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Neuropathology of Infantile Autism

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INTRODUCTION

Infantile autism, a behaviorally defined disorder initially described by Kanner (1), is a syndrome which, by definition, is manifested by 36 months of age and is characterized by disordered language and cognitive skills, impaired social interactions, abnormal responses to sensory stimuli, events and objects, poor eye contact, an insis~ tence on sameness, an unusual capacity for rote memorization, repetitive and stereotypic behavior, and a normal physical appearance (2). Disturbances in elementary motor function, when present, are subtle and motor milestones are usually normal (see 3 for review). The prevalence rates are estimated to be 10-13 per 10,000, and the disorder is more commonly seen in boys than in girls, with a ratio of 2.5-4.0:1 (4-6).

Based on the clinical features of the disorder, a number of possible sites of brain abnormality in autism have been hypothesized. Early investigators speculated on the involvement of the limbic system (7), medial temporal lobe (8-11), thalamus (12), basal ganglia (13), and vestibular system (14). A few Magnetic Resonance Imaging (MRI) studies have reported abnormalities of the cerebellar vermis, but the results have not been uniformly replicated (see 15 for review). Imaging studies have also yielded variable observations in regard to brainstem size and structure (16-19). Although an early pneumoencephalographic study (20) reported abnormalities in the region of the medial temporal lobe, subsequent Computerized Tomographic (CT) and MRI investigations have failed to demonstrate definitive findings in this region (6, 21-23). Initial studies using Positron Emission Tomography (PET) suggested a dysfunction of the frontal and parietal lobes, thalamus, caudate nucleus, lenticular nucleus, and insula in adult autistic subjects (24), and using ^{31}P NMR spectroscopy, suggested involvement of the dorsal prefrontal cortex (25). More recent PET investigations have observed reduced volume and metabolic activity in the right anterior cingulate gyros in 7 high-functioning autistic adults (26), and abnormalities of serotonin synthesis in the dentatothalamicortical pathway in 7 autistic boys

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(27). Using ^{31}P NMR spectroscopy in a study of 11 adolescent and adult autistic males, Minshew et al (25) noted involvement of the dorsal prefrontal cortex, which was unrelated to age or IQ (25). Regional blood flow studies have also implicated frontal lobe involvement, with the findings suggesting a delay in maturation in this area (28). In addition to studies highlighting regional differences, there is evidence from both imaging and pathological investigations suggesting that the brain of autistic individuals may be generally enlarged for age and sex (16, 29, 30). Piven et al (16) have observed that there be may some regional selectivity of brain enlargement with relative sparing of the frontal lobe as well as reduced size of the posterior part of the corpus callosum relative to the total brain size.

Relatively few neuropathological studies have been performed on autistic subjects. Early investigations include Aarkrog's (31) report of a "slight thickening of the arterioles, slight connective tissue increase in the leptomeninges and some cell increase" in a frontal lobe biopsy, and the report of Williams et al (32) indicating a lack of a consistent pathology in the hippocampus, parahippocampal gyros, thalamus, hypothalamus, striatum, and midbrain tectum from 4 individuals with autistic behavior. Ritvo et al (33) has reported a decrease in the number of Purkinje cells in the vermis and hemispheres of the cerebellum. Coleman et al (34) counted neuronal and glial cells in multiple cortical regions of an autistic brain and in 2 age- and sex-matched controls and found no differences. However, examination of the brainstem from this same patient showed a marked reduction in the number of neurons in the facial nucleus and superior olive, as well as shortening of the brainstem between the trapezoid body and the inferior olive (35). The authors suggested that these findings could indicate that the brain abnormalities associated with autism might have their onset around the time of neural tube closure. In a recent autopsy study, Guerin et al (36) reported slight thickening of the meninges, mild ventricular dilatation, thinning of the corpus callosum, scattered perivascular lymphocyte infiltrates, and a few microglial nodules in the lower brainstem in the brain of a 16-year-old autistic boy with mental retardation.

Our own systematic surveys of the whole brain serial sections of 9 autistic brains and comparable controls have shown selective abnormalities in the forebrain limbic system and in the cerebellum and in its related inferior olive

in the brainstem, as well as evidence for a pathological process that extends from the period of fetal development into adulthood. Six of these brains were midsagittally cut, with one hemisphere available for the histological studies. The autistic brains were systematically compared with identically processed age- and sex-matched controls using a comparison microscope in which corresponding areas of the brain were viewed side by side in the same field of view at the same magnification. In areas in which consistent abnormalities were found, quantitative and semiquantitative analysis was performed (37-39). The findings in these brains will be reviewed in relationship to the anatomy of the affected regions, the clinical manifestations of infantile autism, and reported observations using in vivo imaging techniques.

Brain Size and Configuration

Brain weight is available for 19 autistic individuals. Eight of the l 1 brains from individuals less than 12 years of age showed a significant increase in weight as compared with controls. This is in contrast to those of 6 of 8 individuals older than 18 years of age, where brain weight was less than expected (40), but the differences did not reach statistical significance.

Neocortex

No abnormality has been noted in the external configuration of the cerebral cortex. With the comparison microscopic examination, 8 of the 9 brains have shown unusually small and more closely packed neurons and less distinct laminar architecture in the anterior cingulate gyrus; in 1 brain there was a minor malformation of the orbitofrontal cortex in 1 hemisphere. The remainder of the cerebral cortex appeared unremarkable.

Allocortex and Subcortical Forebrain Areas

Systematic survey of the forebrain has shown no abnormalities in the striatum, pallidum, thalamus, hypothalamus, basal forebrain, bed nucleus of the stria terminalis, or in myelination. In all 9 brains, the forebrain abnormalities were confined to the limbic system. The neurons in the hippocampal fields CAI-4, subiculum, entorhinal cortex, mammillary body, amygdala, and medial septal nucleus were unusually small and more densely distributed than in age- and sex-matched controls. With the Golgi method for the demonstration of neuronal processes, the neurons in CAI and CA4 showed reduced complexity and extent of their dendritic arbors (41). In the amygdala, small neuronal size and increased cell packing density were most pronounced medially in the cortical, medial, and central nuclei, whereas the lateral nucleus appeared to be comparable to controls in 8 of the 9 brains. The basolateral complex of the amygdala showed an intermediate degree of involvement. The single exception to this pattern of involvement of the amygdala was observed in a 12-year-old autistic boy with normal intelligence and significant behavior problems. In this brain the entire amygdala was diffusely abnormal.

Similar to the findings noted in the hippocampus and amygdala, the neurons of the medial septal nucleus also demonstrated reduced cell size and increase cell packing density in all brains. However, the adjacent nucleus of the vertical limb of the diagonal band of Broca showed unusually large, plentiful, but otherwise normal-appearing neurons in all autistic subjects less than 12 years of age. In contrast, these same neurons were noted to be small and markedly reduced in number in all of the autistic patients older than 18 years of age (42). Details of the relative degree of involvement of the hippocampal fields, entorhinal cortex, mammillary body, septum, and amygdala in 6 of the 9 autistic brains is presented in the paper by Bauman and Kemper (38).

Cerebellum and Brainstem

Midsagittal photographs of 11 autistic brains, in which the vermis was cut in the midline, show a variable pattern in the size of the lobules of the vermis and widening of the cerebellar folia in several of the brains (Figure 1). On microscopic examination of the cerebellum, all 9 brains showed a variable reduction in the number of Purkinje cells, and in a few of the brains, pallor of the granule cell layer. Reduced numbers of Purkinje cells were noted, predominantly in the posterolateral neocerebellar cortex and adjacent archicerebellar cortex, while the vermis was spared (43, 44). The extent of this decrease in the number of Purkinje cells was not related to the age or functional level of the patient and there has been no evidence of the reactive gliosis usually seen following Purkinje cell loss in childhood or at older ages. Similar to the findings noted in the neurons in the nucleus of the diagonal band of Broca, the neurons in the globose, emboliform, and fastigial cerebellar nuclei appear to differ with age. In all of the younger autistic brains, these neurons were enlarged in size and present in adequate numbers, and in brains of all the autistic subjects older than 22 years, the neurons were pale and reduced in number. The neurons in the dentate nucleus were enlarged in the brains of the younger autistic individuals without the later atrophy and cell loss noted in the other cerebellar nuclei (42). In the brainstem, the only abnormality noted was found in the inferior olive, a change that occurred in the part of the olive that projects to the cerebellar cortex with the most marked decrease in the number of Purkinje cells (45). The neurons in this part of the inferior olive in all of the younger brains were enlarged but otherwise normal in appearance and number. In subjects older than 22 years, these same neurons were present in adequate numbers, but were abnormally small and pale. In all of the autistic brains, some of the neurons of the inferior olivary nucleus tended to cluster at the periphery of the inferior con-

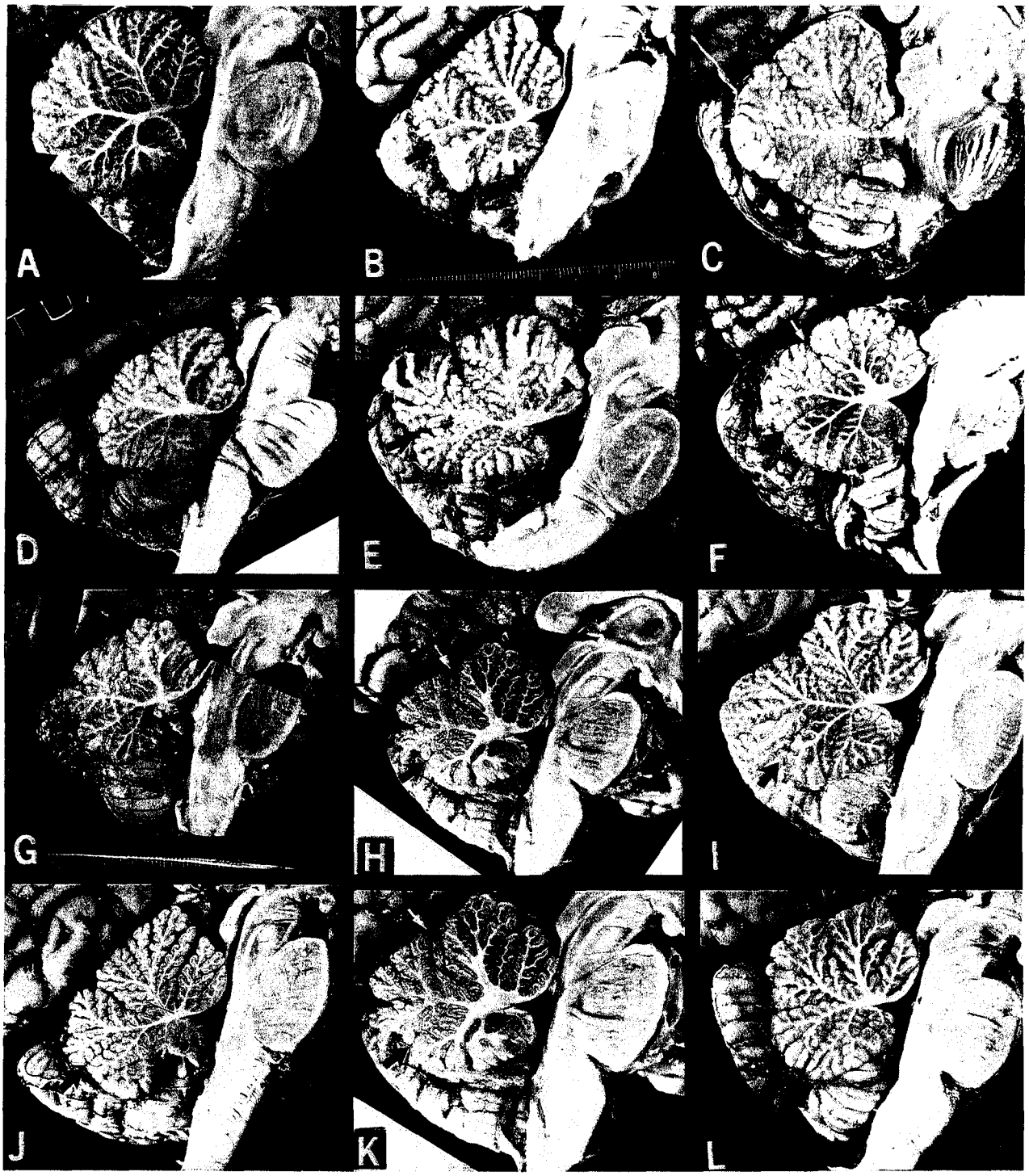

Fig. 1. Identically enlarged photographs of the midsagittal sections of a control 30-year-old male brain (at A) and 11 brains of autistic individuals at 6 years (at B), 8 years (at C), 10 years (at D), 19 years (at E), 20 years (at F), 21 years (at G), 28 years (at H), 35 years (at I), and 54 years of age (at J). In K and L, the brains of autistic individuals with Asperger's syndrome and normal intelligence are shown. The arrows indicate the location of the fissura prima (upper arrow) and fissura praepyramidalis (lower arrow), which divide the vermis into an anterior lobule (lobules I-V), lobules VI and VII, and the posterior vermal lobules VII-X. Note the variability of the size of the different lobules in the autistic brains with a lack of a consistent pattern and the widening of the spaces between the folia of the different lobules in several of the brains (B, D, E, and J).

volutions. In 1 brain there was a widened fourth ventricle with a corresponding thinning and elongation of the superior cerebellar peduncle (37).

Nature of the Pathological Changes

There are 3 different neuropathologies in these brains: a curtailment of the normal development of neurons in the forebrain limbic system; an apparent congenital decrease in the number of Purkinje cells; and age-related changes in cell size and number of neurons in the nucleus of the diagonal band of Broca, in the cerebellar nuclei, and in the inferior olive.

The small, densely distributed neurons in the limbic system in the brains of these autistic individuals would be an expected finding during an earlier stage of maturation, a time at which neuronal size and the complexity of the neuropil has not reach adult proportions. In this sense, these changes in the limbic system can be characterized as a curtailment of normal maturation. A curtailment of maturation is the most common finding in the brain of individuals with mental retardation, with the most striking changes occurring in the cerebral cortex (46). This is the neuronal substrate with the most prolonged period of maturation (47). In the autistic individuals, this pattern is different than that found in mental retardation, inasmuch as it appears to be confined to the limbic system, a neuronal substrate with cycles of maturation shorter than that of the cerebral cortex (60).

The decrease in the number of cells in the cerebellar cortex appears to be a congenital lesion. This hypothesis is supported by 2 observations. First, the decrease in cell number occurs without the expected gliosis, suggesting that these abnormalities were acquired early in development. Second, there is a failure of the occurrence of retrograde atrophy in the inferior olivary neurons. Loss of neurons in this nucleus has been regularly observed following cerebellar lesions in the immature postnatal and adult animal (62) and in neonatal and adult humans (45, 48, 49). The occurrence of the retrograde olivary cell loss is believed to be secondary to the tight relationship of the olivary climbing fiber axons to the Purkinje cell dendrites (50). In the fetal monkey, it has been shown that the olivary climbing fibers from the inferior olive initially synapse in a transitory zone located beneath the Purkinje cell, a layer called the lamina dissecans (51). Since this zone is no longer evident in the human fetus after 30 weeks of gestation (52), it is likely that the cerebellar cortical lesion, if it were due to Purkinje cell loss, occurred at or before this time. Another possible explanation for the lack of loss of inferior olivary neurons in these brains is that, rather than a loss of Purkinje cells, there may have been fewer of these cells present from the beginning.

The age-related changes in the neurons of the diagonal band of Broca, in the cerebellar nuclei, and in the inferior olive are an unusual neuropathology. In the autistic brains, this appears to be a prolonged process that extends from neuronal hypertrophy in childhood to atrophy and, in some of these nuclei, to cell loss in later adult life. As an acute event, neuronal swelling is known to follow transection of an axon (axonal reaction), and is then followed by atrophy and cell loss. Cell swelling followed by atrophy is also known as an anterograde transneuronal event in the inferior olive following lesions of the central tegmental tract or dentate nucleus (53). Thus, the swelling followed by atrophy of some neurons in these autistic brains suggests a disturbance in the synaptic relationships of these nuclei. These hypertrophic and atrophic changes are most marked in the cerebellar circuits in the autistic brains, and occur in association with an apparent congenital decrease in the number of neurons in the cerebellar cortex. The cerebellar nuclear changes appear to be topographically largely independent of the cerebellar cortical changes. The cerebellar nuclear pathology is most marked in the fastigial, globose, and emboliform nuclei, nuclei that receive Purkinje cell projections from the histologically best-preserved cortical areas of the vermis, and paramedian lobes of the cerebellar cortex. The least involved cerebellar nucleus, the dentate, receives its Purkinje cell projection from the most involved cortical area, the lateral lobes of the cerebellum. We have speculated elsewhere (39) that the age-related changes in the cerebellar nuclei may also be understood as a disturbance of the prenatal development of their circuitry, with a timing of the onset of this abnormality similar to that noted for the establishment of the definitive olivocerebellar circuit. At the stage in cerebellar development during which the olivocerebellar fibers are confined to the lamina dissecans, there is already advanced myelination in the olivocerebellar tracts in the inferior cerebellar peduncle. At this stage of development, the myelinated fibers extend to the cerebellar nuclei, but not to the cerebellar cortex, suggesting that a functional circuit between these 2 areas already exists at this time. An abnormality that has an impact on the intimate relationship between the Purkinje cells and the inferior olivary nucleus at this stage or at a later stage of fetal development might favor the persistence of this fetal circuit over the definitive, postnatal olivocerebellar cortical circuit. An abnormal retention of this fetal circuit might account for the presence of "compensatory" postnatal neuronal enlargement of the neurons in the cerebellar nuclei and inferior olive. Since this proposed fetal circuit was not "programmed" to function as the dominant postnatal pathway, it is possible that it will eventually lead to atrophy and loss of neurons in the older autistic individuals. By analogy, the hypertrophy and atrophy of neurons in the nucleus of the vertical limb of the diagonal band of Broca may also be related to a persistence of an abnormal circuit between this nucleus and the heavily involved hippocampal complex.

Relationship to Clinical and Other Features of Infantile Autism

The abnormalities in the anterior cingulate gyrus, hippocampus, subiculum, entorhinal cortex, and mammillary body are in an interrelated forebrain circuit proposed by Papez as a substrate for memory and emotion (54), and in the closely related septal nuclei and amygdala. Experimental lesions in these regions have produced deficits in these and other behaviors, many of which resemble those seen in childhood autism. Hyperactivity, impaired social interaction, hyperexploratory behavior, and the inability to recognize or remember the significance of visually or manually examined objects have been observed following bilateral medial temporal lobe ablations in monkeys (55) and in similar neurosurgical lesions in humans (56). Bilateral removal of the amygdala in monkeys has resulted in indiscriminate examination of objects, loss of fear to normally aversive stimuli, withdrawal from previously rewarding social interactions, poor adaptability to novel situations, and reduced ability to attach meaning to a specific situation based on past experience (57). Murray and Mishkin (58) have also shown that bilateral ablations of the amygdala result in a severe impairment of crossmodal associative memory, suggesting that the amygdala may be important for the integration and generalization of modality specific information by multiple sensory systems in the brain, a task which is frequently difficult for autistic individuals. The strongest support for a role of an early acquired lesion in the amygdala, hippocampus, and adjacent cerebral cortex for the behavioral manifestations of autism is provided by Bachevalier and Merjanian (59). These investigators found striking autistic behavior following bilateral ablation of the amygdala and hippocampus in neonatal monkeys. In a later study, Malkova et al (60) found that the socioemotional behavioral deficits in these monkeys increased with age and remained a profound deficit into adulthood. In contrast, comparable lesions placed in adult monkeys resulted in only a relatively mild deficit in this behavior.

In the forebrain, 2 different memory systems have been recognized. One is declarative or explicit memory that is associated with a rapid, one-trial learning that links different kinds of memories and experiences into "cognitive learning." The other is habit or procedural memory that is not accessible to conscious recollection and is acquired by repeated presentation of the same stimulus (61, 62). Habitual memory is believed to be mediated by the striatum and cerebral cortex (61), areas almost entirely spared in these autistic brains. In contrast, the limbic area abnormalities are in a position to disrupt explicit memory. Although early studies have emphasized the combined role of bilateral lesions in the hippocampus and amygdala for the disruption of declarative memory (63, 64), more recent studies have focused on role of the hippocampus and entorhinal cortex in this function. In man (65) and in nonhuman primates (66), lesions confined to area CA I of the hippocampus have been shown to produce declarative memory deficits. Further, in recent monkey experiments, Meunier et al (89) have emphasized the importance of selective lesions in the rhinal cortices (entorhinal and adjacent perirhinal area) in the disruption of these memory processes. All of these areas have been found to be consistently involved in the brain of autistic individuals. Habit or procedural learning appears to be already well developed shortly after birth in both monkeys and humans, whereas explicit memory is more slow to mature (62, 68). While the effect of an early disturbance to the limbic system structures is unknown, it is likely that prenatally acquired lesions in these regions could disrupt or distort the acquisition and interpretation of information. Such a disturbance in information processing could lead to the disordered cognition, language, and social interaction associated with autism. In contrast, the preservation of the habit memory system could account for the need for sameness, preoccupation with a narrow range of interests and activities, and for the unusual capacity for rote memorization observed in some autistic individuals. Further, since there is evidence that representational memory in humans is normally acquired some time after birth, it is possible that a developmental abnormality in this limbic system memory circuit could become clinically evident after birth, accounting for what appears to be a deterioration in social, language, and cognitive abilities, features frequently reported to be part of the early history of childhood autism.

It is also possible that the cerebral cortical abnormalities seen in infantile autism with PET scans (24), ^{31}P NMR spectroscopy (25), or regional blood flow studies (28) could be secondary to the pathological changes in the limbic system, since area CAI of the hippocampus, the subiculum, the entorhinal cortex, and the amygdala all have substantial afferent and efferent cortical connections (69-70). The one area where there is agreement between imaging studies and pathology is in the cingulate gyrus. In this location Hazendar et al (26) have noted that the right anterior cingulate gyros appears to be smaller and metabolically less active than in controls.

The relationship of the cerebellar findings to those in the forebrain and to the clinical features of autism are less obvious. Congenital abnormalities of the cerebellum are associated with few if any neurological symptoms (48). Studies in animals have demonstrated the existence of a direct pathway between the fastigial nucleus and the amygdala and septal nuclei, and a reciprocal circuitry between this nucleus and the hippocampus, suggesting that the cerebellum may play a role in the regulation of emotion and higher cortical thought (72, 73).

Recent studies have suggested that the cerebellum may play a role in the perception and control of timing

involving both motor and sensory systems (74), that it may be important in mental imagery and anticipatory planning (75), and that it is involved in some aspects of language processing (76). Further, the cerebellum has been implicated in the control of attention, particularly the voluntary shift of selective attention between different sensory modalities (77, 78). It has also been suggested that the cerebellum may play a role in cognitive planning, a function which is independent of memory and which is most significant in novel situations (79). In addition to these functions, the cerebellum also appears to play a role in the regulation of the speed, consistency, and appropriateness of mental and cognitive processes, as well as in the control and integration of motor and sensory information and activity (80). Studies in humans with cerebellar lesions (81) have shown that the cerebellum plays a role in the acquisition of classical conditioned reflex responses.

CONCLUSIONS

At this point, our knowledge of the anatomy of autism is primarily descriptive. The available anatomical evidence indicates that the neuropathology of infantile autism has its origins in the prenatal development of the brain, with an ongoing pathological process that continues into adult life. The consistent abnormalities in the limbic forebrain, although subtle and evident only after comparisons with appropriate controls, have provided the strongest correlation with the clinical features of the disorder. In contrast, the relationship of the more conspicuous neuropathology in the cerebellum to the syndrome of infantile autism has provided an ongoing challenge. Further complicating the clinical correlation of the cerebellar cortical findings to the clinical features of this disorder has been the inconsistencies noted on imaging studies and in gross pathology. We anticipate with interest the results of future studies with more modern techniques and, hopefully, with the development of an appropriate animal model.

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