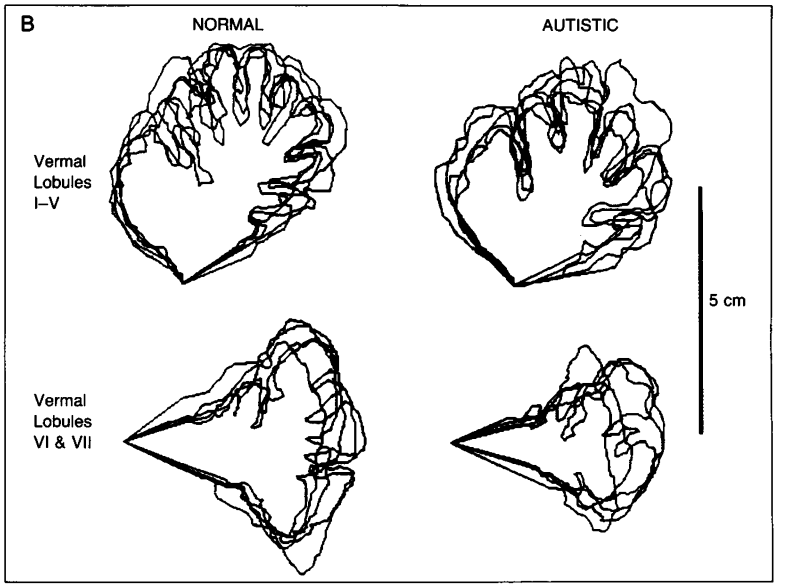


Figure 1. Magnetic Resonance Scans (A) and Tracings (B) of the Vermal Lobules of Five Patients with Autism Who Have Vermal Hypoplasia and Five Controls.

Panel A shows midline sagittal views of the vermis. The patients have vermal hypoplasia, in that their lobules VI and VII are smaller than those in the controls; their lobules I to V and lobule VIII are normal, except for a hypoplastic lobule VIII in the third scan from the bottom. PF denotes primary fissure and PpF prepyramidal fissure.

Panel B shows superimposed outlines of the lobules of five patients and of those of five controls (the same 10 subjects represented in Panel A). Lobules VI and VII of the patients are appreciably smaller than those of the controls; lobules I to V of both groups are similar in area.

phy or encephalomalacia (Fig. 1A). There was no evidence of excessive sulcal widening or abnormal signal intensity within the cerebellar parenchyma. On the contrary, the depth and width of the three major sulci (primary, prepyramidal, and secondary fissures) in the autistic group were similar to those seen in the control group.

Figure 3 shows the difference between the normal mean value for the size of the vermal lobules and the values for the patients with seven neurologic disorders, including autism. The anterior vermis of the group with autism differed from normal by only 2 mm^2; in vermal lobules VI and VII, however, the difference from normal was 56 mm^2. This pattern was not seen in any other group of patients. In the patients with Arnold–Chiari Type I malformation, both the anterior vermis and vermal lobules VI and VII were larger than normal. In contrast, in the patients with Dandy–Walker malformation, olivopontocerebellar dysgenesis, agenesis of the corpus callosum, and cerebellar atrophy, both vermal regions were very much smaller than normal. Finally, in patients with supratentorial abnormalities such as focal lesions in the white matter, both regions were normal (Fig. 3).

Discussion

Our results indicate that autism is strongly associated with anatomical abnormalities in vermal lobules VI and VII of the cerebellum. The abnormalities appear to represent developmental hypoplasia. When the results of magnetic resonance scanning are considered in conjunction with all available postmortem findings regarding the cerebellum of patients with autism,[9,10,12] it appears that abnormalities at the cellular and gross anatomical levels are consistently pres-

ent in various neocerebellar regions in the great majority of these patients, with or without superimposed mental retardation or other neurologic disorders. No other part of the nervous system has been shown to be so consistently abnormal in autism.

Nonetheless, our results also show that in some portion of the spectrum of autism, disorders of the cerebellum may have a different expression or may not be involved (for example, in four of the patients with autism the vermal ratio was within 1 SD of normal).

As suggested in recent discussions of the pathophysiologic features of autism,[15,21] neocerebellar maldevelopment could potentially affect cognitive development in autism in two ways. First, damage to the neocerebellum might directly impair cognitive functions and behavioral control attributed to the neocerebellum.[22-26] For instance, since it has been suggested that the neocerebellum is involved in the acquisition and execution of skilled cognitive and motor operations,[27] early damage to this area might hinder the normal, smooth acquisition and execution of sensorimotor schema from which human intellectual growth proceeds.[28] Second, through direct connections to numerous sites in the brain stem and thalamus, the neural output of damaged neocerebellar circuits might affect the development and functioning of one or more systems involved in attention, cortical modulation, sensory modulation, regulation of autonomic activity, and motor and behavioral initiation.[29-38] Abnormal functioning in each of these systems has often been proposed in theories and studies of autism.[2,15,39-43] For example, anatomical and physiologic evidence indicates that the neocerebellar cortex is connected, through the deep cerebellar nuclei, with all levels of the reticular activating system, including medullary, pontine, mesencephalic, and intralaminar thalamic segments. Disturbances in the functioning of the reticular activating system were among the first neurobiologic explanations of the cognitive deficits of autism.[2]

Neocerebellar maldevelopment may also point to damage at other neural sites, as follows. First, the same event that damages the neocerebellar vermis may also damage other neural components whose dysfunction underlies the cognitive deficits in autism. Sec-

Table 1. Area of Vermal Lobules and IQ Values in Patients with Autism and Controls.

Group	Vermal Lobules				Age/ Sex	Intelligence Quotient		
	Area I–V	Area VI–VII	Area VI–VII: Area I–V	SD of Ratio from Normal		Verbal	Performance	Full-Scale
	square millimeters		*percent*					
Autistic patients								
1	424.2	172.3	40.6	−4.92	22/M	96	112	103
2	395.6	171.0	43.2	−4.51	20/M	80	70	74
3	386.7	194.8	50.4	−3.41	14/M	45	73	55
4	428.3	223.8	52.3	−3.12	30/M	71	78	73
5	367.3	197.1	53.7	−2.90	22/M	105	104	105
6	484.8	270.7	55.8	−2.56	23/M	74	92	80
7	365.8	209.7	57.3	−2.33	22/M	100	112	105
8	452.8	261.7	57.8	−2.26	16/M	81	71	75
9	449.1	260.3	58.0	−2.24	27/M	76	97	83
10	398.6	232.0	58.2	−2.20	20/F	55	87	68
11	394.8	245.4	62.2	−1.59	17/F	55	88	70
12	446.2	277.4	62.2	−1.58	25/M	111	104	108
13	413.4	258.8	62.6	−1.52	20/M	62	71	66
14	468.5	296.7	63.3	−1.40	27/M	89	92	89
15	377.7	259.5	68.7	−0.57	25/M	74	74	73
16	355.4	245.4	69.1	−0.52	6/M	82	92	86
17	499.7	355.4	71.1	−0.20	21/M	70	80	73
18	465.8	356.4	76.5	+0.64	19/M	54	84	68
Mean ±SD	420.8 ±43.5*	249.4 ±52.6†	59.1 ±9.24†		20.9	76.7	87.8	80.8
Controls								
1	401.6	256.8	64.0	−1.30	30/M			
2	511.6	336.1	65.7	−1.04	31/M			
3	417.1	277.9	66.6	−0.89	29/M			
4‡	404.0	276.0	68.3	−0.63	26/M			
5	386.7	270.7	70.0	−0.37	30/M			
6	459.5	324.2	70.6	−0.28	22/M			
7‡	431.0	306.0	71.0	−0.22	37/M			
8‡	422.0	307.0	72.8	+0.06	33/M			
9	470.6	351.7	74.7	+0.36	13/M			
10	427.8	335.7	78.6	+0.96	19/F			
11	403.3	329.8	81.8	+1.45	19/F			
12	339.8	287.0	84.7	+1.86	9/F			
Mean ±SD	422.8 ±43.8	304.9 ±30.9	72.4 ±6.46		24.8			

*Not significantly different from control mean.
†Significantly lower than control mean ($P<0.003$ by analysis of variance).
‡Normal volunteer.

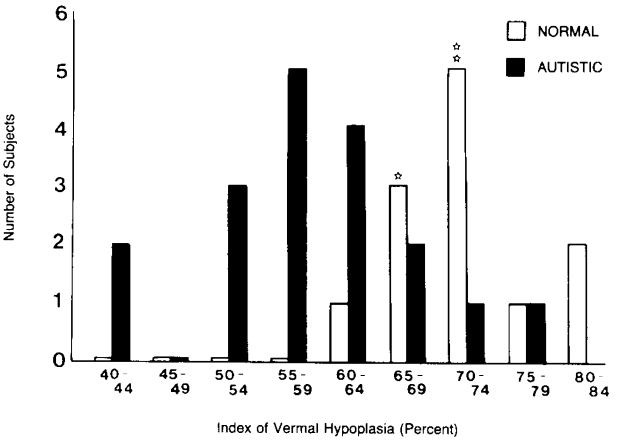


Figure 2. Index of Vermal Hypoplasia in 18 Patients with Autism and 12 Controls.

The index denotes the ratio of the combined area of vermal lobules VI and VII to the combined area of lobules I to V. The values for the three controls who were normal volunteers (stars) fall in the center of the distribution of the values for the nine controls who were patients.

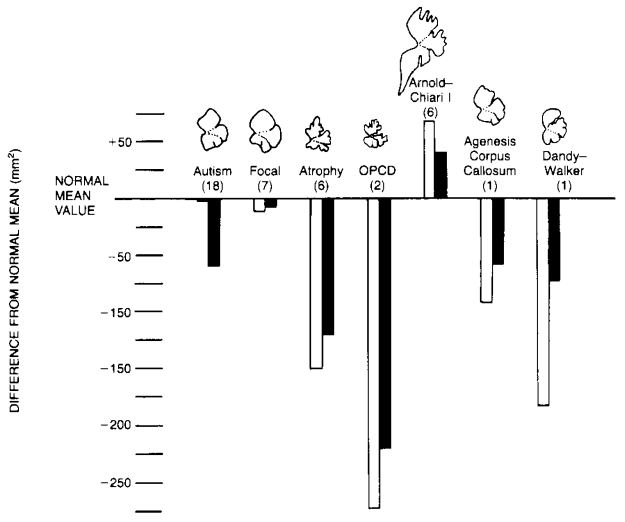


Figure 3. Difference from Normal Value for Combined Area of Vermal Lobules I to V and the Combined Area of Lobules VI and VII in Patients with Seven Neurologic Disorders, Including Autism.
The zero line represents the mean normal value obtained in this study for the midsagittal area of vermal lobules I to V (i.e., 423 mm^2), and each white bar represents a difference from this value. The zero line also represents the normal mean in this study for the midsagittal area of vermal lobules VI and VII (i.e., 305 mm^2), and each black bar represents a difference from this value.
An example of the midline sagittal view of the vermis is shown above each disorder listed. OPCD denotes olivopontocerebellar dysgenesis, and focal denotes focal lesion in cerebral white matter. Values in parentheses represent the number of patients with the disorder.

ond, the limited range of motor and somatosensory activities in the autistic infant (i.e., "neural deprivation" occurring during development) may lead to reduced growth of dendritic and axonal branches in the neocerebellar vermis, in other neural systems, or in both. Third, neocerebellar damage may represent loss resulting from damage to other neural systems that are closely connected with the vermal neocerebellum. The last explanation is unlikely, since the cerebellum sustains very little secondary loss (less than 3.2 percent) even when large regions of motor or somatosensory cortex are excised.[44] The two other explanations may have some validity not yet established.

The observation that vermal lobules VI and VII are abnormal in the majority of patients with autism, but that the anterior vermis is not, may represent an important first step both in determining the timing of environmentally or genetically mediated events that damage the brain and induce this disorder and in identifying any other neural sites that may be concomitantly damaged. Vermal lobules VI and VII are embryologically and phylogenetically distinct from anterior vermal lobules I to V.[30,45-47] These two regions are derived from different primordial tissue,[47] and the timing of neurogenesis and the migration of Purkinje and granule cells destined for these regions also differ.[46,47] An environmentally mediated event that disturbs the migration of Purkinje cells to the posterior vermis could also affect neurogenesis that occurs at that time in the subiculum, CA1 and CA3 of the hippocampal formation, portions of the septum, and the amygdalohippocampal area of the corticomedial complex of the amygdala[47,48] — regions involved in memory and emotional behavior. Microscopical abnormalities in these regions have been reported in a postmortem study of one patient with autism.[10] As a second example, very late intrauterine or postnatal disruption of granule-cell migration may render vermal lobules VI and VII hypoplastic in relation to the anterior vermis, since lobules VI and VII receive their final full complement of granule cells after the anterior vermis does.[46] Such a late insult may simultaneously affect the development of hippocampal granule cells, which, like cerebellar granule cells, are among the last neurons to migrate during development.

Studies of families and twins have suggested that genetic factors operate in autism.[2,49] No genetic mutation is known that selectively affects the neocerebellum but not the anterior cerebellum. However, some mouse mutants undergo selective loss of Purkinje or granule cells.[50-53] In particular, the cerebellum of the "nervous" mouse mutant (nr) is hypoplastic because of postnatal Purkinje-cell degeneration (50 percent loss in the vermis and 90 percent in the hemispheres), which is associated with mitochondrial dysfunction; the hippocampus shows maldevelopment of lamina in CA2 and CA3. The most prominent symptoms in affected mice are hypersensitivity to auditory and somatosensory stimulation; hyperactivity when very young, which decreases to hypoactivity later in development and in adulthood; and dysfunctional breeding behavior. These symptoms are similar to symptoms sometimes present in patients with autism. Surprisingly, motor incoordination is mild in the mutant mouse; the most prominent motor symptom is a tendency toward long delay in initiating motor responses under novel situations (e.g., when placed in water for the first time).[51]

The abnormal vermal morphology of our patients with autism differs from that in patients with the developmental and acquired disorders listed in Figure 3, as well as other forms of cerebellar dysgenesis, such as Down's syndrome.[30,54-56] We are investigating several other neurobehavioral disorders (e.g., Rett syndrome) that present with behavior patterns like those of autism, in order to ascertain whether cerebellar abnormalities are present.

Autism has been an enigma for more than four decades. It has been considered by some to be a psychosocial disorder resulting from abnormal parenting. The cerebellar hypoplasia described above, however, supports the view that autism is instead a developmental neurobiologic disorder.

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