New evidence of cerebellar defects

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deed, the researchers say, a re-analysis of data from several "negative" studies shows clear abnormalities masked by the skewing of data by subjects with undetected hyperplasia.

In all, Courchesne et al. say, "cerebellar abnormalities have been found in 15 autopsy and quantitative MRI reports from nine laboratories involving a total of 226 autistic cases." In a field marked by diverse and often contradictory findings, such near-unanimity is almost unheard of. "Autism," the researchers say, "may be one of the first developmental neuropsychiatric disorders for which substantial concordance exists among several independent microscopic and macroscopic studies as to the location and type of neuroanatomic maldevelopment."

There is evidence, the researchers say, that the degree of impairment in autism correlates with the degree of cerebellar abnormality. Their research shows that "the autistic group that was most clinically impaired...had the most severe vermal hypoplasia, and the group with little or no intellectual impairment had no evidence of vermal abnormality. Autistic groups with impairment in between correspondingly had vermal hypoplasia in between these two extremes." In the group with hyperplasia, all individuals had verbal IQs of 70 or less.

Courchesne et al. also have reported that many autistic individuals have defects of the parietal lobe, one of the four lobes into which each hemisphere of the cerebrum is divided (see ARRI 7/3). Of 21 autistic subjects the researchers studied, 43% showed parietal lobe abnormalities.

Is autism a disorder of attention?

In the past, researchers believed the cerebellum was responsible primarily for coordinating voluntary muscle activity and maintaining equilibrium. But more and more, the "little brain" is being considered as a major player in thought and emotion. Work by Courchesne et al. indicates that, in particular, the cerebellum plays an important role in the shifting of attention.

For example, the researchers conducted an experiment in which normal controls, autistic subjects, and non-autistic subjects with cerebellar damage were asked to shift back and forth between identifying novel visual stimuli (colored squares) and identifying novel sounds. Both autistic subjects and cerebellar patients had problems with the task; they could shift their attention, Courchesne et al. say, but "performance appeared to be more variable, inaccurate, poorly timed, and effortful." By contrast, their performance was not impaired on a task that required focusing, but not shifting, attention.

In addition, the researchers say, "this shift deficit was persistent and profound despite repeated training and experience in these tasks in one autistic patient who was able to be retested on six separate occasions."

This disability, the researchers say, would profoundly affect an individual's ability to explore and understand the world around him—and in particular, to understand social interactions. Autistic individuals, Courchesne et al. suggest, "enter the world unable to smoothly and selectively shift their mental 'spotlight of attention' in a timely fashion in response to rapidly changing social and nonsocial cues, and so will not combine these various and separate affective and sensory cues into a single coherent entity in memory."

"The autistic infant's knowledge of the social world," they say, "would be made up of disconnected fragments of gestural, facial, vocal and emotional information."

Other autistic symptoms may stem from the cerebellum's connections with other brain areas including the limbic system (which controls emotions), and the reticular activating system (which controls arousal). It appears, the researchers say, that "the cerebellum plays [a] role in the coordination of all systems with which it is interconnected, including motor, attention, arousal, sensory, memory, limbic, frontal lobe, parietal lobe, hypothalamic, serotonergic, dopaminergic, noradrenergic, and so forth."

The researchers speculate that the parietal defects seen in almost half of autistic subjects also affect attention. Their studies of subjects with parietal damage, they say, showed that such subjects exhibit "visual attention distributed as a spotlight at the attentional focus with little surrounding processing enhancement."

"Many autistic patients appear to focus intensely on some small element of the environment while ignoring surrounding contextual information," they say, citing the example of an autistic child staring fixedly at a spinning top while ignoring a starting pistol fired near his head.

Defects appear to occur early

In autistic subjects, cerebellar damage apparently occurs before or shortly after birth—possibly as early as in the second trimester of pregnancy. The cause is unknown, but may include genetic defects, oxygen deprivation in utero or during birth, infections, metabolic disorders, and toxic exposure

Individuals whose cerebellar damage occurs in childhood or adulthood—for instance, because of tumors—do not exhibit autism but do show symptoms including memory loss, moodiness, poor concentration, impaired understanding of abstract concepts, language problems, and a dislike of environmental stimulation.

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"Abnormality of cerebellar vermian lobules VI and VII in patients with infantile autism: identification of hypoplastic and hyperplastic subgroups with MR imaging," *AJR*, 162, January 1994; "The brain in infantile autism: posterior fossa structures are abnormal," *Neurology*, February 1994; "Impairment in shifting attention in autistic and cerebellar patients," *Behavioral Neuroscience*, in press; "A new role for the cerebellum in cognitive operations," *Behavioral Neuroscience*, Vol. 106, 1992; "Parietal damage and narrow 'spotlight' spatial attention," *Journal of Cognitive Neuroscience*, January 1994; and "Parietal lobe abnormalities detected with MR in patients with infantile autism," *AJR*, 160, February 1993; all by Eric Courchesne et al. Address:Eric Courchesne, Department of Neurosciences, School of Medicine, University of California, San Diego, La Jolla, CA 92093.

Treatment update: epilepsy drugs

Seizure drugs: not just for seizures?

Anti-convulsant drugs may be a highly effective treatment for some autistic children with no overt signs of a seizure disorder, according to a new report by Audrius Plioplys.

The physician cites case histories of three autistic patients, ranging in age from three to five, with no clinical suggestion of seizures. EEG tests on all three showed abnormalities, and the children were started on the anti-convulsant drug valproic acid. All three showed dramatic improvement in language skills, imaginative play, and social interaction.

Before treatment, Plioplys says, all three children were diagnosed as autistic according to the criteria specified in the Diagnostic and Statistical Manual III-R (DSM-III-R), which sets U.S. standards for diagnosing psychiatric disorders. Following treatment, he notes, "although their autistic symptoms had not fully resolved, each one technically no longer qualified for the diagnosis of autism."

His results strongly suggest, Plioplys says, that researchers should study the effects of anti-convulsants on autistic children who do not have overt seizures, but who have epileptiform abnormalities on EEGs. He adds that testing should include both waking and sleeping EEGs.

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"Autism: electroencephalogram abnormalities and clinical improvement with valproic acid," Audrius V. Plioplys; *Archives of Pediatrics and Adolescent Medicine*, Vol. 148, February 1994, pp. 220-222. Address: Audrius Plioplys, Division of Neurology, Mercy Hospital and Medical Center, Stevenson Expressway at King Drive, Chicago, IL 60616.

Felbamate approved

ARRI recently reported on new seizure drugs that may help autistic individuals with intractable epilepsy (see ARRI 7/4). One of these drugs, felbamate, has now been approved by the FDA for use by individuals aged 14 years and older with partial complex epileptic seizures, and for children with Lennox-Gastaut syndrome (a difficult-to-treat form of childhood epilepsy).

Felbamate is the first of a "new generation" of epilepsy drugs which are expected to be more effective, and have fewer side effects, than many of the drugs currently in use. While felbamate can cause some side effects including decreased appetite, nausea and vomiting, headaches, and insomnia, these effects are usually mild and rarely require discontinuation of the drug. Researchers caution, however, that the drug is new and that its effects on people with specific conditions such as autism is not yet known.

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For information contact the Epilepsy Foundation of America, 1-800-EFA-1000, 4351 Garden City Drive, Landover, MD 20785-2267, or your local Epilepsy Foundation office.