

Autism: Clinical Features and Neurobiological Observations¹

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Since its first description in 1943 (Kanner, 1943), autism has intrigued clinicians and scientists alike, largely because of its association with significant disturbances in cognition and behavior in the absence of obvious physical and brain dysmorphology. For many years, parenting and environmental factors were believed to be to blame for the social aloofness, obsessive need for sameness, perseverative and stereotypic behaviors, and impaired language that characterize this disorder. However, with the advent of improved neurobiological technology and with the awareness of the high incidence of seizures (Deykin & MacMahan, 1979) and abnormal electroencephalograms (Small, 1975) within the autistic population, evidence for neurological basis for the disorder began to mount.

In any consideration of the clinical deficits exhibited by autistic children, disturbances in language development are usually the first concern and are the symptom that most frequently brings the child to the attention of a physician (Rapin, 1991). Initially, some autistic children may appear deaf, failing to respond to being called by their name or to follow simple commands. Rapin and Allen (1987) have suggested that many (if not most) autistic children have impaired comprehension of language and that some may

exhibit a verbal-auditory agnosia or word-deafness (Rapin, Mattis, Rowan et al., 1977).

In the majority of autistic children, expressive language also is significantly delayed, and a significant proportion of these fail to develop any meaningful communication skills (Rutter, 1978). Approximately one-fifth of autistic children appear to develop language at the appropriate time, some of which development can seem to be precocious and associated with an exceptional vocabulary. However, these skills undergo regression, usually between 12 and 18 months of age, following which language development in these children is similar to that of autistic children whose verbal output was delayed from the beginning (Kurita, 1985).

Those children who eventually do develop language display a wide variation in the quantity and quality of communication patterns exhibited. Frequently, little spontaneous language is exhibited, and expressive output is obtained with the assistance of verbal or physical prompts. Some children will demonstrate rote patterns of counting, reciting the alphabet, or repeating scripts they have acquired from television, videotapes, books,

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or parents with little understanding of their meaning. Echolalia may be present, and children perseveratively may repeat a word or the last several words of a sentence just heard. For those children who become fluent speakers, abnormalities of prosody or the melody and intonation of speech may substantially impair communicative intent. Their verbal output may have a sing-song or monotone quality, and they may have difficulty in modulating the volume of their voice. Some highly verbal autistic children may speak pedantically to others, particularly on a favorite topic, with little appreciation of the interest of the listener. Many of these children can appear to have little need of a conversational partner, and social language often is impaired. Typically, they have difficulty in maintaining a topic of conversation, particularly if it is a topic which they themselves have not chosen. They have difficulty with conversational turn taking, do not easily establish or use eye contact during communication, and typically interpret poorly the body language, tone of voice, or facial expression of others (Rapin, 1991).

Nonverbal communication also is impaired in autistic children. They rarely use a pointing response, nor do they exhibit joint attention. Rather than gesture, autistic children will lead the hand of an adult to a desired object or obtain the object themselves (Minshew & Payton, 1988).

Though it is now acknowledged that autistic individuals exhibit a wide range of intellectual abilities, estimates suggest that approximately 75% function within the retarded range [Diagnostic and Statistical Manual of Mental Disorders (fourth edition) (DSM-IV)]. Regardless of the level of function, the profile of cognitive development tends to be uneven (DSM-IV). Many are very concrete, and even very intelligent autistic individuals may experience difficulty with concept formation, reasoning, abstract thought, and insight (Rapin,

1991). Typically, autistic children tend to have better nonverbal than verbal skills and tend to be better visual learners than auditory learners (Rapin, 1991). They tend to have an exceptional memory for details and tend to overgeneralize rules. In contrast, autistic individuals often have difficulty with the processing of information related to the integration and generalization of concepts and the development of abstract thought (Minshew & Payton, 1988). Some autistic persons have shown superior skills for a narrow range of abilities, such as calendars, calculations, music, drawing, and rote verbal tasks, despite otherwise impaired cognitive abilities (Rapin, 1991).

During early childhood, the majority of autistic children demonstrate significant deficits in imaginary or symbolic play. In the high-functioning adult, this deficit may contribute to the inability to develop generic notions in regard to abstract concepts, such as justice, beauty, or jealousy (Grandin, 1995).

Along with language and cognitive impairments, social deficits are one of the most striking clinical manifestations of autism. During infancy, autistic children may be extremely passive babies requiring little attention, or they may be very irritable, difficult to feed, have irregular sleep patterns, and resist cuddling. As young children, they appear to be socially aloof, seemingly unaware of the presence or feelings of others. Alternatively, some autistic children can be overly and inappropriately affectionate, even with strangers. They can become excessively attached to and clingy with one parent and tolerate separation poorly. Autistic children do not know how to make friends or to engage others in their activities or play. They tend to be rigid and do not easily learn socially appropriate behavior, such as initial greetings. Some basic social skills can be taught, but only rarely do they become automatic and used with total ease. The extent to

which socialization abilities are related to or interdigitate with either language or cognitive functioning remains unknown.

Nearly all autistic children appear to have difficulty with the regulation of attention (Dawson & Lew, 1989). Many are easily distractible and hyperactive, rarely giving any task or toy more than momentary interest. Alternatively, others may become hyperfocused and “lock into” a task of particular interest to them, such as the computer, lining up objects, or twirling string. In this case, shifting or transitioning their attention to another activity often is difficult and leads to disruptive behavior (Kinsbourne, 1991).

Although autistic children initially were believed to be motorically normal, more careful observation has found that many demonstrate a generalized hypotonia with hyperextensibility of some of the joints. Posture tends to be poor. Though most of these children meet their developmental gross motor milestones on time, a significant proportion walk late. Gait patterns may lack fluidity, and bilateral motor coordination for such skills as skipping and cutting with scissors may be executed poorly. Some children walk on their toes, but whether this practice is related to a dysfunctional motor pattern or to excessive sensitivity on the bottoms of the feet (or both) is unclear. Refined fine motor skills, such as buttoning, controlling a pencil, or tying shoes, often are exceedingly difficult and (in some cases) are never achieved. In addition, a deficit may be possible in the ability to imitate motor movements and automatically to execute skilled motor tasks or to perform these tasks in a demand situation, suggesting the presence of motor dyspraxia in these children (Rapin, 1991). Poorly executed oral-motor movements can be associated with drooling, poor articulation (resulting in reduced intelligibility), and difficulty in chewing. Repetitive and stereotypical motor

movements are seen in approximately one-third of autistic children. Although the disorder frequently is termed “self-stimulatory” behavior, its etiology and functional significance remains a matter of debate.

Many autistic children appear to have difficulty in modulating the input of sensory information. Some appear to be particularly sensitive to auditory stimuli, such as mechanical noises, school bells, a baby’s cry, or the subtle noises made by fluorescent lighting. Some are particularly sensitive to light touch, such as tags in their shirts, seams in their socks, haircuts, and new unwashed clothing that is perceived as scratchy. Alternatively, these same children may appear impervious to pain, failing to cry even when severely hurt. Some seek comfort from the sensation of pressure and may be found contentedly curled up between two mattresses in their bedroom. Occasionally, some autistic children also appear to be excessively sensitive to odors and others to food textures, which may result in restricted dietary intake.

NEUROPHYSIOLOGICAL STUDIES

Given the variety and complexity of symptoms with which the autistic child presents, some benefit derives from considering possible brain mechanisms that may underlie some of the clinical features of the disorder. Some of the earliest studies that attempted to address this question were neurophysiological investigations that demonstrated abnormal auditory-nerve and brainstem-evoked responses (Student & Schmer, 1978; Tanguay, Edwards, Buchwald, Schwofeld, & Allen, 1982) and rapid eye movement sleep patterns (Tanguay, Ornitz, Forsythe, & Ritvo, 1976). However, in retrospect, these abnormalities were found to be related primarily to the heterogeneity of the study population and to methodological factors. Subsequent investigations on well-documented

autistic subjects have failed to confirm the original reports (Rumsey et al., 1984; Courchesne et al., 1985a).

P300 and negative component (Nc) have been the most common event-related potentials (ERPs) studied in autism. P300s are believed to originate from the modality-nonspecific association cortex in the parietal lobes and are thought to be dependent on the intact connectivity between this cortical region and the hippocampus and limbic cortex (Wood et al., 1984). Nc is believed to originate from the frontal cortex. ERPs are of cortical origin and depend on the brain's intrinsic processing of sensory information, not on the stimulus.

Small or absent auditory P300s and visual P400s have been recorded in autistic subjects who were required to detect random missing stimuli from a regular series of auditory or visual stimuli (Novick, Kurtzberg, & Vaughan, 1979). Because the subjects were able to detect the missing stimuli, the authors suggested that the attenuated ERPs were related to a disturbance in information storage secondary to a dysfunction in the circuitry connecting the inferior parietal cortex with the entorhinal cortex and hippocampus, not to motivational or attentional factors. Further, cross-modulation studies involving both auditory and visual stimuli have suggested an impairment in information processing (Novick et al., 1979). This hypothesis was revised in 1980 when the same authors reported significantly smaller auditory P200 and P300 potentials in autistic subjects in response to pitch changes and deleted stimuli (Novick et al., 1980). It was noted that the depression in the late potentials occurred during tasks that required direct sequential comparison of auditory stimuli and was not limited to conditions in which a temporal interval must be registered. Based on these findings, the authors hypothesized that the abnormalities

were not related to a dysfunction in information storage as previously proposed but to a disturbance in the processing of auditory information and that the abnormality most likely was located in the parietal association cortex. Subsequently, Courchesne et al. (1985b) noted the absence of Nc to novel visual or auditory stimuli in autistic subjects, despite normal task performance and sustained attention, suggesting abnormalities involving the frontal cortex. Thus, evidence appears to point to neurophysiological abnormalities in the parietal and frontal association cortices in autism; they have been hypothesized to be related to inefficient cortical auditory processing or to dysfunctional cortical handling of selective attention (Minschew, 1991).

POSITRON EMISSION TOMOGRAPHY AND FUNCTIONAL IMAGING STUDIES

Relatively few positron emission tomographic (PET) studies have been reported in autism. In 1985, Rumsey et al. noted increased 2-fluoro-2-deoxy-D-glucose uptake throughout the cerebral cortex, hippocampus, thalamus, and basal ganglia in a series of adult high-functioning male autistic subjects. However, substantial overlap occurred in the data between the control and autistic groups in this study. When these data later were subjected to correlation analysis, reduced frontal-parietal intercorrelations were found in the autistic individuals and were hypothesized to be related to an imbalance in mutually inhibitory neuronal circuits associated with attention (Horwitz et al., 1988). Two additional studies have failed to show any statistically significant differences between the autistic and control subjects (De Volder et al., 1987; Herold et al., 1988). More recently, Chugani et al. (1996) studied serotonin synthesis with PET in 10 normal adults in comparison with

4 adult autistic subjects. The results of this study demonstrated significantly higher serotonin synthesis in normal female subjects as compared to male subjects and increased serotonin synthesis in the autistic subjects in comparison with that in controls. These preliminary findings are intriguing and warrant further investigation.

Using (31)P nuclear magnetic resonance spectroscopy, Minshew et al. (1994) reported a decrease in phosphocreatine and adenosine triphosphate levels, borderline decreased phosphomonoesters, and increased phosphodiesterases in the dorsal prefrontal cortex in a group of high-functioning autistic adolescents and young adults, suggesting neuronal membrane alteration and altered energy metabolism in the frontal cortex. The authors hypothesize that these preliminary findings may be reflective of inefficient information processing in autism.

IN VIVO NEUROANATOMY

The first imaging study to suggest a neuroanatomical basis for autism was a pneumoencephalographic study performed on 18 children who presented with retarded language development and autistic behavior (Hauser, DeLong, & Rosman, 1975). Enlargement of the left temporal horn was noted in 15 cases, with some subjects showing enlargement of both temporal horns or mild enlargement of the lateral ventricles, more pronounced on the left. On the basis of these observations, the authors suggested that abnormalities involving the medial temporal lobe structures might play a role in the symptomatology of autism.

The introduction of computed tomography (CT) in the mid-1970s resulted in numerous attempts to further define brain abnormalities in autism. In 1979, Hier, Lemay, and Rosenberger reported a reversal

of the normal left-right parietal-occipital asymmetry in 57% of the autistic subjects who were studied in comparison with mentally retarded and neurological control groups. On the basis of these findings, the failure of normal language development in autism was speculated possibly to be related to the morphological inferiority of the left hemisphere. However, subsequent CT studies failed to replicate these initial findings (Damasio et al., 1980; Tsai, Jacoby, & Steward, 1983; Rumsey et al., 1988). Further CT studies focused on observations of ventricular size (Jacobson et al., 1988; Rumsey et al., 1988) without documentation of consistent abnormalities.

With the emergence of magnetic resonance imaging (MRI) technology, *in vivo* morphometrical studies of the brain have focused on the analysis of specific brain regions. The major focus of these studies has been on the cerebellum (following the initial reports of Courchesne et al. in 1987 and 1988) and on a remeasurement of the same cases in 1989 (Murakami et al., 1989), indicating a selective hypoplasia of lobules VI and VII of the vermis on midsagittal images in autistic subjects. However, five well-designed subsequent studies have failed to replicate these findings (Ritvo & Garber, 1988; Holttum et al., 1992; Filipek et al., 1992; Kleiman, Neff, & Rosman, 1992; Piven et al., 1992). In 1994, Courchesne et al. reanalyzed data from previously published MRI vermian measurements in 78 autistic subjects. Although the majority of the patients were found to demonstrate hypoplasia of lobule VI and VII as originally reported, a small subgroup was noted to have hyperplasia of these same lobules. The authors concluded that, because of the presence of both vermian hypoplasia and hyperplasia and the averaging of these measurements, cerebellar midline abnormalities were not detected in several of

the previously reported series. However, given that only a single midsagittal section was measured, they did not address the possibility that the shape and total volume of the cerebellum, age, intelligence quotient, and other factors unrelated to autism may be significant variables. Further studies involving large numbers of carefully matched subjects will be needed before the significance of cerebellar findings on MRI can be resolved.

Other areas of the brain also have been studied by MRI in autism, including the brainstem and more recently the parietal lobe and corpus callosum (Gaffney et al., 1988; Filipek et al., 1992; Piven et al., 1992). So far, the findings in these studies have been inconsistent, and their significance at this time is uncertain.

HISTOANATOMICAL OBSERVATIONS OF THE BRAIN

Relatively few neuropathological studies have been reported in autism. In large part, this has been due to the limited availability of post-mortem material for study and to the fact that, in most cases, the brains appear to be grossly normal, giving few clues to the location and nature of the neuropathology that underlies this disorder. On the basis of the clinical features of autism, and extrapolating from observations derived from clinical and animal research, a variety of candidate sites of abnormality have been hypothesized. These have included the basal ganglia (Vilensky, Damasio, & Maurer, 1981), the thalamus (Coleman, 1979), the vestibular system (Ornitz & Ritvo, 1968), and structures of the medial temporal lobe (Boucher & Warrington, 1976; Delong, 1978; Damasio & Maurer, 1978; Maurer & Damasio, 1982). Despite these considerations, early neuropathological studies failed to determine any consistent morphological abnormalities (Aarkrog, 1968;

Darby, 1976; Williams et al., 1980; Coleman et al., 1985).

Using the technique of whole-brain serial section (Yakovlev, 1970), the brains of nine well-documented autistic patients have been systematically studied in comparison with identically processed age- and sex-matched control material (Bauman & Kemper, 1995). All cases studied to date have shown no abnormalities of external brain structure or myelin. With the exception of the anterior cingulate gyrus, microscopical analysis of multiple cortical regions in all the autistic brains also have shown no abnormality of cortical lamination, neuronal size or number, or cellular migration consistent with the findings of Coleman et al. (1985). In addition, a systematic survey of the basal ganglia, thalamus, hypothalamus, and basal forebrain failed to delineate any differences from the controls.

Areas of the forebrain that were found to be abnormal were confined to the hippocampus, subiculum, entorhinal cortex, amygdala, mammillary body, anterior cingulate cortex, and septum. These structures are known to be related to each other by interconnecting circuits and make up a major portion of the limbic system of the brain. In comparison with controls, these areas showed reduced neuronal cell size and increased cell-packing density (number of neurons per unit volume), which appeared to be equal bilaterally. Using the rapid Golgi technique, pyramidal neurons of areas CA1 and CA4 of the hippocampus showed reduced complexity and extent of dendritic arbors (Raymond, Bauman, & Kemper, 1996). In the amygdala, small cell size and increased cell-packing density was most pronounced medially in the cortical, medial, and central nuclei, whereas the lateral nucleus appeared to be comparable to controls. The exception to this profile was observed in the brain of a 12-year-old autistic boy with a history of serious behavioral disturbances but

with documented average intelligence. In this case, the findings of small cell size and increased cell-packing density was less robust in the hippocampal complex, compared with that of more severely impaired subjects, but the entire amygdala was diffusely abnormal.

In the septum, reduced cell size and increased cell-packing density were similarly observed in the medial septal nucleus in all cases. However, a different pattern of abnormality was found in the nucleus of the vertical limb of the diagonal band of Broca (NDB). Compared with controls, unusually large but otherwise normal-appearing neurons, present in adequate numbers, were found in all the autistic patients younger than age 12. In contrast, these same neurons were noted to be small and markedly fewer in all the autistic patients older than age 22.

Outside of the forebrain, additional abnormalities in the autistic brains have been limited to the cerebellum and related inferior olive. In all cases, a marked reduction in the number of Purkinje cells was observed throughout the cerebellar hemispheres, most dramatically in the posterolateral neocerebellar cortex and adjacent archicerebellar cortex, with sparing of the vermis (Arin, Bauman, & Kemper, 1991; Bauman & Kemper, 1996). Abnormalities also have been found in the globose, emboliform, and fastigial nuclei located in the roof of the cerebellum which, like the findings in the septum, appear to differ with age. Small pale neurons that are reduced in number are seen in these nuclei in all the autistic patients older than age 22. However, in all the younger autistic subjects, these same neurons and those of the dentate nucleus are enlarged and present in adequate numbers (Bauman & Kemper, 1994).

No evidence of atrophy or cell loss was found in the principal inferior olivary nucleus

of the brainstem in any of the autistic brains, areas known to be related to the abnormal regions of the cerebellum (Holmes & Stewart, 1908). Because of this close relationship, neuronal cell loss and atrophy of the inferior olive invariably have been noted in human neuropathology after the perinatal and postnatal loss of Purkinje cells (Norman, 1940; Greenfield, 1954). In the three oldest cases, the olivary neurons were small and pale but exhibited no evidence of cell loss. In all the younger subjects, these same neurons were enlarged but otherwise normal-appearing.

IMPLICATIONS OF LIMBIC SYSTEM ABNORMALITIES FOR AUTISM

Microscopical analysis of the brain in autism has shown abnormalities that have been confined consistently to the limbic system, the cerebellum, and the related inferior olive. The findings of decreased neuronal cell size and increased cell-packing density that characterize the limbic system are consistent with a pattern of developmental curtailment involving this circuitry. This concept is supported further by the presence of decreased complexity and extent of dendritic arbors observed in the pyramidal cells of the hippocampus.

Given its extensive network of interrelated circuits and widespread connections to other parts of the brain, abnormalities of the limbic system could disrupt significantly the function of the limbic and sensory association neocortex and the reticulate core of the brain. Lesions in experimental animals involving the structures of the medial temporal lobe have shown pronounced effects of emotion, behavior, motivation, and learning, many of which effects resemble the clinical features of autism. Purposeless hyperactivity, severe impairment in social relatedness, hyperexploratory behavior, and the inability to remember or recognize the significance of

visually or manually examined objects have been observed in monkeys after bilateral surgical ablations of the medial temporal lobe (Kluver & Bucy, 1939). Similar behaviors have been noted after comparable neurosurgical lesions in humans (Terzian & Delle-Ore, 1955).

Selective lesions involving specific medial temporal lobe structures, introduced experimentally in adult animals, have provided further insight into the function of each of these individual regions. In the rat, bilateral ablations of the hippocampus produced hyperactive animals with stereotypical motor behavior and unusual responses to novel stimuli (Roberts, Dember, & Brodwick, 1962; Kimble, 1963). Similar surgical lesions in monkeys, confined to the amygdala, resulted in animals who exhibited loss of fear of normally aversive stimuli, compulsive indiscriminate examination of objects, and withdrawal from formerly socially rewarding situations (Mishkin & Aggleton, 1981). Further, these same animals showed a reduced ability to attach meaning to new environments based on past experience, resulting in poor adaptability to novel situations. When ablations were confined to the most medially located amygdalar structures (the central, medial, and cortical nuclei), the influence of familiarization on learning was reduced significantly (Vergnes, 1981). Further evidence for the importance of the amygdala for learning has been supplied by Murray and Mishkin (1985). In these studies, monkeys experienced a severe impairment of cross-modal associative memory after bilateral ablations of the amygdala. These animals failed to recognize visually an object that had been examined previously by taste or touch. These observations suggests that one of the major functions of the amygdala may be the integration and generalization of information that is processed by multiple sensory systems

in the brain, a skill that is typically difficult for autistic individuals.

In 1991, Squire and Zola-Morgan reconsidered the hypothesized relationship of medial temporal lobe structures to memory. They noted that the severe memory loss previously attributed to bilateral combined lesions of the amygdala and hippocampus was the result of inadvertent surgical damage to the cortical regions adjacent to the amygdala, not to the inclusion of the amygdala, as previously believed (Mishkin, 1978). Thus, it appears that structures involved in the medial temporal lobe memory system include the hippocampal formation and related entorhinal, perirhinal, and parahippocampal cortices and that the amygdala is not a component of this system.

Studies in human and nonhuman primates have suggested the presence of at least two memory systems: representational or associative memory, and procedural or habit memory (Mishkin & Appenzeller, 1987; Murray, 1990; Squire & Zola-Morgan, 1991). Representational memory is believed to involve all sensory modalities and mediates the processing of facts, experiences, and events and the integration and generalization of information that leads to higher-order cognition and learning. In contrast, habit memory is involved in skill learning and automatic connections between stimulus and response. The two systems are believed to be anatomically separate, representational memory depending on the hippocampus, amygdala, and areas related to them, whereas the anatomical substrate for habit memory is believed to reside in the striatum and neocortex of the cerebral hemispheres. Neuropathological studies of the brain in autism have shown no abnormalities of the striatum and, with the exception of the anterior cingulate cortex, the neocortex likewise is unremarkable. In contrast, the hippocampal complex, amygdala, entorhinal cortex, septum,

and medial mammillary body have shown significant abnormalities. Thus, the substrate for representational memory appears to be selectively abnormal in the autistic brain, whereas the structures responsible for habit memory appear to be spared.

Though the effect of an early disturbance to the limbic system structures is unknown, likely curtailment of development and prenatally acquired lesions in these regions could disrupt or distort the acquisition and interpretation of information. Such a disturbance in the processing of information could lead to the disordered cognition, social interaction, and language characteristics of the autistic child. In contrast, the preservation of the habit memory system could account for the need for sameness and preoccupation with a narrow range of interests and activities and for the outstanding memory for rote information observed in some autistic individuals.

Studies have suggested that these two neural systems mature at different times in both human and nonhuman primates, the habit system being functional early in life, though the representational system develops later in childhood (Bachevalier & Mishkin, 1991; Overman et al., 1992). Given this pattern of cognitive maturation, possibly a developmentally dysfunctional neuronal circuitry involving the limbic system would have little impact during the first 1 to 2 years of life. However, with development, the effect of this dysfunctional circuitry gradually may become evident, leading to what appears to be social, language, and cognitive deterioration—features frequently reported as part of the early history of childhood autism.

IMPLICATIONS OF CEREBELLAR ABNORMALITIES

Areas of abnormality outside the forebrain in autism have been confined to the cerebellum

and related inferior olive. Marked reduction in the number and size of Purkinje cells has been noted, primarily in the posterior and inferior regions of the hemispheres, with sparing of the vermis and without the presence of significant gliosis. The absence of glial hyperplasia suggests that the lesions have been acquired early in development. Animal studies have shown a progressively decreasing glial response after cerebellar lesions at increasingly early ages (Brodal, 1940).

The preservation of the neurons of the inferior olive further support an early origin for the cerebellar abnormalities. Retrograde loss of olivary neurons regularly occurs after cerebellar lesions in immature postnatal and adult animals (Brodal, 1940) and neonatal (Norman, 1940) and adult humans (Homes & Stewart, 1908; Greenfield, 1954), presumably because of the close relationship of the olivary climbing-fiber axons to the Purkinje cell dendrites (Eccles, Ito, & Szentagothai, 1967).

In the fetal monkey, prior to establishing their definitive relationship with the Purkinje cells dendrites, the olivary climbing fibers have been shown to synapse in a transitory zone beneath the Purkinje cells called the *lamina desiccans* (Rakic, 1971). In the human fetus, this zone is no longer present after 30 to 32 weeks' gestation (Rakic & Sidman, 1970). Therefore, in the absence of retrograde cell loss in the olive in the presence of a marked reduction in the number of Purkinje cells, likely the cerebellar cortical lesions seen in autism have their onset at or before this time.

The relationship of the cerebellar findings to the clinical features of autism is unclear. Dysfunction of the cerebellum beginning before birth may be associated with few if any neurological symptoms (Norman, 1940; Adams, Corselis, & Duchon, 1984). Studies in adult animals have demonstrated both a pathway between the fastigial nucleus of the

cerebellum and the amygdala and septal nuclei of the limbic system and a reciprocal connection between this nucleus and the hippocampus, suggesting that the cerebellum may play a role in the regulation of emotion and higher cortical thought (Heath & Harper, 1974; Heath et al., 1978). The cerebellum also has been implicated in the regulation of affective behavior (Berman, Berman, & Prescott, 1974) and in functional psychiatric disorders (Heath et al., 1979).

More recently, studies in animals and humans have suggested a role for the cerebellum in cognition, including mental imagery and anticipatory planning (Leiner, Leiner, & Dow, 1987) and in some aspects of language processing (Peterson et al., 1989). Further, the cerebellum has been implicated in the control of voluntary shift of selective attention between one sensory modality and another, for example, shifting between auditory and visual attention (Akshoomoff & Courchesne, 1992; Courchesne et al., 1994). Also, the cerebellum has been suggested to play a possible role in cognitive planning, a function independent of memory and most significant in novel situations (Grafman et al., 1992). More recently, studies in monkeys have established that the dorsolateral prefrontal cortex, believed to be involved in spatial working memory, is the target of output from the dentate nucleus of the cerebellum (Middleton & Strick, 1994). This relationship to the prefrontal cortex suggests that the cerebellum may be involved in the planning and timing of future behavior. Thus, a growing body of evidence suggests that the cerebellum is important in the regulation of the speed, consistency, and appropriateness of mental and cognitive processes and in the control of motor and sensory information and activity (Schmahmann, 1991). Therefore, it is likely the anatomical abnormalities observed

in the cerebellum in autism contribute to many of the atypical behaviors and disordered information-processing characteristic of the syndrome. However, the precise functional significance of these abnormalities, their relationship to the findings observed in the limbic system, and their impact on the specific features of autism remain to be elucidated.

CONCLUSION

Although science has made significant advances in our understanding of autism, particularly within the last 15 years, numerous challenges remain. Most now accept that autism is a disorder of neurological development probably occurring or beginning before birth. The most obvious anatomical abnormalities of the brain appear to be selective and appear to be confined to the limbic system and to the cerebellum and related inferior olive. Although now genetics appears possibly to play a significant etiological role, the pathogenic mechanisms for the disorder remain unknown. Future research undoubtedly will be directed toward elucidating the genetic profile associated with autism, thereby offering opportunities for prenatal and more precise and earlier postnatal diagnosis. Equally important will be the pursuit of *in vivo* functional imaging studies and neurochemical analysis of autopsy material, with a particular emphasis on the parts of the brain identified as being abnormal. Autism also is a disorder that offers the clinical investigator an unusual opportunity to study multiple aspects of atypical cognition, emotion, social awareness, language, and behavior from a developmental perspective, and likely, science ultimately may have a better understanding of normal development as the result of these present and future research efforts. ■

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